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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PGNS007US
	Application Number	
Title of Invention	SPATIALLY ENCODED BIOLOGICAL ASSAYS	

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Applicant Information:

Applicant 1

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

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Application Information:

Title of the Invention	SPATIALLY ENCODED BIOLOGICAL ASSAYS		
Attorney Docket Number	PGNS007US	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	5	Suggested Figure for Publication (if any)	1

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PGNS007US
	Application Number	
Title of Invention	SPATIALLY ENCODED BIOLOGICAL ASSAYS	

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61321124	2010-04-05

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Foreign Priority Information:

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			Remove
Application Number	Country[i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			○ Yes ◉ No

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Assignee Information:

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Assignee 1

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PGNS007US
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Title of Invention	SPATIALLY ENCODED BIOLOGICAL ASSAYS	

If the Assignee is an Organization check here. ☒			
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Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	/Sarah Brashears/			Date (YYYY-MM-DD)	2011-04-05
First Name	Sarah	Last Name	Brashears	Registration Number	38087

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UNITED STATES UTILITY PATENT APPLICATION

SPATIALLY ENCODED BIOLOGICAL ASSAYS

MARK CHEE

PROGNOSYS BIOSCIENCES, INC.

PGNS007US

SPATIALLY ENCODED BIOLOGICAL ASSAYS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application 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.,

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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

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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.

[00010] 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.

[00011] 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

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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.

[00012] 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.

[00013] 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.

[00014] 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.

[00015] 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

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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.

[00016] 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.

[00017] 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

[0001] Figure 1 provides a simplified overview of the assay system of the present invention.

[0002] Figure 2 provides a simplified overview of one embodiment of the assay system of the present invention for detecting nucleic acids.

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[0003] Figure 3 is a representational depiction of one embodiment of the assay overviewed in Figure 2.

[0004] Figure 4 illustrates a general mechanism for one embodiment of a combinatorial encoding scheme of the assay systems of the invention.

[0005] Figure 5 provides a simplified, specific example of the embodiment of a combinatorial encoding scheme shown in Figure 4.

DEFINITIONS

[0006] 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.

[0007] 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.

[0008] The term "binding agent" as used herein refers to any agent that specifically binds to a biological molecule of interest.

[0009] "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

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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%.

[00010] "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 5ºC, but are typically greater than 22ºC, and more typically greater than about 30ºC, and typically in excess of 37ºC. 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 5ºC 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 0.01M 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 25ºC. For example, conditions of 5xSSPE (750 mM NaCl, 50 mM sodium phosphate, 5 mM EDTA at pH 7.4) and a temperature of approximately 30ºC are suitable for allele-specific hybridizations, though a suitable temperature depends on the length and/or GC content of the region hybridized.

[00011] "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

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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.

[00012] "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.

[00013] "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.

[00014] 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

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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.

[00015] 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.

[00016] "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

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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.

[00017] 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

[00018] 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

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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.

[00019] 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.

[00020] 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.

[00021] 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

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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.

[00022] 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

[00023] 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.

[00024] 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 datapoints at low cost. The assay results such as the amount or activity of biological targets can then be mapped back to specific location

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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.

[00025] 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.

[00026] 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.

[00027] 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

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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.

[00028] 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.

[00029] 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 by, preferably, sequencing. The sequence of the encoded probes allows the mapping of the assay results back to locations in the biological sample.

[00030] Figure 2 provides a simplified overview of an assay system 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

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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.

[00031] 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.

[00032] 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

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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.

[00033] 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 10,000 targets per location x 10,000 locations would generate 10^8 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 lest 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 redundnacy, 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.

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Assays

[00034] 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.

[00035] 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 measureable areas.

[00036] 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.

[00037] 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

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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.

[00038] 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). 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.

[00039] 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.

[00040] 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

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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); (Illumina, Inc., San Diego, CA)), may be employed.

[00041] 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.

[00042] 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.

[00043] 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

[00044] 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-

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specific information and the coding tags, the number of oligonucleotides required is dramatically reduced, with a concomitant decrease in cost.

[00045] 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.

[00046] Figure 4 at B shows the spatial pattern that may be used for twenty different coding tags, a1 through a10 (coding tag 406 on encoded probe 420) and b1 through b10 (coding tag 408 encoded probe 422). Coding tag a1, 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.

[00047] 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 a1 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 a1, b4.

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[00048] 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 a1, 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 a1 through a4 are deposited in spots in a pattern (here, in a vertical pattern), and encoding oligonucleotides b1 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.

[00049] 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.

[00050] The pool of resulting sequences is shown at 540. A sequence readout was obtained for target-specific oligonucleotide 1 only at a4b1, a4b2, a1b3, 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 a1b4, 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

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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.

[00051] 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.

[00052] 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 oligonucleotides, (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.

[00053] 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

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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

[00054] 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, serial sections of a tissue sample can be analyzed in parallel and the data combined to build a 3D map.

[00055] 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 handler, which can be 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.

[00056] 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

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more assay areas for different reagent distributions and/or biological target determination. The assay areas may be physically separated using barriers or channels.

[00057] 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.

[00058] 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.

[00059] 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.

[00060] 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,

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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.

[00061] 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.

[00062] 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.

[00063] 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.

[00064] 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

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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.

[00065] 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.

[00066] 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.

[00067] 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.

[00068] 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

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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

[00069] 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 be determined by the relative abundances of the resolvable labels.

[00070] 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^{TM} 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;

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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

[00071] 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 trancripts 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.

[00072] 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

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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.

[00073] 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.

[00074] 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 be 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

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potential for use in diagnostics. The technology of the invention promises to greatly increase the power of such approaches.

EXAMPLES

[00075] 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.

[00076] 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

[00077] 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.

[00078] 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

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the assays that are carried out may employ either ligation, or extension followed by ligation as this may be useful in determining certain polymorphisms.

[00079] Once the *in situ* part of the assay is complete, the reaction products are eluted and analyzed by qPCR to determine 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

[00080] 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.

[00081] 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 $1mm^2$ 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.

[00082] 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.

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[00083] 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.

[00084] 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.

[00085] 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.

[00086] 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.

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Example 4: Adapting the Assay to a Biological Sample.

[00087] 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.

[00088] 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.

[00089] 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

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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.

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I claim:

1. 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.

2. The assay system of claim 1, wherein the biological targets are nucleic acids and the encoded probes are oligonucleotides.
3. The assay system of claim 2, where there are two encoded probes for each of the multiple nucleic acid targets.
4. The assay system of claim 1, wherein the multiple biological targets are proteins, the probe regions of the encoding probes are proteins and the coding tags comprise oligonucleotides.
5. The assay system of claim 4, wherein the multiple biological targets comprise enzymes.
6. The assay system of claim 1, wherein probe regions of the encoded probes comprise antibodies.
7. The assay system of claim 1, wherein the probe regions of the encoded probes are aptamers.
8. The assay system of claim 1, wherein the probe regions of the encoded probes are small molecules.

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9. The assay system of claim 1, further comprising an amplification step between the separating step and the determining step.
10. The assay system of claim 1, wherein the determining step is performed by nucleic acid sequencing.
11. The assay system of claim 10, wherein the sequencing is high-throughput digital nucleic acid sequencing.
12. The assay system of claim 1, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20.
13. The assay system of claim 12, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 50.
14. The assay system of claim 13, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 75.
15. The assay system of claim 14, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 100.
16. The assay system of claim 15, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000.
17. The assay system of claim 16, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 10,000.
18. The assay system of claim 17, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 100,000.
19. The assay system of claim 18, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000,000.
20. The assay system of claim 11, wherein the sequence of at least one hundred thousand encoding probes are determined in parallel.
21. The assay system of claim 20, wherein the sequence of at least five hundred thousand encoding probes are determined in parallel.
22. The assay system of claim 21, wherein the sequence of at least one million encoding probes are determined in parallel.
23. The assay system of claim 1, wherein the known spatial pattern is determined by histological features of the sample.

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24. The assay system of claim 1, wherein software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step and the associating step.
25. The assay system of claim 1, wherein 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.
26. The assay system of claim 1, wherein the probe regions of the encoding probes are nucleic acids and the separating step is accomplished by a washing of the sample.
27. An assay system to determine spatial patterns of abundance or activity or both of multiple nucleic acid targets at multiple sites in a sample, wherein 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, wherein 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.

28. The assay system of claim 27, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20.
29. The assay system of claim 28, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 50.
30. The assay system of claim 29, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 75.

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31. The assay system of claim 30, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 10,000.
32. The assay system of claim 31, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 100,000.
33. The assay system of claim 32, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000,000.
34. The assay system of claim 33, wherein the sequence of at least one hundred thousand encoding probes are determined in parallel.
35. The assay system of claim 34, wherein the sequence of at least one million encoding probes are determined in parallel.
36. The assay system of claim 27, where two oligonucleotide probes are delivered for each of the multiple nucleic acid targets.
37. The assay system of claim 27, wherein the coupling step is performed by ligation.
38. The assay system of claim 27, wherein the coupling step is performed by extension followed by ligation.
39. The assay system of claim 27, further comprising an amplification step between the coupling step and the determining step.
40. An assay system to determine spatial patterns of abundance or activity or both of multiple protein 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 protein targets to the multiple sites in the sample in a known spatial pattern, wherein 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

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associating the abundance or activity or both of the multiple protein targets to the locations of the multiple sites in the sample.

41. The assay system of claim 40, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20.
42. The assay system of claim 41, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 50.
43. The assay system of claim 42, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 75.
44. The assay system of claim 43, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 100.
45. The assay system of claim 44, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 500.
46. The assay system of claim 45, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1000.
47. The assay system of claim 46, wherein the sequence of at least ten thousand encoding probes are determined in parallel.
48. The assay system of claim 40, wherein the sequence of at least one hundred thousand encoding probes are determined in parallel.
49. The assay system of claim 48, wherein the sequence of at least one million encoding probes are determined in parallel.
50. The assay system of claim 40, further comprising an amplification step between the coupling step and the determining step.
51. The assay system of claim 40, wherein the protein targets are enzymes, and the probe regions of the encoded probes are substrates, putative substrates of both for the enzymes.
52. The assay system of claim 40, wherein the probe regions of the encoded probes are affinity capture agents.
53. The assay system of claim 52, wherein the probe regions of the encoded probes are antibodies.
54. The assay system of claim 52, wherein the probe regions of the encoded probes are aptamers.

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55. The assay system of claim 40, wherein separating encoded probes that interact with the protein targets from encoded probes that do not interact with the protein targets is accomplished by an affinity capture agent that distinguishes encoded probes that interact with the protein targets from encoded probes that do not interact with the protein targets.
56. The assay system of claim 36, wherein the coding tags are oligonucleotides.
57. 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 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.

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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.

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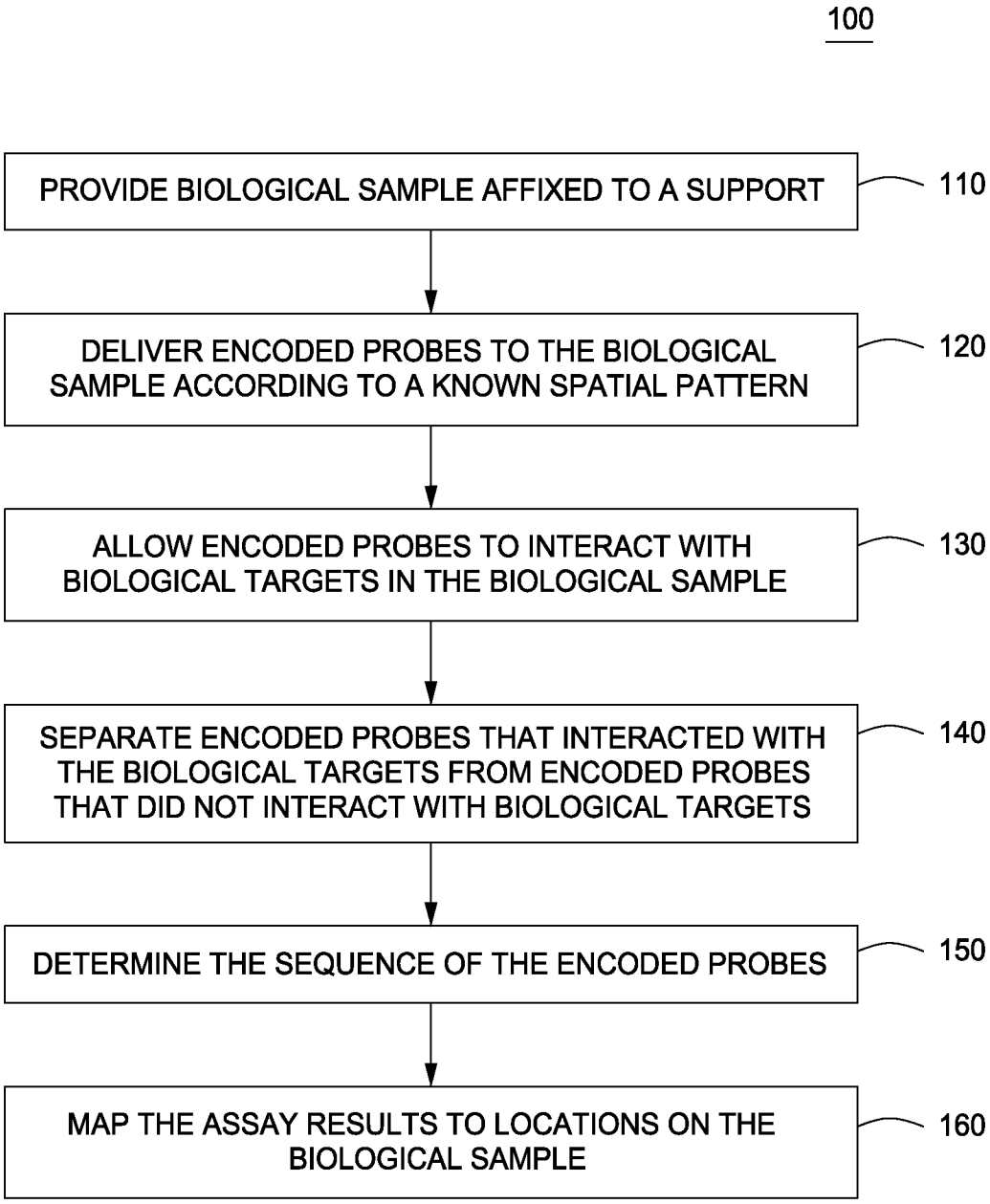

100
PROVIDE BIOLOGICAL SAMPLE AFFIXED TO A SUPPORT
110
DELIVER ENCODED PROBES TO THE BIOLOGICAL SAMPLE ACCORDING TO A KNOWN SPATIAL PATTERN
120
ALLOW ENCODED PROBES TO INTERACT WITH BIOLOGICAL TARGETS IN THE BIOLOGICAL SAMPLE
130
SEPARATE ENCODED PROBES THAT INTERACTED WITH THE BIOLOGICAL TARGETS FROM 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

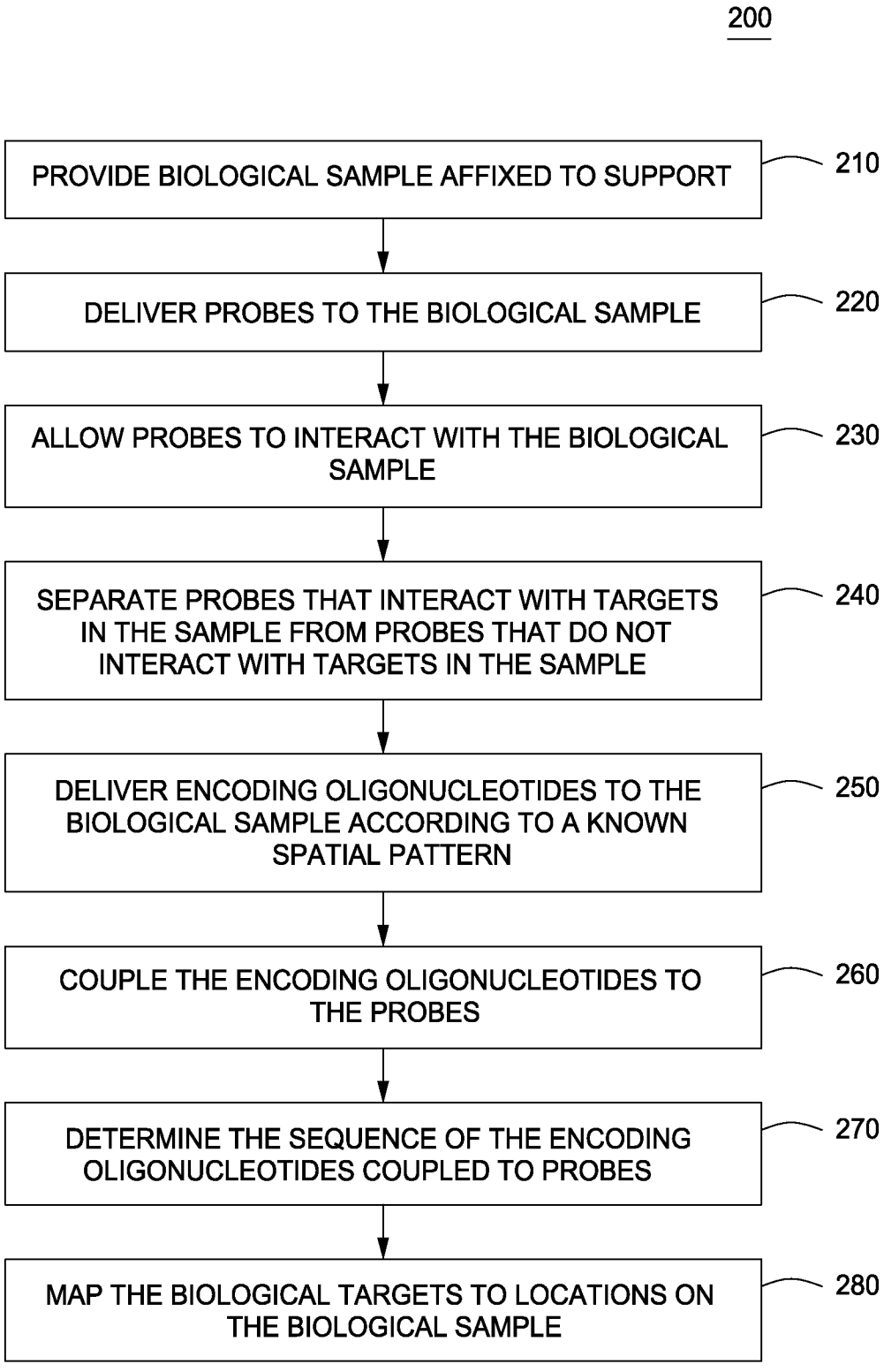

200
PROVIDE BIOLOGICAL SAMPLE AFFIXED TO SUPPORT
210
DELIVER PROBES TO THE BIOLOGICAL SAMPLE
220
ALLOW PROBES TO INTERACT WITH THE BIOLOGICAL SAMPLE
230
SEPARATE PROBES THAT INTERACT WITH TARGETS IN THE SAMPLE FROM PROBES THAT DO NOT INTERACT WITH TARGETS IN THE SAMPLE
240
DELIVER ENCODING OLIGONUCLEOTIDES 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

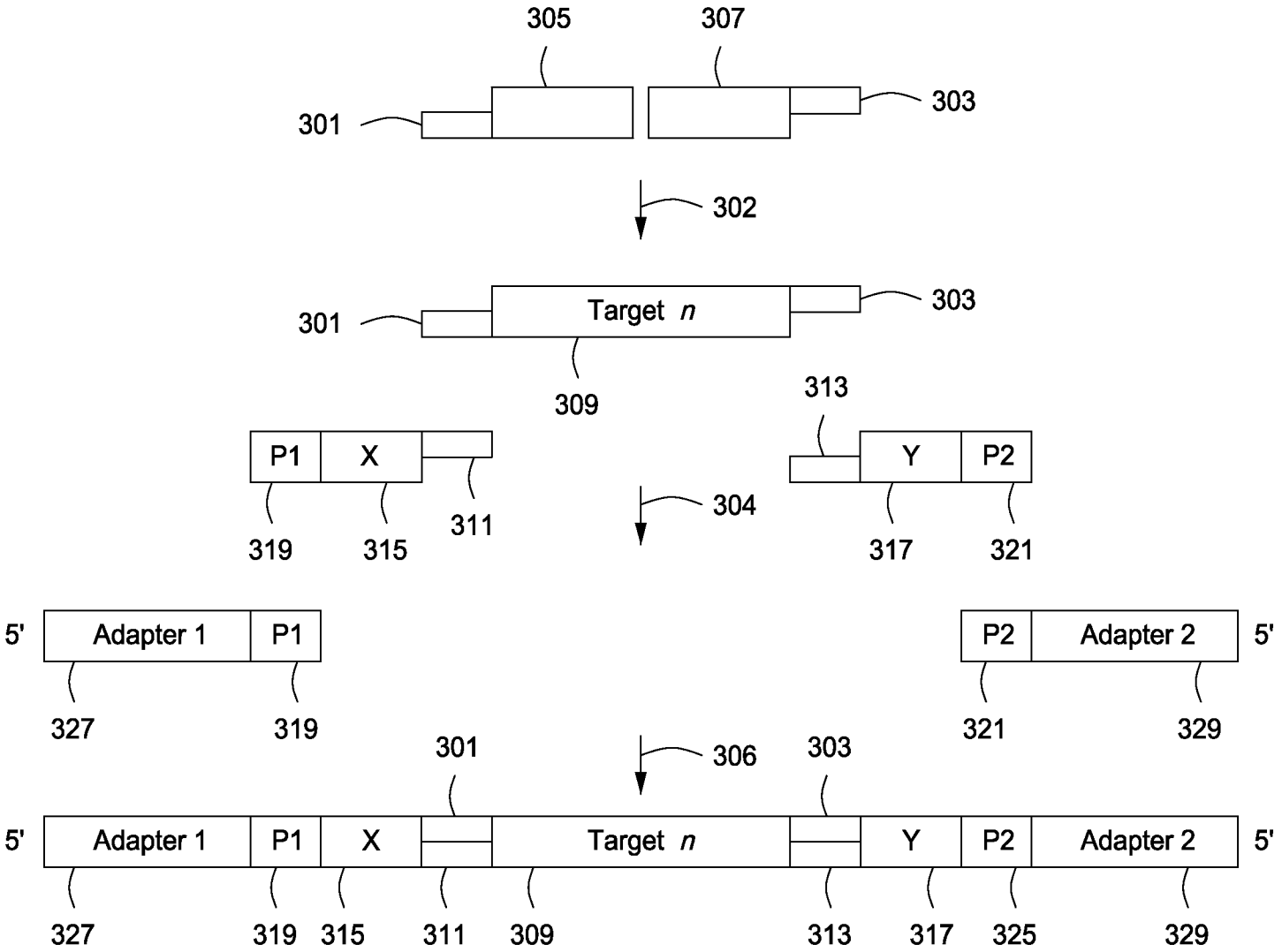

305
307
301
303
302
301
Target n
303
309
313
P1
X
Y
P2
304
319
315
311
317
321
5'
Adapter 1
P1
P2
Adapter 2
5'
327
319
321
329
301
306
303
5'
Adapter 1
P1
X
Target n
Y
P2
Adapter 2
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327
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311
309
313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

FIG. 3

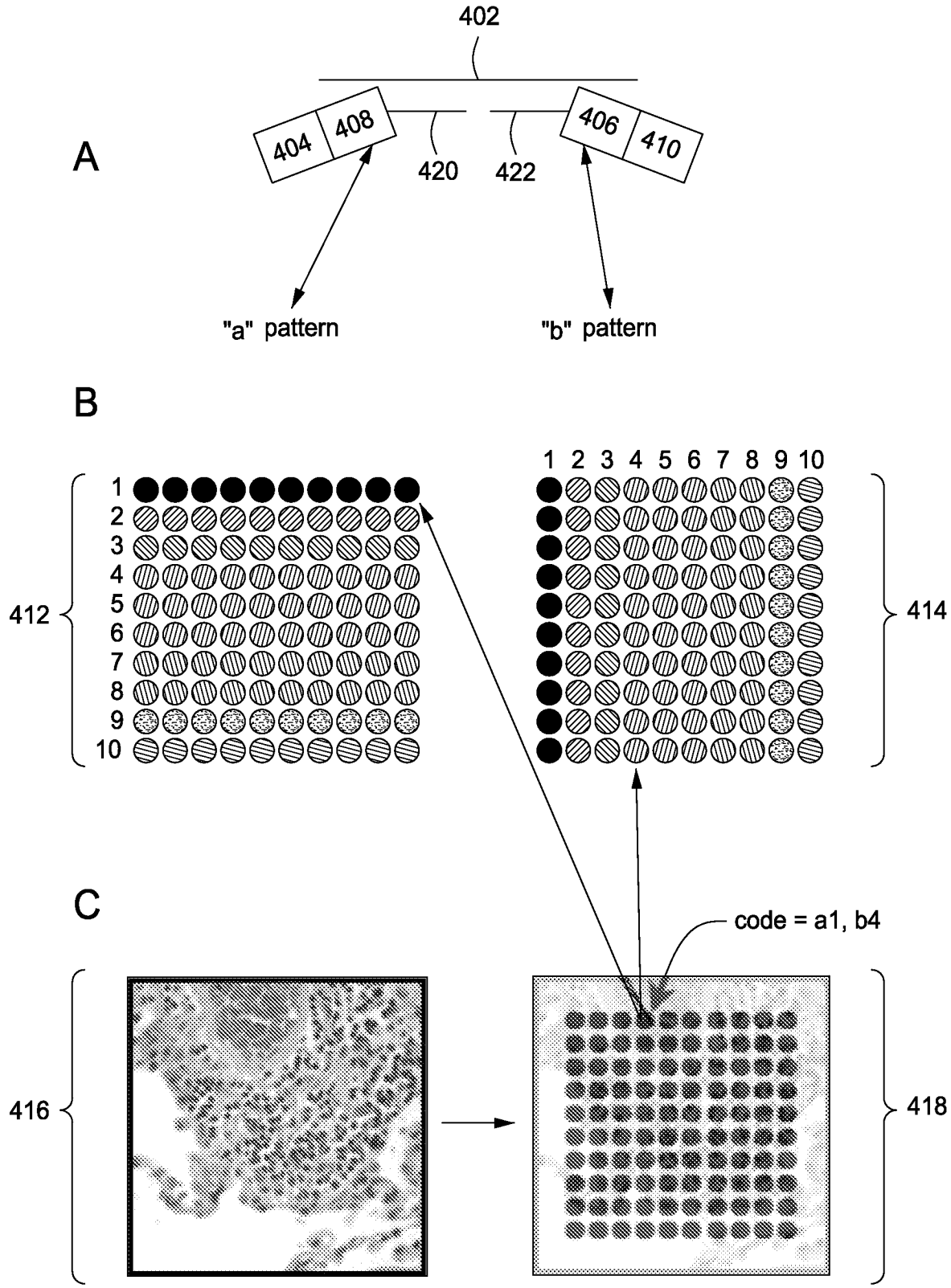

A
402
404
408
420
422
406
410
"a" pattern
"b" pattern
B
1 2 3 4 5 6 7 8 9 10
412
414
C
code = a1, b4
416
418

FIG. 4

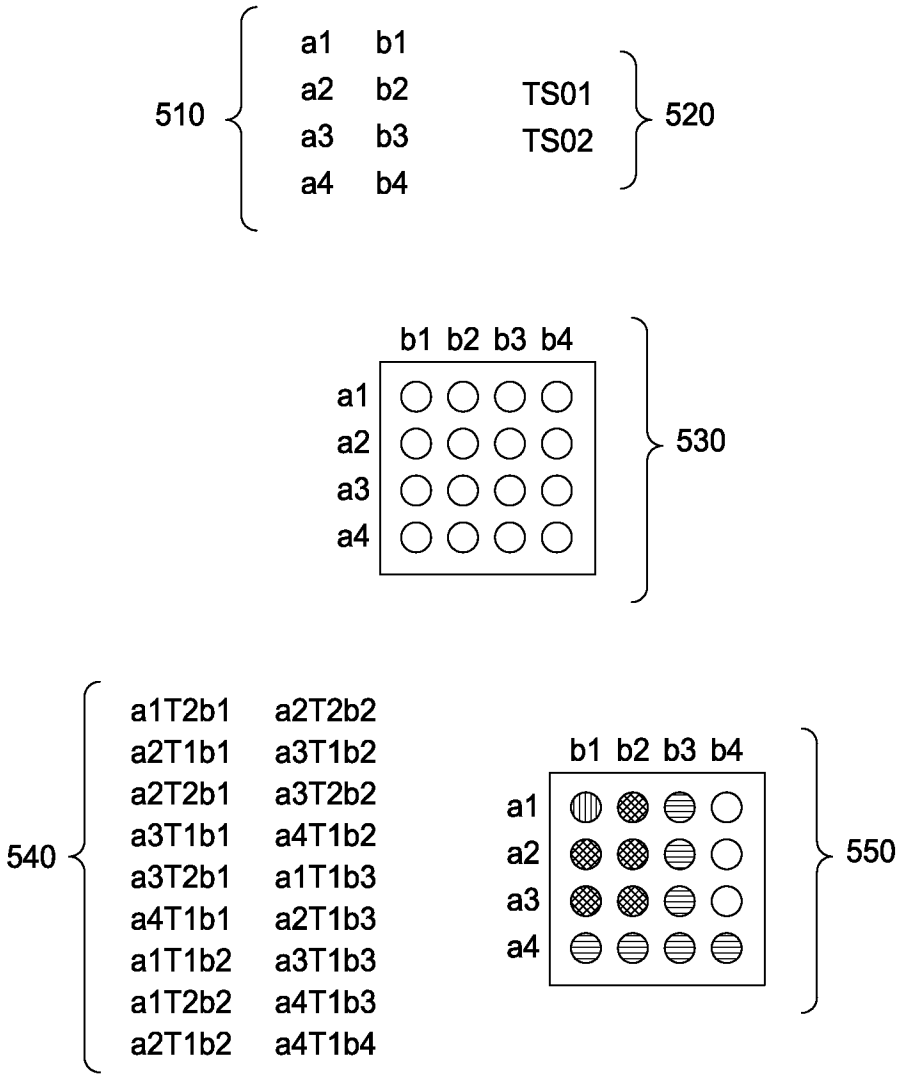

510
a1 b1
a2 b2
a3 b3
a4 b4
TS01
TS02
520
b1 b2 b3 b4
a1
a2
a3
a4
530
540
a1T2b1 a2T2b2
a2T1b1 a3T1b2
a2T2b1 a3T2b2
a3T1b1 a4T1b2
a3T2b1 a1T1b3
a4T1b1 a2T1b3
a1T1b2 a3T1b3
a1T2b2 a4T1b3
a2T1b2 a4T1b4
b1 b2 b3 b4
a1
a2
a3
a4
550

FIG. 5

DECLARATION FOR PATENT APPLICATION

■ **Declaration Submitted with Initial Filing**
☐ **Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16(e) required)**

As a below named inventor, I hereby declare that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

SPATIALLY ENCODED BIOLOGICAL ASSAYS

the specification of which

■ is attached hereto.

☐ was filed on _____ as US Provisional Application Serial No _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) specifically referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C.
			YES:____ NO:____
			YES:____ NO:____

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL	FILING DATE
61/321,124	April 5, 2010

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL	FILING DATE	STATUS(patented/pending/abandoned)

DECLARATION FOR PATENT APPLICATION
(continued)

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.

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Residence: Encinitas, CA

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Mark Chee
Inventor's Signature

3/31/2011
Date

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:	Dianna Louise DeVore/Sarah Brashears
Attorney Docket Number:	PGNS007US

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	82	82
Utility Search Fee	2111	1	270	270
Utility Examination Fee	2311	1	110	110
Pages:				
Claims:				
Claims in excess of 20	2202	37	26	962
Independent claims in excess of 3	2201	1	110	110
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1534**

Electronic Acknowledgement Receipt

EFS ID:	9817130
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	57580
Filer:	Dianna Louise DeVore/Sarah Brashears
Filer Authorized By:	Dianna Louise DeVore
Attorney Docket Number:	PGNS007US
Receipt Date:	05-APR-2011
Filing Date:	
Time Stamp:	21:05:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1534
RAM confirmation Number	6527
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Application Data Sheet	PGNS007US_ADS_AsFiled.pdf	42271 6e8f45bdf7890b7fadde7a51e4fe9be8ecace202	no	3
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2		PGNS007US_App_Figs_AsFiled.pdf	1026787 e6ba91d1b42ee8633ca49e84f4b3e4de7fee88ab	yes	47

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	35
	Claims	36	41
	Abstract	42	42
	Drawings-only black and white line drawings	43	47

Warnings:					
Information:					
3	Oath or Declaration filed	PGNS007US_Declaration.pdf	657845 a5a34b7c2a9127c87d619cf5431f01dc9b4d7b2a	no	2
Warnings:					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	37906 4f5ada52c8f1585e7415ad6a2c416da6252afcdc	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1764809		

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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.

SCORE Placeholder Sheet for IFW Content

Application Number: 13080616 Document Date: 4/5/2011

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Drawings – Other than Black and White Line Drawings

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

To access the documents in the SCORE database, refer to instructions developed by SIRA.

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Form Revision Date: February 8, 2006

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/080,616

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	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	57 minus 20 =	* 37	x 26 =	962	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1	x 110 =	110			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 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	1534		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	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
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.

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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
13/080,616	04/05/2011	1656	1534	PGNS007US	57	4

CONFIRMATION NO. 2142

57580
Convergent Law Group LLP
P.O. BOX 1329
MOUNTAIN VIEW, CA 94042

FILING RECEIPT

OC000000047195184

Date Mailed: 04/21/2011

Receipt is acknowledged of this non-provisional 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 APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Mark S. Chee, Encinitas, CA;

Assignment For Published Patent Application

Prognosys Biosciences, Inc., La Jolla, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/321,124 04/05/2010

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If Required, Foreign Filing License Granted: 04/15/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/080,616**

Projected Publication Date: 10/06/2011

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****

Title

SPATIALLY ENCODED BIOLOGICAL ASSAYS

Preliminary Class

435

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/080,616	04/05/2011	Mark S. Chee	PGNS007US

CONFIRMATION NO. 2142

57580
Convergent Law Group LLP
P.O. BOX 1329
MOUNTAIN VIEW, CA 94042

PUBLICATION NOTICE



Title:SPATIALLY ENCODED BIOLOGICAL ASSAYS

Publication No.US-2011-0245111-A1
Publication Date:10/06/2011

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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/.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	13/080,616
Filing Date	05-April-2011
First Named Inventor	Mark Chee
Art Unit	1773
Examiner Name	Not Assigned
Attorney Docket Number	PGNS007US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number - Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	6,210,894	04-03-2001	Brennan	
	2	6,344,316	02-05-2002	Lockhart et al.	
	3	6,632,641	10-14-2003	Brennan et al.	
	4	6,878,515	04-12-2007	Landegren et al.	
	5	7,544,473	06-09-2009	Brenner	
	6	7,378,242	05-27-2008	Hurt, et al.	
	7	2003/0232382	06-23-2003	Brennan et al.	
	8	2006/0046313	03-02-2006	Roth et al.	
	9	2003/0224419	12-04-2003	Corcoran et al.	
	10	2005/0164292	07-28-2005	Faroqui et al.	
	11	2005/0255548	11-17-2005	Lipovsek et al.	
	12	2006/0134669	06-22-2006	Casasanta III	
	13	2006/0275799	12-07-2006	Banerjee et al.	
	14	2008/0312103	12-18-2008	Nemoto et al.	
	15	2009/0291854	11-26-2009	Weisinger-Mayr et al.	
	16	2005/0260653	11-24-2005	LaBaer et al.	
	17	2010/0184614	07-22-2010	Ye et al.	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 4

Complete if Known	
Application Number	13/080,616
Filing Date	05-April-2011
First Named Inventor	Mark Chee
Art Unit	1773
Examiner Name	Not Assigned
Attorney Docket Number	PGNS007US

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] - Number[4] - Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	18	WO 2007/073171	06-28-2007	Van Elij et al.		

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 4

Complete if Known	
Application Number	13/080,616
Filing Date	05-April-2011
First Named Inventor	Mark Chee
Art Unit	1773
Examiner Name	Not Assigned
Attorney Docket Number	PGNS007US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	19	FREDRIKSSON, et al., "Protein detection using proximity-dependent DNA ligation assays," Nature Biotech., 20:473-77 (2002)	
	20	FREDRIKSSON, et al., "Multiplexed protein detection by proximity ligation for cancer detection," Nature Methods, 4(4):327-29 (2007	
	21	KOZLOV ,et al., "A High-Complexity Multiplexed Solution-Phase Assay for Profiling Protease Activity on Microarrays," Comb. Chem. And High Throughput, 11:24-35 (2008)	
	22	NIEMEYER, "The developments of semisynthetic DNA/protein conjugates," Trends Biotechnol, 20(9):395-401(2002)	
	23	CHANDRA, et al., "Cell-free synthesis-based protein microarrays and their applications," Proteomics ePub, 5(6):717-30 (2009)	
	24	RAMACHANDRAN et al., "Next-generation high-density self-assembling functional protein arrays,: Nature Methods, 5(6):535-38 (2008)	
	25	Search Report for PCT/US2010/059327 (PGNS005PCT)	
	26	Search Report for PCT/US2011/031308 (PGNS007PCT)	
	27	Search Report for PCT/US2011/031163 (PGNS008PCT)	

Examiner Signature		Date Considered	

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[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.
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Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/080,616
				Filing Date	05-April-2011
				First Named Inventor	Mark Chee
				Art Unit	1773
				Examiner Name	Not Assigned
Sheet		of		Attorney Docket Number	PGNS007US

Dear Sir/Madam:

The references being cited on this form PTO/SB/08 are being called to the attention of the Examiner. It is respectfully requested that the cited references be considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

As provided by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all relevant information.

This Information Disclosure Statement is being filed before the issuance of the first Office Action on the merits; thus, applicants do not believe that any fees are due.

Respectfully submitted,

/SarahBrashears/

Sarah J. Brashears
Registration No. 38,087

Date: 30 November 2011

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.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
DIANNA L. DEVORE
CONVERGENT LAW GROUP LLP
475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference PGNS005PCT	Date of mailing *(day/month/year)* 29 MAR 2011 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 10/59327	International filing date *(day/month/year)* 07 December 2010 (07.12.2010)
Applicant PROGNOSYS BIOSCIENCES, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PGNS005PCT	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/59327	International filing date *(day/month/year)* 07 December 2010 (07.12.2010)	(Earliest) Priority Date *(day/month/year)* 07 December 2009 (07.12.2009)
Applicant PROGNOSYS BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 20 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/59327

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; G01N 33/50 (2011.01)
USPC - 435/6, 435/7.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 435/6, 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/6, 435/7.1; 435/4 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases : PubWEST (PGPB, EPAB, JPAB, USPT); Google Scholar
Search terms: Array, microarray, protein array, protein biochip, protein in situ array, microfabrication, cell-free protein biosynthesis, cell-free expression, in vitro transcription/translation, nucleic acid programmable protein array (NAPPA),

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/0312103 A1 (NEMOTO et al.). 18 December 2008 (18.12.2008) Especially para [0008], [0020], [0039], sheet 1 fig 1a,b.	1
X ----- Y	US 2005/0260653 A1 (LaBaer et al.). 24 November 2005 (24.11.2005). Especially sheet 1 fig 1, para [0005], [0015], [0022], [0040], [0046], [0055], [0088], [0115], [0367], [0445], [0446], [0458].	22, 24-29, 31-35 ---------- 2-21, 23, 30
Y	NIEMEYER. The developments of semisynthetic DNA?protein conjugates. Trends Biotechnol September 2002 Vol 20 No 9 Pages 395-401. Especially pg 400 fig 6.	2-21, 23, 30
Y	HENDERSON et al. High sensitivity multianalyte immunoassay using covalent DNA-labeled antibodies and polymerase chain reaction. Nucl Acids Res 11 February 1995 Vol 23 No 3 Pages 522-529. Especially pg 523 fig 2.	11
Y	RAMACHANDRAN et al. Next-generation high-density self-assembling functional protein arrays. Nat Methods June 2008 Vol 5 No 6 Pages 535-538. Especially pg 537 left col para 1, pg 538 fig 3B.	16-21
A	CHANDRA et al. Cell-free synthesis-based protein microarrays and their applications. Proteomics ePub 1 December 2009 Vol 10 No 4 Pages717-730. Especially pg 717-722.	1-35
A	US 2006/0275799 A1 (BANERJEE et al.) 7 December 2006 (07.12.2006). Especially abstract, sheet 1 fig 1 (Methods of ligating two oligonucleotides together on a microarray).	12-15
A	US 2005/0164292 A1 (FAROOQUI et al.). 28 July 2005 (28.07.2005). Especially abstract, shee sheet 1 fig 1. (Oligonucleotide-antibody conjugation methods)	1-35

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2011 (14.03.2011)	29 MAR 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: DIANNA L. DEVORE
CONVERGENT LAW GROUP LLP
475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	29 MAR 2011
Applicant's or agent's file reference PGNS005PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/59327	07 December 2010 (07.12.2010)	07 December 2009 (07.12.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68; G01N 33/50 (2011.01)
USPC - 435/6, 435/7.1

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	14 March 2011 (14.03.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2-21,23,30	YES
	Claims	1,22,24-29,31-35	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-35	NO
Industrial applicability (IA)	Claims	1-35	YES
	Claims	NONE	NO

2. Citations and explanations:

Claim 1 lacks novelty under PCT Article 33(2) as being anticipated by US 2008/0312103 A1 to NEMOTO et al. (hereinafter "Nemoto").

As to claim 1, Nemoto teaches an array comprising a substrate having a surface;
two or more individual constructs associated on the surface of the substrate (para [0020]; "An mRNA chip comprising a plurality of the immobilized mRNA-puromycin conjugates described"), wherein the individual constructs comprise: an oligonucleotide encoding a peptide of interest (para [0020] mRNA); and the peptide of interest (para [0039]; "synthesizing a protein by adding the mRNA-PM conjugate immobilized on a solid phase to a translation system"); wherein the oligonucleotide is associated with the substrate surface (para [0008]; "a solid phase binding site for binding an mRNA-puromycin conjugate"; sheet 1 fig 1a, b), and the peptide is associated with the oligonucleotide (para [0039]; "synthesizing a protein by adding the mRNA-PM conjugate immobilized on a solid phase to a translation system. Namely, when a conjugate in which puromycin is ligated to mRNA through the linker is contacted with a translation system, an in vitro virus virion is known to be formed in which the mRNA is ligated with a translated protein through the puromycin"; sheet 1 fig 1a, b).

Claims 22, 24-29, 31-35 lack novelty under PCT Article 33(2) as being anticipated by US 2005/0260653 A1 (LABAER et al.) (hereinafter "LaBaer").

As to claim 22, LaBaer teaches a method for constructing an array (abstract; "Arrays of polypeptides can be generated by translation of nucleic acid sequences encoding the polypeptides at individual addresses on the array") comprising:
a) synthesizing a set of nucleic acid sequences of known sequence on a solid substrate (para [0005]; " In one aspect, the invention features a method that includes: disposing, on a substrate, one or more nucleic acids that include a coding region and an anchoring agent, maintaining the substrate under conditions which enable the anchoring agent of each disposed nucleic acid to stably attached to the substrate"; para [0015]; " In one embodiment, the coding region encodes a polypeptide that includes a first amino acid sequence, e.g., an amino acid sequence of interest").
b) attaching one or more additional nucleic acid regions to the nucleic acids on the solid substrate to provide extended nucleic acids on the substrate (para [0445-0446]; "[0445] Capture Probes. The substrate can include an attached nucleic acid capture probe at each address. In one aspect, capture probes can be used to create a self-assembling array. A unique capture probe at each address selectively hybridizes to a nucleic acid encoding a test amino acid sequence, thereby organizing each encoding nucleic acid to a unique address. The capture nucleic acid can be covalently attached or bound, e.g., to a polycationic surface on the substrate. [0446] The capture probe can itself be synthesized in situ, e.g. by a light-directed method ..., or by being spotted or disposed at the addresses. The capture probe can hybridize to the nucleic acid encoding the test polypeptide. In a preferred embodiment, the capture probe anneals to the T7 promoter region of a single stranded nucleic acid encoding the test amino acid sequence. In another embodiment, the capture probe is ligated to the encoding nucleic acid sequence")
c) performing in vitro transcription and translation utilizing the extended nucleic acids as a template for production of peptides (para [0458]; " The fusion proteins will be generated with commercially available in vitro transcription/translation kits such as the Promega TNT Coupled Reticulocyte Lysate Systems or TNT Coupled Wheat Germ Extract Systems"; para [0022]); and
d) attaching the produced peptides on known locations on the solid substrate (para [0015]; " In one embodiment, the coding region encodes a polypeptide that includes a first amino acid sequence, e.g., an amino acid sequence of interest, and an affinity tag. The affinity tag binds to a binding agent. The method can also include disposing the binding agent on the substrate. In some cases, it is useful to prepare a solution that includes the nucleic acid and the binding agent, and to dispose the solution onto the substrate"; sheet 1 fig 1).

----------continued in Supplemental Box----------

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
No valid CRF was filed in response to the ISA/225 of 10 December 2010, therefore no sequence information was available for the ISR.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V-2 (Citations and Explanations)

As to claim 24, LaBaer further teaches that the nucleic acids are chemically synthesized directly on the solid substrate (para [0446]; "The capture probe can itself be synthesized in situ, e.g., by a light-directed method").

As to claim 25, LaBaer further teaches that the additional nucleic acids in step b) are attached via enzymatic ligation (para [0446]; "In another embodiment, the capture probe is ligated to the encoding nucleic acid sequence").

As to claim 26, LaBaer further teaches that the set of nucleic acids comprises at least 1,000 nucleic acid sequences on the substrate (para [0367]; For example, a single array containing 10,000 arrayed elements, for example, can be sufficient to yield 10,000 results (e.g., quantitative results)").

As to claim 27, LaBaer further teaches that the set of nucleic acids comprises at least 5,000 nucleic acid sequences on the substrate (para [0367]).

As to claim 28, LaBaer further teaches that the set of nucleic acids comprises at least 10,000 nucleic acid sequences on the substrate (para [0367]).

As to claim 29, LaBaer teaches a method for constructing a peptide array (abstract), comprising:
a) manufacturing a nucleic acid microarray comprising a set of chemicall synthesized oligonucleotides encoding amino acid sequences (para [0005], [0015]);
b) attaching one or more additional nucleic acid regions to the nucleic acids on the solid substrate to provide extended nucleic acids on the substrate (para [0446]);
c) performing in vitro transcription and translation utilizing the extended nucleic acids as a template for production of peptides (para [0458], [0022]) ; and
d) attaching the produced peptides on the solid substrate (para [0015]; sheet 1 fig 1).

As to claim 31, LaBaer further teaches that the nucleic acids are chemically synthesized directly on the solid substrate (para [0446]; "The capture probe can itself be synthesized in situ, e.g., by a light-directed method").

As to claim 32, LaBaer further teaches that the additional nucleic acids in step b) are attached via enzymatic ligation (para [0446]; "In another embodiment, the capture probe is ligated to the encoding nucleic acid sequence").

As to claim 33, LaBaer further teaches that the set of nucleic acids comprises at least 1,000 nucleic acid sequences on the substrate (para [0367]; For example, a single array containing 10,000 arrayed elements, for example, can be sufficient to yield 10,000 results (e.g., quantitative results)").

As to claim 34, LaBaer further teaches that the set of nucleic acids comprises at least 5,000 nucleic acid sequences on the substrate (para [0367]).

As to claim 35, LaBaer further teaches that the set of nucleic acids comprises at least 10,000 nucleic acid sequences on the substrate (para [0367]).

Claims 2-10, 12-15, 23,30 lack an inventive step under PCT Article 33(3) as being obvious over US 2005/0260653 A1 (LABAER et al.) (hereinafter "LaBaer") in view of the publication titled " The developments of semisynthetic DNA.protein conjugates" By NIEMEYER et al. (hereinafter "Niemeyer").

As to claim 2, LaBaer teaches a substrate having a surface; two or more individual constructs associated on the surface of the substrate, wherein the individual constructs comprise: an oligonucleotide comprising a region encoding a peptide of interest, a region encoding an affinity tag and an untranslated region (para [0005]; " In one aspect, the invention features a method that includes: disposing, on a substrate, one or more nucleic acids that include a coding region and an anchoring agent, maintaining the substrate under conditions which enable the anchoring agent of each disposed nucleic acid to stably attached to the substrate"; para [0015]; " In one embodiment, the coding region encodes a polypeptide that includes a first amino acid sequence, e.g., an amino acid sequence of interest, and an affinity tag. The affinity tag binds to a binding agent"; para [0056]; "The nucleic acid can further include one or more of: a transcription promoter; a transcription regulatory sequence; a untranslated leader sequence; a sequence encoding a cleavage site; a recombination site; a 3' untranslated sequence") the peptide of interest and an affinity tag (para [0022]; " In one embodiment, the step of contacting the substrate with a translation effector includes disposing or flowing the translation effector onto the surface, for example, using a single dispensing action or multiple dispensing actions. In one embodiment, the substrate is also contacted with a transcription effector"); and a capture agent that selectively binds to the affinity tag (para [0046]; " In another aspect, the invention features a method that includes: contemporaneously providing (e.g., depositing)----------continued in next Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous Supplemental Box

(claim 2 continued): (i) a binding agent that can interact with a tag and (ii) a nucleic acid that can be stably attached to a substrate and that includes a sequence encoding a first amino acid sequence and the tag onto a substrate"; sheet 1 fig 1) wherein the oligonucleotide is associated with the substrate surface (para [0005]). LaBaer does not teach that the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Consequently it would have been obvious to one of ordinary skill in the art to combine an oligonucleotide comprising a region encoding a peptide of interest, a region encoding an affinity tag and an untranslated region, as taught by LaBaer, with the peptide of interest and an affinity tag, again as taught by LaBaer, with a capture agent that selectively binds to the affinity tag, again as taught by LaBaer, with the oligonucleotide is associated with the substrate surface, again as taught by LaBaer, with the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent, as taught by Niemeyer, because it would have enabled construction of a oligonucleotide-peptide microarray.

As to claim 3, LaBaer further teaches that the untranslated region comprises a transcriptional start site and a ribosomal binding site (para [0115]; " The nucleic acid can further include one or more of: a transcription promoter; a transcription regulatory sequence; a untranslated leader sequence; a transcriptional terminator; and an internal ribosome entry site").

As to claim 4, Niemeyer further teaches that the capture agent is associated with the oligonucleotide (pg 400 fig 6).

As to claim 5, LaBaer teaches that the oligonucleotide is associated with the substrate surface via a linker (para [0040]; " In another aspect, the invention features a method that includes: providing a substrate that includes a plurality of addresses, each addresses including a nucleic acid that includes a coding region and an anchoring agent that stably attaches the nucleic acid to the substrate").

As to claim 6, LaBaer further teaches that the capture agent is associated with the linker (para [0129]; " "The binding agent can be attached to the substrate. For example, the substrate can be derivatized and the binding agent covalent attached thereto").

As to claim 7, LaBaer further teaches that the substrate is a planar support (para [0008]; " The substrate can be planar, e.g., have a horizontal plane in which the addresses are located at different discrete locations. The surface of the substrate can be flat (e.g., a glass slide) ").

As to claim 8, LaBaer further teaches that the substrate is a bead (para [0088]; " In yet another embodiment, an insoluble substrate (e.g., a bead or particle), is disposed at each address of the plurality, and the binding agent is attached to the insoluble substrate").

As to claim 9, LaBaer further teaches that the oligonucleotide is double-stranded (para [0055]; "The nucleic acid can be a RNA, or a DNA (e.g., a single-stranded DNA, or a double stranded DNA").

As to claim 10, Niemeyer further teaches that the oligonucleotide further comprises a region used for introduction of the capture agent to the oligonucleotide (pg 400 fig 6; A microarray of capture oligonucleotides is used as the immobilization matrix. Note that owing to the specificity of Watson.Crick base pairing, many different compounds can be sites pecifically immobilized simultaneously in a single step").

As to claim 12, LaBaer teaches a method of constructing an array (abstract), comprising the steps of:
(a) providing a surface comprising two or more constructs, the constructs
comprising a single-stranded oligonucleotide region encoding a peptide of interest
and an affinity tag (para [0005], [0015]; [0055]-" (para [0055]; "The nucleic acid can be a RNA, or a DNA (e.g., a single-stranded DNA, or a double stranded DNA");
(d) subjecting the double-stranded oligonucleotide region to a transcription
and translation event to produce a peptide comprising the peptide of interest and
the affinity tag (para [0458]; [0022]) wherein the protein produced in step (d) is captured by the capture agent of the construct following translation, thereby forming individual constructs
comprising the peptide associated with a substrate encoding the peptide (sheet 1 fig 1; para [0015]). LaBaer does not teach that the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). In addition, LaBaer does not teach (b) converting the single-stranded oligonucleotide region into a double stranded oligonucleotide region.----------claim continued in next Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous Supplemental Box

(continuation of claim 12)-----However, an artisan of ordinary skill in the art would have readily appreciated that sequence specific regulators of eukaryotic gene expression (e.g. transcription binding, recognition and promoter sites), axiomatically, act through double stranded DNA targets only. Consequently, it would have been obvious that single-stranded oligonucleotides would have had to have been converted to a double stranded oligonucleotide before initiating transcription/translation. Furthermore, LaBaer does not teach (c); introducing an untranslated region comprising a ribosomal start site to the 5' end of the double-stranded oligonucleotide region, wherein the untranslated region is associated with a capture agent with the ability to form a binding pair with the affinity tag. However, LaBaer does teach modular construction of the oligonucleotide microarray involving hybridization, possible extension, and ligation of 2 separate oligonucleotides at each addressable position on the microarray (para [0445-0446]. An artisan of ordinary skill in the art would have readily appreciated that such universal elements as ribosomal binding sites and/or an untranslated region for attachment of a capture agent with the ability to form a binding pair with the affinity tag could have been engineered into the modular second oligonucleotide. Indeed, Niemeyer teaches association of an oligonucleotide attached to a capture agent through hybridization to the microarray attached oligonucleotide (pg 400 fig 6). Consequently, it would have been obvious to one of ordinary skill in the art to combine claim limitations (a), (b) and (d), as taught by LaBaer, with claim limitation (c), as taught by LaBaer in view of the observations of an artisan of ordinary skill in the art concerning introducing modular elements such as a ribosomal binding site into a microarray by way of a two oligonucleotide ligation at each addressable position of the microarray, with oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent, as taught by Niemeyer, because it would have enabled construction of a supramolecular array that would function as a protein biochip.

As to claim 13, LaBaer teaches a method of constructing an array (abstract), comprising the steps of:
(a) providing a substrate comprising a surface with two or more constructs associated on the surface , the constructs comprising a single-stranded oligonucleotide encoding a peptide of interest and an affinity tag (para [0005], [0015], [0055]);
(e) subjecting the double-stranded oligonucleotide to a transcription and translation event to produce a peptide from the double-stranded oligonucleotide; wherein the protein produced in step (e) is captured by the capture agent of the construct; and wherein the resulting array comprises discrete units comprising a nucleic acid associated with substrate and the peptide encoded by the nucleotide also associated with the substrate through a capture agent (sheet 1 fig 1; para [0015]). LaBaer does not specifically teach the peptide encoded by the nucleic acid is associated by the nucleic acid. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). In addition, LaBaer does not teach (d) converting the single-stranded oligonucleotide region into a double stranded oligonucleotide region. However, an artisan of ordinary skill in the art would have readily appreciated that sequence specific regulators of eukaryotic gene expression (e.g. transcription binding, recognition and promoter sites), axiomatically, act through double stranded DNA targets only. Consequently, it would have been obvious that single-stranded oligonucleotides would have had to have been converted to a double stranded oligonucleotide before initiating transcription/translation (i.e. claim limitation (e)). Furthermore, LaBaer does not teach (b) ligating a second, universal oligonucleotide to the oligonucleotides of the constructs, wherein the universal oligonucleotide comprises an untranslated region comprising a ribosomal binding site. However, LaBaer does teach modular construction of the oligonucleotide microarray involving hybridization, possible extension, and ligation of 2 separate oligonucleotides at each addressable position on the microarray (para [0445-0446]. An artisan of ordinary skill in the art would have readily appreciated that such universal elements as ribosomal binding sites and/or an untranslated region for attachment of a capture agent with the ability to form a binding pair with the affinity tag could have been engineered into the modular second oligonucleotide. Indeed, Niemeyer teaches association of an oligonucleotide attached to a capture agent through hybridization to the microarray attached oligonucleotide (pg 400 fig 6), thus fulfilling claim limitation (c). Consequently, it would have been obvious to one of ordinary skill in the art to combine claim limitations (a), (d) and (e), as taught by LaBaer, with claim limitation (b), as taught by LaBaer, in view of the observations of an artisan of ordinary skill in the art concerning introducing modular elements such as a ribosomal binding site into a two oligonucleotide ligation of a microarray, with claim limitation (c), as taught by Niemeyer, because it would have enabled construction of a supramolecular array that would function as a protein biochip.

As to claim 14, LaBaer teaches method of constructing an array (abstract), comprising the steps of:
(a) providing a surface comprising two or more constructs, the constructs comprising a single-stranded oligonucleotide region (para [0055]) having a sequence that is the sequence encoding a peptide of interest and an affinity tag (para [0005], [0015]); LaBaer does not teach the single stranded nucleotide is a reverse complement sequence encoding the peptide of interest. However, an artisan of ordinary skill in the art would have readily appreciated that a reverse complement sequence could have readily hybridized with a mRNA molecule and could have utilized it to hybridize with mRNA introduced to the microRNA. Furthermore, LaBaer does not teach (b) converting the single-stranded oligonucleotide region into a double stranded oligonucleotide region. However, an artisan of ordinary skill in the art would have readily appreciated that sequence specific regulators of eukaryotic gene expression (e.g. transcription binding, recognition and promoter sites), axiomatically, act through double stranded DNA targets only. Consequently, it would have been obvious that single-stranded oligonucleotides would have had to have been converted to a double stranded oligonucleotide before initiating transcription/translation (i.e. claim limitation (d)). LaBaer further teaches (d) subjecting the double-stranded oligonucleotide region to a transcription and translation event to produce a peptide comprising the peptide of interest and the affinity tag wherein the protein produced in step (d) is captured by the capture agent of the construct following translation, thereby forming individual constructs comprising the peptide associated with the substrate and an oligonucleotide encoding the peptide associated with the substrate. LaBaer does not specifically teach the peptide encoded by the nucleic acid is associated with the nucleic acid. ----------claim continued in next Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous Supplemental Box

(continuation of claim 14)----------However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1).
LaBaer does not teach (c); introducing an untranslated region comprising a ribosomal start site to the 5' end of the double-stranded oligonucleotide region, wherein the untranslated region is associated with a capture agent with the ability to form a binding pair with the affinity tag. However, LaBaer does teach modular construction of the oligonucleotide microarray involving hybridization, possible extension, and ligation of 2 separate oligonucleotides at each addressable position on the microarray (para [0445-0446]. An artisan of ordinary skill in the art would have readily appreciated that such universal elements as ribosomal binding sites and/or an untranslated region for attachment of a capture agent with the ability to form a binding pair with the affinity tag could have been engineered into the modular second oligonucleotide. Indeed, Niemeyer teaches association of an oligonucleotide attached to a capture agent through hybridization to the microarray attached oligonucleotide (pg 400 fig 6). Consequently, it would have been obvious to one of ordinary skill in the art to combine claim limitations (a), (b) and (d), as taught by LaBaer, in view of the observations of an artisan of ordinary skill, with claim limitation (c), as taught by LaBaer, in view of the observations of an artisan of ordinary skill in the art concerning introducing modular elements such as a ribosomal binding site into a microarray by way of a two oligonucleotide ligation step of the microarray, with attachment of a peptide of interest to an oligonucleotide encoding the peptide via a capture agent, as taught by Niemeyer, because it would have enabled construction of a supramolecular array that would function as a protein biochip.

As to claim 15, LaBaer teaches a method of constructing an array (abstract), comprising the steps of: (a) providing a surface comprising two or more constructs, the constructs
comprising a single-stranded oligonucleotide region (para [0055]) having a sequence that is the
sequence encoding a peptide of interest and an affinity tag (para [0005], [0015]); LaBaer does not teach the single stranded nucleotide is a reverse complement sequence encoding the peptide of interest. However, an artisan of ordinary skill in the art would have readily appreciated that a reverse complement sequence could have readily hybridized with a mRNA molecule and could have utilized it to hybridize with mRNA introduced to the microRNA. LaBaer further does not teach (d) converting the single-stranded oligonucleotide regions of the constructs into double-stranded oligonucleotide regions. However, an artisan of ordinary skill in the art would have readily appreciated that sequence specific regulators of eukaryotic gene expression (e.g. transcription binding, recognition and promoter sites), axiomatically, act through double stranded DNA targets only. Consequently, it would have been obvious that single-stranded oligonucleotides would have had to have been converted to a double stranded oligonucleotide before initiating transcription/translation (i.e. claim limitation (e)). LaBaer further teaches (e) subjecting the double-stranded oligonucleotide region to a transcription and translation event to produce a peptide comprising the peptide of interest and the affinity tag wherein the protein produced in step (e) is captured by the capture agent of the construct following translation, thereby forming individual constructs comprising the peptide associated with the substrate and an oligonucleotide encoding the peptide associated with the substrate. LaBaer does not specifically teach the peptide encoded by the nucleic acid is associated by the nucleic acid. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Furthermore, LaBaer does not teach (b) ligating a second, universal oligonucleotide to the oligonucleotides of the constructs, wherein the universal oligonucleotide comprises an untranslated region comprising a ribosomal binding site. However, LaBaer does teach modular construction of the oligonucleotide microarray involving hybridization, possible extension, and ligation of 2 separate oligonucleotides at each addressable position on the microarray (para [0445-0446]. An artisan of ordinary skill in the art would have readily appreciated that such universal elements as ribosomal binding sites and/or an untranslated region for attachment of a capture agent with the ability to form a binding pair with the affinity tag could have been engineered into the modular second oligonucleotide. Indeed, Niemeyer teaches association of an oligonucleotide attached to a capture agent through hybridization to the microarray attached oligonucleotide (pg 400 fig 6), thus fulfilling claim limitation (c). Consequently, it would have been obvious to one of ordinary skill in the art to combine claim limitations (a), (d) and (e), as taught by LaBaer, with claim limitation (b), as taught by LaBaer, in view of the observations of an artisan of ordinary skill in the art concerning introducing modular elements such as a ribosomal binding site into a two oligonucleotide ligation of a microarray, with claim limitation (c), as taught by Niemeyer, because it would have enabled construction of a supramolecular array that would function as a protein biochip.

As to claim 23 and 30, LaBaer teaches that the produced peptides are bound to the substrate (para [0015], sheet 1 fig 1). LaBaer does not teach that the produced peptides are attached to their respective nucleic acid substrates. However, Niemeyer teaches that the produced peptides are attached to their respective nucleic acid substrates (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Consequently it would have been obvious to one of ordinary skill in the art to combine peptides produced by in vitro transcription/translation of an array, as taught by LaBaer, with the produced peptides are attached to their respective nucleic acid substrates, as taught by Niemeyer, because it would have enabled construction of a protein array where the produced peptides are at discrete spatially addressable locations on the array.
----------continued in next Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
previous Supplemental Box

Claim 11 lacks an inventive step under PCT Article 33(3) as being obvious over LaBaer, in view of Niemeyer, in further view of the publication titled " High sensitivity multianalyte immunoassay using covalent DNA-labeled antibodies and polymerase chain reaction" by HENDERSON et al. (hereinafter "Henderson").

As to claim 11, Niemeyer teaches association of capture agent with substrate attached oligonucleotide by DNA annealing (pg 400 fig 6). Neither Niemeyer nor LaBaer teaches that the region is associated to the oligonucleotide via a linker molecule. However, Henderson teaches a region is associated to the oligonucleotide via a linker molecule (pg 523 fig 2; "Design of DNA-antibody reporter conjugates--chemical crosslinker). An artisan of ordinary skill in the art would have readily appreciated that a linker region was well known in the art for covalently linking DNA directly to a protein molecule such as an antibody (i.e. capture agent). Consequently, it would have been obvious to one of ordinary skill in the art to combine association of capture agent with substrate attached oligonucleotide, as taught by Niemeyer, with region of association is a linker, as taught by Henderson, because it would have enabled attaching the capture agent directly to the oligonucleotide.

Claims 16-21 lack an inventive step under PCT Article 33(3) as being obvious over LaBaer, in view of Niemeyer, in further view of the publication titled " Next-generation high-density self-assembling functional protein arrays" by RAMACHANDRAN et al. (hereinafter "Ramachandran").

As to claim 16, LaBaer teaches a method of identifying an agent that binds to a peptide of interest, comprising: providing an array (abstract) comprising:
a substrate having a surface (para [0005]);
two or more individual constructs associated on the surface of the substrate, wherein the individual constructs comprise:
(i) an oligonucleotide encoding a peptide of interest (para [0005], [0015]) and
(ii) the peptide of interest (para [0022]; wherein the oligonucleotide is associated with the substrate surface (para [0005]). LaBaer does not teach that the peptide is associated with the oligonucleotide. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Furthermore, LaBaer does not specifically teach exposing the array to an agent; and detecting the presence or absence of binding of the agent to the peptide of interest. However, Ramachandran teaches exposing the array to an agent; and detecting the presence or absence of binding of the agent to the peptide of interest (pg 537 left col para 1; " To confirm protein function on high-density arrays, we printed an array expressing 647 unique genes in duplicate, including 449 genes that we had not previously tested (Fig. 3a and Supplementary Table 3 online). We tested for binary interactions between several well characterized interacting pairs including Jun-Fos and p53-MDM2 (Fig. 3b). We co-expressed the query protein along with the arrayed proteins by adding the appropriate cDNA clone (without a GST tag) to the cell-free expression lysate. After protein expression and washing, we treated the arrays with protein-specific antibodies to detect the query protein, revealing the positions where it bound. Using Jun, Fos and MDM2 as queries, we detected selective binding to their appropriate interacting partners"; pg 538 fig 3B). An artisan of ordinary skill in the art would have readily appreciated that binding of a protein through protein-protein interaction was well known in the art at the time of the invention. Consequently, it would have been obvious to one of ordinary skill in the art to combine an oligonucleotide bound to a substrate encoding a protein of interest, as taught by LaBaer, with a peptide of interest associated with an array, also taught by LaBaer, with peptide is associated with the oligonucleotide, as taught by Niemeyer, with detecting the presence or absence of binding of an agent to the peptide of interest, as taught by Ramachandran, because it would have enabled a functional protein biochip that identifies an agent that binds to a peptide of interest.

As to claim 17, Ramachandran further teaches the agent is provided in a sample, and wherein presence of binding to the peptide of interest indicates the presence of the agent in a sample (pg 537 left col para 1; pg 538 fig 3B).

As to claim 18, Ramachandran further teaches that the agent is provided in a sample, and wherein absence of binding to the peptide of interest indicates an absence of the agent in a sample (pg 537 left col para 1; pg 538 fig 3B).
----------continued in next Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
previous Supplemental Box

As to claim 19, LaBaer teaches a method of identifying an agent that binds to a peptide of interest, comprising:
providing an array (abstract) comprising:
a substrate having a surface (para [0005]); two or more individual constructs associated on the surface of the substrate, wherein the individual constructs comprise:
(i) an oligonucleotide comprising a region encoding a peptide of interest, a region encoding an affinity tag, and an untranslated region (para [0005], [0015], [0056])
(ii) a peptide comprising the peptide of interest and an affinity tag (para [0022]); and
(iii) a capture agent that selectively binds to the affinity tag (para [0046]); wherein the oligonucleotide is associated with the substrate surface (para [0005]). LaBaer does not teach that the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Furthermore, LaBaer does not teach exposing the array to an agent; and detecting the presence or absence of binding of the agent to the peptide of interest. However, Ramachandran teaches exposing the array to an agent (pg 537 left col para 1); and detecting the presence or absence of binding of the agent to the peptide of interest (pg 537 left col para 1, pg 538 fig 3B). An artisan of ordinary skill in the art would have readily appreciated that binding of a protein through protein-protein interaction was well known in the art at the time of the invention. Consequently, it would have been obvious to one of ordinary skill in the art to combine an oligonucleotide bound to a substrate encoding a protein of interest, as taught by LaBaer, with a peptide of interest associated with an array, also taught by LaBaer, with capture agent that selectively binds to affinity tag, also as taught by LaBaer, with peptide is associated with the oligonucleotide, as taught by Niemeyer, with detecting the presence or absence of binding of an agent to the peptide of interest, as taught by Ramachandran, because it would have enabled a functional protein biochip that identifies an agent that binds to a peptide of interest.

As to claim 20, Ramachandran further teaches that the agent is provided in a sample (pg 537 left col para 1), and wherein the presence of binding to the peptide of interest indicates the presence of the agent in a sample (pg 538 fig 3B).

As to claim 21, Ramachandran the agent is provided in a sample (pg 537 left col para 1), and wherein absence of binding to the peptide of interest indicates an absence of the agent in a sample (pg 538 fig 3B).

Claims 1-35 have industrial applicability as defined in PCT Article 33(4) because the subject matter can be made or used by industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SARAH BRASHEARS
CONVERGENT LAW GROUP LLP
475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	07 JUN 2011
Applicant's or agent's file reference: PGNS007PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/US 11/31308	International filing date *(day/month/year)*: 05 April 2011 (05.04.2011)
Applicant: PROGNOSYS BIOSCIENCES, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PGNS007PCT	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 11/31308	International filing date *(day/month/year)* 05 April 2011 (05.04.2011)	(Earliest) Priority Date *(day/month/year)* 05 April 2010 (05.04.2010)
Applicant PROGNOSYS BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. 1

   ☒ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/31308

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2011.01)
USPC - 435/6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C12Q 1/68 (2011.01)
USPC - 435/6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
435/7.9,287.2,7.1,91.2,4

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST - DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=YES; OP=ADJ; Google Scholar
search terms: probe, analyt$, gene or marker, biomarker, oligonucle$, polymer, oligomer, polynucleo$, nucleotid$, nucleic, dna, rna, deoxyribonuc$, protein, affix$, attach$, immobil$, bound, tether$, teather$, support, surface, substrate, solid, multip$, many, differen$,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2006/0046313 A1 (ROTH et al.) 02 March 2006 (02.03.2006) para [0027]; [0031]-[0033]; [0036]; [0038]; [0042]; [0043]; [0047]; [0053]; [0055]; [0069]; [0073]; [0083]-[0085]; [0090]-[0092]; [0097]; [0098]; [0102]-[0105]; [0122]-[0124]; [0138]; [0140].	1-3, 6-37, 39-55, 57 ------ 4, 5, 38, 56
Y	US 6,344,316 B1 (LOCKHART et al.) 05 February 2002 (05.02.2002) abstract; col. 24, ln 8-61.	4, 5, 38, 56

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2011 (25.05.2011)	0 7 JUN 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

From the
INTERNATIONAL SEARCHING AUTHORITY

To: SARAH BRASHEARS
CONVERGENT LAW GROUP LLP
475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 JUN 2011
Applicant's or agent's file reference PGNS007PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 11/31308	05 April 2011 (05.04.2011)	05 April 2010 (05.04.2010)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68 (2011.01)
USPC - 435/6

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	25 May 2011 (25.05.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31308

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31308

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	4, 5, 38, 56	YES
	Claims	1-3, 6-37, 39-55, 57	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-57	NO
Industrial applicability (IA)	Claims	1-57	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-3, 6-37, 39-55 and 57 lack novelty under PCT Article 33(2) as being anticipated by US 2006/0046313 A1, Roth et al., (hereinafter Roth).

Regarding claim 1, Roth teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (para [0032] and [0140]), wherein the assay system performs the following steps:
providing a sample affixed to a support (para [0033] - 'The invention reverse phase protein assay includes forming one or more arrays of cell lysates obtained from one or more tissue samples from a patient. For example, individual cells of a cell population obtained from a patient tissue sample may be lysed and extracted 310 to form an array. If cell lysates are obtained from more than one tissue sample, two or more arrays may be formed, with an array containing the cell lysates from a particular tissue sample of the patient In an array of defined locations 320 on a substrate, a mixture of extracted cell proteins 330, 331, 332 is immobilized at (for example, spotted onto) individual defined locations,');
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 (para [0033] - 'Then the cell lysate spots at the defined locations are contacted with a mixture of COIN-labeled probes 330, 332 under conditions suitable to form analyte-COIN complexes 341, 342, 343 as the probes bind individual protein in the spots through both specific and degenerate binding.', and para [0097]);
allowing the encoded probes to interact with the biological targets (para [0033]);
separating encoded probes that interact with the biological targets from encoded probes that do not interact with the biological targets (para [0033] - 'After removal of unbound COIN-labeled probes from the array');
determining all or a portion of a sequence of the encoded probes (para [0104] and [0122]), and
associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample (para [0033] - 'the array 350 may be scanned 340 to detect SERS signals at the defined locations 320 so as to identify and compile data regarding the presence of the known analytes in the tissue sample.').

Regarding claim 27, Roth teaches an assay system to determine spatial patterns of abundance or activity or both of multiple nucleic acid targets at multiple sites in a sample (para [0032] and [0140]), wherein the assay system performs the following steps:
providing a sample affixed to a support (para [0033]);
delivering oligonucleotide probes for multiple nucleic acid targets to the multiple sites in the sample in a known spatial pattern (para [0033] and [0097]);
allowing the oligonucleotide probes to hybridize with the nucleic acid targets (para [0033] and [0102]-[0103]);
washing unhybridized encoded oligonucleotide probes from the sample (para [0033] and [0102]-[0103]);
delivering one or more encoding agents to locations of the multiple sites in the sample according to a known spatial pattern, wherein the combination of encoding agents delivered to each site is different (para [0086] and [0097] - encoding agents are 'Raman-active organic compounds');
coupling the encoding agents and the oligonucleotide probes to form encoded probes (para [0086]);
determining all or a portion of a sequence of the encoded probes using high throughput sequencing (para [0104] and [0122]), and
associating the abundance or activity or both of multiple biological targets to the locations of multiple sites in the sample (para [0033], [0104] and [0122]).

----------continued in next supplemental box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31308

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
citations and explanations from box V.2

Regarding claim 40, Roth teaches an assay system to determine spatial patterns of abundance or activity or both of multiple protein targets at multiple sites in a sample (para [0032] and [0140]), wherein the assay system performs the following steps:
providing a sample affixed to a support (para [0033]);
delivering encoded probes for the multiple protein targets to the multiple sites in the sample in a known spatial pattern, wherein 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 (para [0033], [0092] and [0097]);
allowing the encoded probes to interact with the protein targets (para [0033]);
separating encoded probes that interact with the protein targets from encoded probes that do not interact with the protein targets (para [0033]);
determining all or a portion of a sequence of the encoded probes by high throughput sequencing (para [0104] and [0122]), and
associating the abundance or activity or both of the multiple protein targets to the locations of the multiple sites in the sample (para [0033]).

Regarding claim 2, Roth teaches the biological targets are nucleic acids and the encoded probes are oligonucleotides (para [0102]-[0103]).

Regarding claim 3, Roth teaches there are two encoded probes for each of the multiple nucleic acid targets (para [0047] and [0091]).

Regarding claim 6, Roth teaches probe regions of the encoded probes comprise antibodies (para [0069]).

Regarding claim 7, Roth teaches the probe regions of the encoded probes are aptamers (para [0069]).

Regarding claim 8, Roth teaches the probe regions of the encoded probes are small molecules (para [0069]).

Regarding claims 9, 39 and 50, Roth teaches an amplification step between the separating step and the determining step (para [0105]).

Regarding claim 10, Roth teaches the determining step is performed by nucleic acid sequencing (para [0104] and [0122]).

Regarding claim 11, Roth teaches the sequencing is high-throughput digital nucleic acid sequencing (para [0039], [0122]-[0124]).

Regarding claims 12-19, 28-33, 41-46, Roth teaches the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000,000 (para [0097]-[0098] and [0138]).

Regarding claims 20-22, 34, 35, 47-49, Roth teaches the sequence of at least one million encoding probes are determined in parallel (para [0097]-[0098], [0104] and [0138]).

Regarding claim 23, Roth teaches the known spatial pattern is determined by histological features of the sample (para [0036] and [0038]).

Regarding claim 24, Roth teaches software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step and the associating step (para [0123]-[0124]).

Regarding claim 25, Roth teaches the probe regions of the encoded probes are proteins (para [0092]), and the separating step is accomplished by encoded probes that interact with the biological targets being captured by an affinity capture agent (para [0027] - 'contacting a biological sample 110 with a substrate 100 having a set of capture antibodies 120 that bind specifically to different proteins attached at defined locations on the substrate 100 to allow formation of antibody-protein complexes 130. The antibody-protein complexes are then contacted with a set of COIN-labeled probes 140 comprising a probe moiety 150 that binds specifically to a known protein analyte').

Regarding claim 26, Roth teaches the probe regions of the encoding probes are nucleic acids and the separating step is accomplished by a washing of the sample (para [0084]-[0085]).

Regarding claim 36, Roth teaches two oligonucleotide probes are delivered for each of the multiple nucleic acid targets (para [0083] - 'the term "oligonucleotide" is used herein to refer to a polynucleotide that is used as a primer or a probe. Generally, an oligonucleotide useful as a probe or primer that selectively hybridizes to a selected nucleotide sequence is at least 6 nucleotides to about 9 nucleotides in length.' --oligonucleotide probes are used as primers; later amplification would require the primers are in pairs).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous supplemental box

Regarding claim 37, Roth teaches the coupling step is performed by ligation (para [0083] - 'Polynucleotide probes used in the invention methods are useful for detecting and hybridizing under suitable conditions to complementary polynucleotides in a biological sample by pairing a known polynucleotide probe with a known Raman-active COIN comprising one or more Raman-active organic compounds, as described herein. A covalent phosphodiester bond generally ligates the nucleotides of a polynucleotide sequence. However, the covalent bond also may be any of numerous other bonds, including a thiodiester bond, a phosphorothioate bond, a peptide-like amide bond or any other bond known to those in the art as useful for linking nucleotides to produce synthetic polynucleotides').

Regarding claim 51, Roth teaches the protein targets are enzymes (para [0090]), and the probe regions of the encoded probes are substrates, putative substrates of both for the enzymes (para [0069] and [0090]).

Regarding claim 52, Roth teaches the probe regions of the encoded probes are affinity capture agents (para [0043]).

Regarding claim 53, Roth teaches the probe regions of the encoded probes are antibodies (para [0069]).

Regarding claim 54, Roth teaches the probe regions of the encoded probes are aptamers (para [0069]).

Regarding claim 55, Roth teaches separating encoded probes that interact with the protein targets from encoded probes that do not interact with the protein targets is accomplished by an affinity capture agent that distinguishes encoded probes that interact with the protein targets from encoded probes that do not interact with the protein targets (para [0027] and [0042]-[0043]).

Regarding claim 57, Roth teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (para [0032] and [0140]), wherein the assay system performs the following steps:
providing a sample affixed to a support (para [0033]);
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 and identifies the biological target (para [0033], [0092] and [0097]);
allowing the encoded probes to interact with the biological targets (para [0033]);
determining all or a portion of a sequence of the encoded probes (para [0104] and [0122]), and
associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample (para [0033]).

Claims 4, 5, 38 and 56 lack an inventive step under PCT Article 33(3) as being obvious over Roth in view of US 6,344,316 B1, Lockhart et al., (hereinafter Lockhart).

Regarding claim 4, Roth teaches the multiple biological targets are proteins (para [0069]), the probe regions of the encoding probes are proteins (para [0073]). Roth does not specifically teach the coding tags comprise oligonucleotides. However, Roth does teach the coding tags are unique and florescent for scanning based detection (para [0031] and [0055]). Lockhart teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (abstract), comprising encoded probes for the multiple biological targets (abstract), wherein the coding tags comprise oligonucleotides (abstract and col. 24, ln 8-30). It would have been obvious to one of ordinary skill in the art to have prepared 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 coding tags comprise oligonucleotides, in view of Roth teaching the coding tags are unique and florescent for scanning based detection (para [0031] and [0055]), and in light of Lockhart teaching unique and florescent coding tags comprising oligonucleotides (col. 24, ln 37-61), since a skilled artisan would have readily appreciated use of the labeling methods taught by Lockhart applied to the probes taught by Roth, since they can be detected in a microarray.

Regarding claim 5, Roth teaches the multiple biological targets comprise enzymes (para [0090]).

Regarding claim 38, Roth does not specifically teach the coupling step is performed by extension followed by ligation. Lockhart teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (abstract), comprising coupling the one or more encoding agents and one or more oligonucleotide probes to form encoded probes (abstract and col. 24, ln 8-30), wherein the coupling step is performed by extension followed by ligation (col. 24, ln 8-30). It would have been obvious to one of ordinary skill in the art to have prepared 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 coupling step is performed by extension followed by ligation, in view of Roth teaching the probe is coupled to the encoding agents by various methods including ligation (para [0083]), and in light of Lockhart teaching coupling of one or more encoding agents and one or more oligonucleotide probes to form encoded probes (col. 24, ln 8-30), wherein the coupling step is performed by extension followed by ligation (col. 24, ln 8-30), since a skilled artisan would have readily appreciated use of the coupling methods taught by Lockhart applied to the probes taught by Roth, since they are both polynucleotide based probes, and could therefore be coupled via extension.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31308

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous supplemental box

Regarding claim 56, Roth does not specifically teach the coding tags are oligonucleotides. However, Roth does teach the coding tags are unique and florescent for scanning based detection (para [0031] and [0055]). Lockhart teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (abstract), comprising encoded probes for the multiple biological targets (abstract), wherein the coding tags comprise oligonucleotides (abstract and col. 24, ln 8-30). It would have been obvious to one of ordinary skill in the art to have prepared 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 coding tags comprise oligonucleotides, in view of Roth teaching the coding tags are unique and florescent for scanning based detection (para [0031] and [0055]), and in light of Lockhart teaching unique and florescent coding tags comprising oligonucleotides (col. 24, ln 37-61), since a skilled artisan would have readily appreciated use of the labeling methods taught by Lockhart applied to the probes taught by Roth, since they can be detected in a microarray.

Claims 1-57 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in the industry.

SEARCHHISTORY

Application Number	PCT/US 11/31308
Search Conducted By	DEM
Search Approved By	BP

US/IPC Classifications Searched	IPC(8) - C12Q 1/68 (2011.01) USPC - 435/6
Date Conducted	05/23/11

Documentation Searched	IPC(8) - C12Q 1/68 (2011.01) USPC - 435/6,7.9,287.2,7.1,91.2,4
Search Terms Used	probe, analyt$, gene or marker, biomarker, oligonucle$, polymer, oligomer, polynucleo$, nucleotid$, nucleic, dna, rna, deoxyribonuc$, protein, affix$, attach$, immobil$, bound, tether$, teather$, support, surface, substrate, solid, multip$, many, differen$, array, plural$, multit$, thousan$, million$ or number or panel, spatia$, patter$ or order or order$ or locatio$ or activity or distribut$, cell or sample or tissue, addressable, multiplex, multiplex$,
Date Conducted	05/23/11

Documentation Searched	Pub WEST
Files Searched	PGPB, USPT, EPAB, JPAB
Date Conducted	05/23/11

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=YES; OP=ADJ			
L47	L46 and L45	6	L47	L47
L46	L44 and (spatia$ near4 (patter$ or order or order$ or locatio$ or activity or distribut$))	13	L46	L46
L45	L44 and (spatial or spatial$ or distribution or location).ab,ti,clm.	33	L45	L45
L44	L43 and ((multip$ or many or differen$ or array or plural$ or multit$ or thousan$ or million$ or number or panel)	148	L44	L44

SEARCHHISTORY

	near4 (probe or analyt$ or gene or marker or biomarker or oligonucle$ or polymer or oligomer or polynucleo$ or nucleotid$ or nucleic or dna or rna or deoxyribonuc$ or protein or target)).ab,ti,clm.			
L43	L42 and (protein or peptide or oligopep$ or polypep$)	251	L43	L43
L42	L41 and (oligonuc$ or polynucleo$ or nucleotid$ or nucleic or dna or rna or deoxyribonuc$)	289	L42	L42
L41	L40 and probe.ab,ti,clm.	340	L41	L41
L40	@pd<20100405 and (sample near3 (affix$ or attach$ or immobil$ or bound or tether$ or teather$) near6 (support or surface or substrate or solid)).ab,ti,clm.	1677	L40	L40
L39	L38 and ((cell or sample or tissue) near7 (location or site or spatial$)).ab,ti,clm.	5	L39	L39
L38	L9 and (sample near3 (affix$ or attach$ or immobil$ or bound or tether$ or teather$) near6 (support or surface or substrate or solid)).ab,ti,clm.	27	L38	L38
L37	L9 and (sample near5 (affix$ or attach$ or immobil$ or bound or tether$ or teather$) near3 (support or surface or substrate or solid))	259	L37	L37
L36	L14 and ((cell or sample or tissue) near7 (location or site or spatial$)).ab,ti,clm.	7	L36	L36
L35	L34 and (probe near7 (location or site or spatial$))	8	L35	L35
L34	L33 and (amplif$ or pcr)	12	L34	L34
L33	L29 and ((determin$ or detec$ or measur$ or assay or assay$) near6 (paral$ or simultan$))	12	L33	L33
L32	L30 and ((determin$ or detec$ or measur$ or assay or assay$) near6 (paral$ or simultan$))	5	L32	L32
L31	L25 and ((determin$ or detec$ or measur$ or assay or assay$) near6 (paral$ or simultan$))	84	L31	L31
L30	L24 and ((determin$ or detec$ or measur$ or assay or assay$) near6 (paral$ or simultan$)).ab,ti,clm.	5	L30	L30
L29	L24 and (protein or peptide or oligopep$ or polypep$).ab,ti,clm.	14	L29	L29
L28	L26 and L10	2	L28	L28
L27	L26 and L11	0	L27	L27
L26	L25 and L7	90	L26	L26
L25	@pd<20100405 and (mark near2 chee).in.	185	L25	L25
L24	L23 or L22	19	L24	L24
L23	L21 and ((determin$ or identif$) near3 sequence)	16	L23	L23
L22	L21 and (sequencing or sequenced)	17	L22	L22
L21	L16 or L19	21	L21	L21
L20	L19 and (sequencing or sequenced)	13	L20	L20
L19	L14 and (spatial or spatial$ or distribution or location).ab,ti,clm.	15	L19	L19

SEARCHHISTORY

L18	L15 and (spatial or spatial$ or distribution or location).ab,ti,clm.	4	L18	L18
L17	L16 and (spatial or spatial$ or distribution or location).ab,ti,clm.	4	L17	L17
L16	L14 and (spatia$ near4 (patter$ or order or order$ or locatio$ or activity or distribut$))	10	L16	L16
L15	L14 and (spatia$ near4 (patter$ or order or order$ or locatio$ or activity))	9	L15	L15
L14	L13 and (oligonuc$ or polynucleo$ or nucleotid$ or nucleic or dna or rna or deoxyribonuc$).ab,ti,clm.	90	L14	L14
L13	L12 and (oligonuc$ or polynucleo$ or nucleotid$ or nucleic or dna or rna or deoxyribonuc$)	91	L13	L13
L12	L11 and ((wash or wash$ or rinse or rins$ or separat$) near7 (associat$ or bound or unboun$ or free))	91	L12	L12
L11	L10 and probe.ab,ti,clm.	122	L11	L11
L10	L9 and (sample near5 (affix$ or attach$ or immobil$ or bound or tether$ or teather$) near6 (support or surface or substrate or solid))	284	L10	L10
L9	L8 and (million or "1,000,000")	1380	L9	L9
L8	L7 and ((probe or analyt$ or gene or marker or biomarker or oligonucle$ or polymer or oligomer or polynucleo$ or nucleotid$ or nucleic or dna or rna or deoxyribonuc$ or protein) near5 (affix$ or attach$ or immobil$ or bound or tether$ or teather$) near6 (support or surface or substrate or solid))	4229	L8	L8
L7	L6 or L5	8067	L7	L7
L6	L3 and ((multip$ or many or differen$ or array or plural$ or multit$ or thousan$ or million$ or number or panel) near4 (probe or analyt$ or gene or marker or biomarker or oligonucle$ or polymer or oligomer or polynucleo$ or nucleotid$ or nucleic or dna or rna or deoxyribonuc$ or protein or target)).ab,ti.	7327	L6	L6
L5	L3 and (multiplex or multiplex$).ab,ti,clm.	1398	L5	L5
L4	L3 and (multiplex or multiplex$)	10159	L4	L4
L3	L1 and @pd<20100405	77284	L3	L3
L2	L1 and @pd<20100405	77284	L2	L2
L1	(C12Q1/68.ipc. or (435/6,7.9,287.2,7.1,91.2,4).ccls.)	85528	L1	L1

DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ

L7	L5 and ((tag or tagged or tagging or label or label$) near9 (floro$ or flour$ or flores$))	1	L7	L7
L6	L5 and ((tag or tagged or tagging or label or label$) near9 (floro$ or flour$))	1	L6	L6
L5	L4 and (ligat$ near12 probe)	43	L5	L5
L4	L3 and ligat$	95	L4	L4

SEARCHHISTORY

L3 @pd<20100405 and (mark near2 chee).in. 185 L3 L3

Documentation Searched	Google
Files Searched	Google Scholar
Date Conducted	05/23/11

Results 1 - 10 of about 11,900. (0.14 sec) (multiplex OR multiplexed) nucleotides proteins (captu immobilized) t

Results 1 - 10 of about 4,720. (0.23 sec) (multiplex OR multiplexed) nucleotides proteins (captu immobilized) tissue (spatial OR spa

Results 1 - 10 of about 3,280. (0.17 sec) (multiplex OR multiplexed) nucleotides proteins (captu immobilized) tissue (spatial OR spatially) addres

Results 1 - 3 of 3. (0.09 sec) (multiplex OR multiplexed) nucleotides proteins "immobilized ti

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SARAH BRASHEARS
CONVERGENT LAW GROUP LLP
475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	23 MAY 2011
Applicant's or agent's file reference: PGNS008PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/US 11/31163	International filing date *(day/month/year)*: 05 April 2011 (05.04.2011)
Applicant: PROGNOSYS BIOSCIENCES, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300
Facsimile No. 571-273-3201	Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PGNS008PCT	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 11/31163	International filing date *(day/month/year)* 05 April 2011 (05.04.2011)	(Earliest) Priority Date *(day/month/year)* 05 April 2010 (05.04.2010)
Applicant PROGNOSYS BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 9 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. 1

   ☒ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/31163

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2011.01)
USPC - 435/6, 287.2, 7.1, 91.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 435/6, 287.2, 7.1, 91.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - C12Q 1/68; C12M 3/00 (2011.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,EPAB,JPAB) and Google (non-patent literature): high-throughput, binding event, co-localized, affinity, COLA, array, microarray, bead, sequence, digital, computer, electronic, software, DNA, RNA, nucleotide, nucleic acid, aptamer, identify, ascertain, determine, count, measure

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0134669 A1 (Casasanta) 22 June 2006 (22.06.2006). Para [0006], [0012]-[0014].	1-37
Y	US 2003/0224419 A1 (Corcoran et al.) 4 December 2003 (04.12.2003). Fig 5; Para [0002], [0021], [0022], [0082], [0083], [0096].	1-37
Y	US 7,378,242 B2 (Hurt) 27 May 2008 (27.05.2008). Col 3, ln 64-col 4, ln 16; col 6, ln 55-60.	13-15, 30-37
A, P	US 2010/0184614 A1 (Ye et al.) 22 July 2010 (22.07.2010), entire document.	1-37
A	US 2009/0291854 A1 (Wiesinger-Mayr et al.) 26 November 2009 (26.11.2009). Para [0035].	1-37

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2011 (13.05.2011)	23 MAY 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: SARAH BRASHEARS
CONVERGENT LAW GROUP LLP
475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	23 MAY 2011
Applicant's or agent's file reference PGNS008PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 11/31163	05 April 2011 (05.04.2011)	05 April 2010 (05.04.2010)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68 (2011.01)
USPC - 435/6, 287.2, 7.1, 91.2

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	16 May 2011 (16.05.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31163

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31163

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-37	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-37	NO
Industrial applicability (IA)	Claims	1-37	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-12 and 16-29 lack an inventive step under PCT Article 33(3) as being obvious over US 2006/0134669 A1 (Casasanta), in view of US 2003/0224419 A1 to Corcoran et al. (hereinafter "Corcoran").

As to claim 1, Casasanta teaches a method for identifying binding agents that form a binding pair, comprising:
a) providing a first set of binding constructs immobilized on a support surface, wherein each binding construct of the first set of binding constructs comprises a first binding agent and a first nucleic acid tag unique to the first binding agent (para [0014]...first component of the binding pair is immobilized on a spot of the microarray and the second component is bound to a protein...binding pairs can include...complementary strands of DNA or RNA);
b) providing a second set of binding constructs in solution, wherein each binding construct of the second set of binding constructs comprises a second binding agent and a second nucleic acid tag unique to the second binding agent, and wherein either or both of the first and second sets of binding constructs comprises at least ten different binding agents (para [0014]...second component of the binding pair is introduced to the microarray by...solution flooding);
c) combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs, thereby co-locating the first nucleic acid tags and the second nucleic acid tags (para [0014]...complementary strands of DNA or RNA are bound together, therefore are co-located);
d) creating binding event identifiers from the co-located first and second nucleic acid tags (para [0012]...spectral shifts can be measured for respective molecular binding events).

Casasanta does not specify what Corcoran does in an alternative ligation-based sequencing scheme (para [0022]), namely:
e) determining a sequence of each binding event identifier, wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair (para [0002]...massively parallel signature sequencing).

Neither Casasanta nor Corcoran specify at least ten different binding agents. Casasanta does teach testing a variety of binding pair types (para [0014]...antigen/antibody, peptide/peptide, complementary DNA/RNA), discriminating between different spots (para [0018]) and testing up to 1000 spots (para [0013]). It would have been obvious to one skilled in the art to use at least ten different binding agents, for greater economy of testing scale. Further, it would have been obvious to one skilled in the art to combine the binding pair sequence of Corcoran with the method of Casasanta to enable more specific detection of binding events between a variety of biological molecules.

As to claim 2, Corcoran further teaches wherein the sequence of the binding event identifier is determined by digital readout 36, 38 (Fig 3...display controller, display device).

As to claim 3, Corcoran further teaches wherein the sequence of the binding event identifier is determined by high throughput digital sequencing (para [0022]...massively parallel signature sequencing...identify simultaneously signatures of very large numbers of DNAs attached to microbeads disposed in closely packed arrays).

As to claims 4-7, Casasanta and Corcoran make obvious the method of claim 1. Neither specifies wherein either or both of the first and second sets of binding constructs comprises at least twenty-five, one hundred, one thousand or at least five thousand different binding agents, respectively. Casasanta teaches a 36x28 microarray having 1008 spots (para [0013]) and that the binding pairs may comprise complementary strands of DNA or RNA (para [0014]). Corcoran teaches each binding pair has a unique signature (para [0002]...massively parallel signature sequencing; [0021]...element-to-element differences within microarrays; [0022]...ligation-based sequencing scheme). It would have been obvious to one skilled in the art to use the Corcoran digital sequencing method of an array of any number of spots, to uniquely identify the sequences that are bound.

As to claims 8, Corcoran further teaches wherein the sequences of the binding event identifiers are determined in parallel (para [0002]...massively parallel signature sequencing)

As to claims 9-10, Casasanta and Corcoran make obvious the method of claim 8. Casasanta teaches microarrays having 1008 spots (para [0013]). Corcoran teaches identifying in parallel (para [0002]) sequences of binding pairs on a microarray (para [0002]; [0083]...microbead array display). Neither specifies the sequence of 100,000 binding events determined in parallel. However, it would have been obvious to one skilled in the art that the technique of Corcoran could be applied to microarrays of any dimension.

Please continue to the supplemental page

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31163

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Citations and Explanations, Box V(2):

As to claim 11, Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches wherein the binding event identifier is created by coupling the first and second nucleic acid tags (Fig 5...note the sticky ends and the two ligation steps).

As to claim 12, Casasanta and Corcoran make obvious the method of claim 10. Corcoran further teaches wherein the coupling of the first and second tags is accomplished by ligation (Fig 5...note the sticky ends and the two ligation steps).

As to claim 16, Casasanta and Corcoran make obvious the method of claim 1. Casasanta further teaches wherein at least one of the first and second binding agents is a peptide (para [0006]...peptide-peptide pair).

As to claim 17, Casasanta and Corcoran make obvious the method of claim 16. Casasanta further teaches wherein the first and second binding agents are peptides (para [0006]...peptide-peptide pair).

As to claim 18, Casasanta and Corcoran make obvious the method of claim 16. Casasanta further teaches wherein the second binding agent is an antibody (para [0006]...hapten-antibody pair, antigen-antibody pair).

As to claim 19, Casasanta and Corcoran make obvious the method of claim 16, wherein the second binding agent is a small molecule (para [0006]...peptides can be small molecules; avidin and biotin are small molecules).

As to claim 20, Casasanta and Corcoran make obvious the method of claim 1. Casasanta further teaches wherein the first or second binding agent is an aptamer (para [0014]...biotin, antigen, antibody, oligonucleotides are all aptamers).

As to claim 21, Casasanta and Corcoran make obvious the method of claim 20. Casasanta further teaches wherein the first binding agent is a peptide and the second binding agent is an aptamer (para [0014]...first component immobilized on a spot in the microarray...second component introduced by solution flooding...combinations can include antigen/antibody, peptide/peptide, or complementary strands of DNA or RNA...all of these potential components of the binding pair can function as aptamers).

As to claim 22, Casasanta and Corcoran make obvious the method of claim 1. Casasanta further teaches wherein the support is a microarray 8 (para [0012]).

As to claim 23, Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches wherein the support is a bead (Fig 5...see 'image microbeads').

As to claim 24, Casasanta and Corcoran make obvious the method of claim 1. Casasanta further teaches the step of adding a third binding agent in the combining step (para [0014]...third chemical component can bind the complex of the first component and the second component).

As to claim 25, Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches the step of identifying binding agents that bind promiscuously (para [0096]...optical measurements were adjusted for system background noise, which can result from nonspecific binding of probes...or incomplete ligation).

As to claim 26, Casasanta and Corcoran make obvious the method of claim 25. Corcoran further teaches wherein data from promiscuous binding agents is subtracted from binder identifier results of the determining step (para [0096]...optical measurements were adjusted for system background noise, which can result from nonspecific binding of probes...or incomplete ligation).

As to claim 27, Casasanta and Corcoran make obvious the method of claim 25. Corcoran further teaches wherein a quantitative metric can be derived for the extent of promiscuity of promiscuous binding agents (para [0096]...computing the background noise for each signal set...and subtracting that computed value from each of the four fluorescence values...).

As to claim 28. Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches wherein false positives are identified within the binding event identifiers and data from the false positives subtracted from binder identifier results of the determining step (para [0096]...computing the background noise for each signal set...and subtracting that computed value from each of the four fluorescence values...).

As to claim 29, Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches the step of determining the number of each binding event identifier sequenced (para [0021]...counting of tags or signatures of DNA fragments).

Claims 13-15 and 30-37 lack an inventive step under PCT Article 33(3) as being obvious over Casasanta, in view of Corcoran and further in view of US 7,378,242 B2 (Hurt).

As to claim 13, Casasanta and Corcoran make obvious the method of claim 10. Neither specifies wherein the coupling of the first and second tags is accomplished by primer extension. Hurt teaches coupling strands of DNA by primer extension (col 3, ln 64-col 4, ln 16). It would have been obvious to one skilled in the art to couple the first and second tags by primer extension, as taught by Hurt, with the method of Casasanta and Corcoran, to more precisely control the nucleotide sequence.

Please continue

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31163

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Citations and Explanations, Box V(2):

As to claim 14, Casasanta and Corcoran make obvious the method of claim 1. Neither teaches wherein one or both of the first and second binding constructs comprise a primer sequence. Hurt teaches binding two pieces of DNA by primer extension (col 3, ln 64-col 4, ln 16). It would have been obvious to one skilled in the art to couple the first and second tags by primer extension, as taught by Hurt, with the method of Casasanta and Corcoran, to more precisely control the nucleotide sequence.

As to claim 15, Casasanta, Corcoran and Hurt make obvious the method of claim 13. Hurt further teaches the step of amplifying the binding event identifier after the creating step and before the determining step (col 6, ln 55-60...multiple temperature cycles can be used to amplify the extension product...different temperatures can be used for the three steps: association of the primer to the template, extension, and separation of the LPE product from the template).

As to claim 30, Casasanta teaches a method for identifying binding agents that form a binding pair, comprising:

a) providing a first set of binding constructs immobilized on a support surface, wherein each binding construct of the first set of binding constructs comprises a first binding agent, and a first nucleic acid tag unique to the first binding agent (para [0014]...first component of the binding pair is immobilized on a spot of the microarray and the second component is bound to a protein...binding pairs can include...complementary strands of DNA or RNA);
b) providing a second set of binding constructs in solution, wherein each binding construct of the second set of binding constructs comprises a second binding agent, and a second nucleic acid tag unique to the second binding agent, and wherein either or both of the first and second sets of binding constructs comprises at least ten different binding agents (para [0014]...second component of the binding pair is introduced to the microarray by...solution flooding);
c) combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs, thereby co-locating the first nucleic acid tags and the second nucleic acid tags (para [0014]...complementary strands of DNA or RNA are bound together, therefore are co-located);
d) creating binding event identifiers from the co-located first and second nucleic acid tags (para [0012]...spectral shifts can be measured for respective molecular binding events).

Casasanta does not specify:
wherein the first set of binding constructs also comprises a first primer region,
wherein the second set of binding constructs comprises a second primer region, or
e) determining a sequence of at least one thousand binding event identifiers, wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair; and
f) determining the frequency of each binding event identifier sequenced.

Casasanta teaches a 36x28 microarray having 1008 spots (para [0013]) and that the binding pairs may comprise complementary strands of DNA or RNA (para [0014]). Corcoran teaches each binding pair has a unique signature (para [0002]...massively parallel signature sequencing; [0021]...element-to-element differences within microarrays; [0022]...ligation-based sequencing scheme). It would have been obvious to one skilled in the art to use the Corcoran digital sequencing method of an array of any number of spots, to uniquely identify the sequences that are bound. Corcoran further teaches the step of determining the number of each binding event identifier sequenced (para [0021]...counting of tags or signatures of DNA fragments). It would have been obvious to one skilled in the art to determine the frequency of each binding event identifier sequences, to enable analysis of broader trends in binding events.

Hurt teaches coupling strands of DNA by primer extension (col 3, ln 64-col 4, ln 16). It would have been obvious to one skilled in the art to couple the first and second tags by primer extension, as taught by Hurt, with the method of Casasanta and Corcoran, to more precisely control the nucleotide sequence.

As to claim 31, Casasanta, Corcoran and Hurt make obvious the method of claim 30. Corcoran further teaches wherein the sequences of the binding event identifiers are determined in parallel (para [0002]...massively parallel signature sequencing).

As to claims 32-33, Casasanta, Corcoran, and Hurt make obvious the method of claim 31. None specifies wherein the sequence of at least 1,000 or 100,000 binding event identifiers, respectively, are determined in parallel. Casasanta teaches a 36x28 microarray having 1008 spots (para [0013]) and that the binding pairs may comprise complementary strands of DNA or RNA (para [0014]). Corcoran teaches determining the sequences of the binding event identifiers in parallel (para [0002]...massively parallel signature sequencing; [0021]...element-to-element differences within microarrays; [0022]...ligation-based sequencing scheme). It would have been obvious to one skilled in the art to use the Corcoran digital sequencing method of an array of any number of spots, to uniquely identify the sequences that are bound.

Please continue

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31163

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Citations and Explanations, Box V(2):

As to claim 34, Casasanta teaches a method for characterizing the specificity of binding between binding agents that form a binding pair, comprising:
a) providing a first set of binding constructs immobilized on a support surface, wherein each binding construct of the first set of binding constructs comprises a first binding agent, and a first nucleic acid tag unique to the first binding agent (para [0014]...first component of the binding pair is immobilized on a spot of the microarray and the second component is bound to a protein...binding pairs can include...complementary strands of DNA or RNA);
b) providing a second set of binding constructs in solution, wherein each binding construct of the second set of binding constructs comprises a second binding agent, and a second nucleic acid tag unique to the second binding agent, and wherein either or both of the first and second sets of binding constructs comprises at least ten different binding agents (para [0014]...second component of the binding pair is introduced to the microarray by...solution flooding);
c) combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs, thereby co-locating the first nucleic acid tags and the second nucleic acid tags (para [0014]...complementary strands of DNA or RNA are bound together, therefore are co-located);
d) creating binding event identifiers from the co-located first and second nucleic acid tags (para [0012]...spectral shifts can be measured for respective molecular binding events).

Casasanta does not specify what Corcoran does in an alternative ligation-based sequencing scheme (para [0022]), namely:
e) determining a sequence of each binding event identifier, wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair (para [0002]...massively parallel signature sequencing). It would have been obvious to one skilled in the art to determine the frequency of each binding event identifier sequences, to enable analysis of broader trends in binding events.

Neither Casasanta nor Corcoran specifies:
wherein the first set of binding constructs also comprises a first primer region,
wherein the second set of binding constructs comprises a second primer region. Hurt teaches coupling strands of DNA by primer extension (col 3, ln 64-col 4, ln 16). It would have been obvious to one skilled in the art to couple the first and second tags by primer extension, as taught by Hurt, with the method of Casasanta and Corcoran, to more precisely control and track the nucleotide sequence.

As to claims 35-36, Casasanta, Corcoran and Hurt make obvious the method of claim 34, but do not specify wherein the sequence of at least 1,000 or 100,000 binding event identifiers, respectively, are determined in parallel. Casasanta teaches a 36x28 microarray having 1008 spots (para [0013]) and that the binding pairs may comprise complementary strands of DNA or RNA (para [0014]). Corcoran teaches determining the sequences of the binding event identifiers in parallel (para [0002]...massively parallel signature sequencing; [0021]...element-to-element differences within microarrays; [0022]...ligation-based sequencing scheme). It would have been obvious to one skilled in the art to use the Corcoran digital sequencing method of an array of any number of spots, to uniquely identify the sequences that are bound.

As to claim 37, Casasanta, Corcoran and Hurt make obvious the method of claim 34. Hurt further teaches the step of amplifying the binding event identifier after the creating step and before the determining step (col 6, ln 55-60...multiple temperature cycles can be used to amplify the extension product...different temperatures can be used for the three steps: association of the primer to the template, extension, and separation of the LPE product from the template).

Claims 1-37 have industrial applicability as defined by PCT Article 33(4) because the subject can be made or used in industry.

SEARCH HISTORY

Application Number	PCT/US 11/31163
Search Conducted By	LAW
Search Approved By	BP

US/IPC Classifications Searched	USPC - 435/6, 287.2, 7.1, 91.2 IPC(8) - C12Q 1/68; C12M 3/00 (2011.01)
Date Conducted	05/13/11

Documentation Searched	USPC - 435/6, 287.2, 7.1, 91.2 IPC(8) - C12Q 1/68; C12M 3/00 (2011.01)
Search Terms Used	high-throughput, binding event, co-localized, affinity, COLA, array, microarray, bead, sequence, digital, computer, electronic, software, DNA, RNA, nucleotide, nucleic acid, aptamer, identify, ascertain, determine, count, measure
Date Conducted	05/13/11

Electronic Database Searched	PubWEST
Files Searched	PGPB,USPT,EPAB,JPAB
Date Conducted	05/13/11
Search Logic:	

DATE: Friday, May 13, 2011 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid

DB=PGPB,USPT,EPAB,JPAB; PLUR=NO; OP=ADJ

SEARCH HISTORY

L17	L15 and sequenc$	5	L17	L17
L16	(l11 or l12) and sequenc$	33	L16	L16
L15	(l11 or l12) and digital$	6	L15	L15
L14	L13 and digital$	0	L14	L14
L13	L10 and microbead$	0	L13	L13
L12	L10 and bead$	28	L12	L12
L11	L10 and microarray$	12	L11	L11
L10	L9 and "binding event$".ab.	53	L10	L10
L9	435/6,287.2,7.1,91.2.ccls. or c12q1/68.ipc. or c12m3/00.ipc.	79444	L9	L9
L8	L7 and (digital with sequenc$)	1	L8	L8
L7	"binding event$".ab.	148	L7	L7
L6	L5 and microarray$	259	L6	L6
L5	l1 and (identif$ or measur$ or count$).ab.	605	L5	L5
L4	COLA assay	0	L4	L4
L3	co-localized affinity	0	L3	L3
L2	L1 and "co-localized affinity"	0	L2	L2
L1	"high throughput" and "binding event$"	2199	L1	L1

END OF SEARCH HISTORY

DATE: Friday, May 13, 2011 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,EPAB,JPAB; PLUR=NO; OP=ADJ			
L22	L20 and (bind$ or hybridi$).ab.	7	L22	L22
L21	L20 and "binding event$"	12	L21	L21
L20	(microarray$ with (digital$ or computer$ or electronic$ or software) with (identif$ or ascertain$ or determin$) with (dna or rna or nucleotide$ or "nucleic acid$") with sequenc$)	683	L20	L20
L19	(microarray$ same (digital$ or computer$ or electronic$ or software) with (identif$ or ascertain$ or determin$) with (dna or rna or nucleotide$ or "nucleic acid$") with sequenc$)	749	L19	L19
L18	L17 and microarray$	5092	L18	L18
L17	((digital$ or computer$ or electronic$ or software) with (identif$ or ascertain$ or determin$) with (dna or rna or	15397	L17	L17

SEARCH HISTORY

	nucleotide$ or "nucleic acid$") with sequenc$)			
L16	microarray same "binding event$"	36	L16	L16
L15	microarray same "binding event"	36	L15	L15
L14	L13 and ((digital$ or computer$ or electronic$ or software) with (identif$ or ascertain$ or determin$) with (dna or rna or nucleotide$ or "nucleic acid$") with sequenc$)	7	L14	L14
L13	((microarray$ or bead$) same "Binding event$")	303	L13	L13
L12	L11 and ((digital$ or computer$ or electronic$ or software) with (identif$ or ascertain$ or determin$) with (dna or rna or nucleotide$ or "nucleic acid$") with sequenc$)	0	L12	L12
L11	((microarray$ or bead$) and "Binding event$").ab.	8	L11	L11
L10	L8 and ((digital$ or computer$ or electronic$ or software) with (identif$ or ascertain$ or determin$) with (dna or rna or nucleotide$ or "nucleic acid$") with sequenc$)	0	L10	L10
L9	L8 and ((identif$ or ascertain$ or determin$) with (dna or rna or nucleotide$ or "nucleic acid$") with sequenc$)	3	L9	L9
L8	L7 and microarray$	12	L8	L8
L7	L1 and "Binding event$".ab.	53	L7	L7
L6	l4 and microarray$.ab.	2	L6	L6
L5	L4 and microarray$	112	L5	L5
L4	L2 and ((digital$ or electronic$ or computer$ or software) with (identif$ or ascertain$ or determin$) with (dna or rna or nucleotide$ or "nucleic acid$") with sequenc$)	334	L4	L4
L3	L2 and ((identif$ or ascertain$ or determin$) with (dna or rna or nucleotide$ or "nucleic acid$") with sequenc$)	1278	L3	L3
L2	L1 and "binding event$"	2158	L2	L2
L1	435/6,287.2,7.1,91.2.ccls. or c12q1/68.ipc. or c12m3/00.ipc.	79444	L1	L1

END OF SEARCH HISTORY

Electronic Database Searched	Google
Files Searched	non-patent literature
Date Conducted	05/13/11
Search Logic:	
aptamer - about 197,000 results co-localization affinity assay - about 2,590,000 results co-localization affinity assay microarray - about 82,100 results	

SEARCH HISTORY

co-localization affinity assay microarray DNA sequence software - about 76,900 results
co-localization affinity assay microarray DNA sequence (digital OR software) - about 51,800 results

Electronic Acknowledgement Receipt

EFS ID:	11514468
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	57580
Filer:	Sarah J. Brashears
Filer Authorized By:	
Attorney Docket Number:	PGNS007US
Receipt Date:	30-NOV-2011
Filing Date:	05-APR-2011
Time Stamp:	17:22:48
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)	PGNS007US_IDS.pdf	175163 c555a32e148b7814af85abb428fc8b54bf1cb7c7	no	5

Warnings:	
Information:	

This is not an USPTO supplied IDS fillable form					
2	Foreign Reference	zz_WO2007_073171.pdf	3156352 0eec482751c116fbdb8599ee399dd78d06ec9f7a	no	61
Warnings:					
Information:					
3	Non Patent Literature	Niemeyer_2002c.pdf	6486085 ab7e248f5942f26ea4f1997003489cfa3e8a20c8	no	7
Warnings:					
Information:					
4	Non Patent Literature	Chandra_2010.pdf	288987 65755a3a72bc02372a5cb62b18404aa37a5afe42	no	14
Warnings:					
Information:					
5	Non Patent Literature	Ramachandran_2008.pdf	2196929 213de1d3916ec6c1224cab6fc2defa62156c5a4d	no	4
Warnings:					
Information:					
6	Non Patent Literature	zz_2010_59327_Search_Report.pdf	865795 6b33b2cb6f30c90fde8a90be3ff257cc24762f25	no	13
Warnings:					
Information:					
7	Non Patent Literature	zz_2011_31308_Search_Report.pdf	743417 4f6db7d726742975de6bdcbdb283a3eccda0483a	no	13
Warnings:					
Information:					
8	Non Patent Literature	zz_2011_31163_Search_Report.pdf	909461 b094035e044289dfc3a25c939fcdaa96e418b23d	no	13
Warnings:					
Information:					
9	Non Patent Literature	Fredriksson_2002c.pdf	1405113 6911536fee48c5b3dc176baf9dd072facaddbe21	no	5
Warnings:					
Information:					
10	Non Patent Literature	Fredriksson_2007c.pdf	131062 da04cd0f43a85e4b8fbc829ef7719c31334bdfa0	no	3

Warnings:					
Information:					
11	Non Patent Literature	Kozlov_2008c.pdf	397336 8e6cfbe570bb08bed919999ab202ae14e4fd37be	no	12
Warnings:					
Information:					
			Total Files Size (in bytes):	16755700	

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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.

THIS DOCUMENT IS BEING FILED ELECTRONICALLY ON JANUARY 20, 2012

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Mark S. Chee	Attorney Docket No. : PGNS007US
Serial No.	13/080,616	Group Art Unit No.: 1773
Filed:	05 April 2011	Examiner: Not Assigned

Confirmation No. 2142

For: Spatially Encoded Biological Assays

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

PRELIMINARY AMENDMENT

Dear Sir:

This Preliminary Amendment is submitted in the above-referenced case to make notice of rights of the Federal Government in the invention. Applicants respectfully request entry of this amendment and the remarks prior to examination of the above-referenced case.

The Amendment to the Specification begins on page 2 of this paper.

Remarks begin on page 3 of this paper.

Curio EX1012-p. 111
Curio v Prognosys

AMENDMENT TO THE SPECIFICATION:

This amendment introduces no new matter and is submitted to give notice of rights of the Federal Government in the invention that is the subject of the present application.

PLEASE INSERT THE FOLLOWING PARAGRAPH AFTER THE TITLE AND BEFORE THE FIELD OF THE INVENTION:

This invention was made with government support under 1R43GM096706 awarded by the National Institute of General Medical Sciences division of the National Institutes of Health. The government has certain rights in the invention.

REMARKS

Applicant submits this Preliminary Amendment to give notice of rights of the Federal Government in the invention that is the subject of the present application. Should any issues remain, please contact the undersigned at the phone number below.

Respectfully submitted,

/Sarah J Brashears/

Sarah Brashears
Attorney for Applicants
Registration No. 38,087

Dated: 20 January 2012

CONVERGENT LAW GROUP, LLP
475 N. Whisman Rd., St.400
Mountain View, CA 94043
Phone (650) 641-2485
Facsimile (650) 641-2485

Curio EX1012-p. 113
Curio v Prognosys

Electronic Acknowledgement Receipt

EFS ID:	11883012
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	57580
Filer:	Sarah J. Brashears/Debbie Nishihara
Filer Authorized By:	Sarah J. Brashears
Attorney Docket Number:	PGNS007US
Receipt Date:	20-JAN-2012
Filing Date:	05-APR-2011
Time Stamp:	12:57:29
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		PGNS007US_PrelimAmend_As Filed_1_20_12.pdf	28362 f214c6eaf56025d365daec604ef495af21da52c7	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	3
Warnings:			
Information:			
	Total Files Size (in bytes):	28362	

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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.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/080,616	04/05/2011	

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	82		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 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	82		TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 01/20/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 57	Minus	** 57	= 0	X $30 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $125 =	0	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	0	OR	TOTAL ADD'L FEE	

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GLORIA TRAMMELL/

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.

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

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

I hereby appoint:

[X] Practitioners associated with the Customer Number: 25225

OR

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

Name	Registration Number	Name	Registration Number

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

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

[X] The address associated with Customer Number: 25225

OR

[ ] Firm or Individual Name					
Address					
City		State		Zip	
Country		Telephone		Email	

Assignee Name and Address:

Prognosys Biosciences, Inc.
11125 Flintkote Avenue
Suite A
San Diego, California 92121

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

SIGNATURE of Assignee of Record

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

Signature	Mark S Chee	Date	7/17/13
Name	MARK CHEE	Telephone	858-459-2428
Title	CEO		

sd-621711

Electronic Acknowledgement Receipt

EFS ID:	16383102
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	57580
Filer:	Bu Yin/Diane Blevins
Filer Authorized By:	Bu Yin
Attorney Docket Number:	PGNS007US
Receipt Date:	22-JUL-2013
Filing Date:	05-APR-2011
Time Stamp:	20:05:53
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	Miscellaneous Incoming Letter	69993-20002_00_-_Trans_of_POA_and_373b.pdf	25073 4407f086820f2c71f64d1a63ba981585d68dcb5f	no	1
Warnings:					
Information:					

2	Assignee showing of ownership per 37 CFR 3.73.	69993-20002_00_-_373b_and_Assignment.pdf	462178 1dc396535ee30c42040479ce383c43b2359ea337	no	4
Warnings:					
Information:					
3	Power of Attorney	69993-20002_00_-_POA.pdf	155043 eb0560a8b4e30abc0fb5d256114c53c4f4e9e8b9	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	642294	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/21 (07-09)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	6

Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1656
Examiner Name	Not Yet Assigned
Attorney Docket Number	699932000200

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [x] Power of Attorney, Revocation Change of Correspondence Address (1 page)
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Statement Under 37 CFR 3.73(b) (4 pages, including copy of Assignment)

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP (Customer No. 25225)		
Signature	/Bu Yin/		
Printed name	Bu Yin		
Date	July 22, 2013	Reg. No.	68,930

I hereby certify that this paper and the accompanying documents listed above are being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: July 22, 2013 Signature: /Diane Blevins/ (Diane Blevins)

sd-622007

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Mark S. Chee

Application No./Patent No.: 13/080,616 Filed/Issue Date: April 5, 2011

Titled: SPATIALLY ENCODED BIOLOGICAL ASSAYS

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

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] an assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above by virtue of either:

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

OR

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

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

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

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

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

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

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

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

/Bu Yin/	July 22, 2013
Signature	Date
Bu Yin	Reg No. 68,930
Printed or Typed Name	Title

Attorney Docket No. 699932000200

sd-621712

ASSIGNMENT

This assignment is by:

1. Mark S. CHEE
   11125 Flintkote Avenue, Suite A, San Diego, California 92121
   San Diego, California 92121

(referred to in this Assignment as "Assignor"), who resides at or have a mailing address as listed above.

This Assignment is to:

Assignee: Prognosys Biosciences, Inc.
Address: 11125 Flintkote Avenue, Suite A, San Diego, California 92121
A corporation duly organized under and pursuant to the laws of: Delaware

(referred to in this Assignment as "Assignee"), who desire to acquire the entire right, title and interest in said inventions and said application for letters patent of the United States, and in any United States or foreign, letters patent or patents, to be obtained therefor and thereon.

Assignor has invented certain new and useful inventions in:

SPATIALLY ENCODED BIOLOGICAL ASSAYS

for which the following application has been filed in the United States of America.

Serial No.: 13/080,616 Filing Date: April 5, 2011

For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged,

1. Assignor hereby sells, assigns, transfers and sets over, to Assignee, its successors, legal representatives and assigns, the entire right, title and interest in and to the above-mentioned inventions, application for letters patent, and any and all letters patent or patents in the United States of America and all foreign countries which may be granted therefor and thereon, and in and to any and all provisionals, divisions, continuations, continuations-in-part and substitutions of said application, or reissues, re-examinations or extensions of said letters patent or patents, and all rights under the International Convention for the Protection of Industrial Property, the same to be held and enjoyed by Assignee (including any right to institute actions and to recover for past, present and future infringement), for its own use and the use of its successors, legal representatives and assigns, to the full end of the term or terms for which letters patent or patents may be granted, as fully and entirely as the same would have been held and enjoyed by Assignor, had this sale and assignment not been made.

2. Assignor represents, warrants and covenants that, at the time of execution and delivery of this agreement, Assignor is the sole and lawful owner of the entire right, title and interest in and to said inventions and said application for letters patent, and that the same are unencumbered and that Assignor has good and full right and lawful authority to sell and convey the same in the manner set forth in this agreement.

3. Assignor shall promptly sign and execute all papers and documents, take all lawful oaths, and do all acts necessary, required or useful for the procurement, maintenance, enforcement, defense or otherwise to secure title thereto to the Assignee, at the sole cost and expense of Assignee, its successors, legal representatives and assigns, in each case including, without limitation, arising from or relating to (a) said inventions, or said application for letters patent; (b) letters patent for said inventions in any country, including any reissue, re-examination or extension of or interference proceedings; or (c) any provisional, division, continuation, continuation-in-part, or substitutions of any application for letters patent or any reissues, re-examinations, extensions or interference proceedings involving any letters patent, to be obtained thereon. To be clear, for purposes of this paragraph, "desirable" shall include, without limitation, any act necessary or useful in connection with United States laws and/or international conventions.

4. Assignor hereby authorizes and requests the Commissioner of Patents in the United States to issue the above mentioned letters patents of the United States to Assignee as the assignee of said inventions and the letters patent to be issued thereon for the sole use of Assignee, its successors, legal representatives and assigns.

5. "I hereby grant Assignee's attorneys, all of Morrison & Foerster LLP, the power to insert on this assignment any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark office for recordation of this document, including the power to insert on this assignment the application number and filing date of said application when known."

In witness whereby, executed by the undersigned on the date(s) opposite the undersigned name(s).

Date: 7/17/13

Signature: Mark S Chee
Mark S. Chee

sd-621709

ALL-PURPOSE ACKNOWLEDGMENT NOTARY FOR CALIFORNIA

STATE OF CALIFORNIA)
COUNTY OF SAN DIEGO)

On July 17, 2013 (Date), before me, Lisa E. Watts, NotaryPublic (Name And Title Of Officer (e.g. "Jane Doe, Notary Public")),

personally appeared Mark S. Chee (Name of Signer(s)),

who proved to me on the basis of satisfactory evidence to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

LISA EILEEN WATTS
Commission # 1962677
Notary Public - California
San Diego County
My Comm. Expires Dec 4, 2015

Lisa E Watts
Signature of Notary Public

OPTIONAL

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/080,616	04/05/2011	Mark S. Chee	PGNS007US

CONFIRMATION NO. 2142

25225
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

POA ACCEPTANCE LETTER

OC000000062795491

Date Mailed: 07/30/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/22/2013.

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.

/mbeyene/

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

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 5

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	MERKLING, SALLY ANNE
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-6,258,558	07-10-2001	Szostak et al.	
	2.	US-6,261,804	07-17-2001	Szostak et al.	
	3.	US-6,281,804	08-28-2001	Haller et al.	
	4.	US-6,416,950	07-09-2002	Lohse et al.	
	5.	US-6,485,982	11-26-2002	Charlton	
	6.	US-6,518,018	02-11-2003	Szostak et al.	
	7.	US-6,579,695	06-17-2003	Lambalot et al.	
	8.	US-6,800,453	10-05-2004	Labaer et al.	
	9.	US-7,118,883	10-10-2006	Inoue et al.	
	10.	US-7,192,735	03-20-2007	Lambalot et al.	
	11.	US-7,229,769	06-12-2007	Kozlov et al.	
	12.	US-7,270,950	09-18-2007	Szostak et al.	
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	14.	US-7,674,752	03-09-2010	He et al.	
	15.	US-7,858,321	12-28-2010	Glezer et al.	
	16.	US-8,207,093	06-26-2012	Szostak et al.	
	17.	US-2003/0138879	07-24-2003	Lambalot et al.	
	18.	US-2003/0235852	12-25-2003	Roberts et al.	
	19.	US-2003/0087232	05-08-2003	Christians et al.	
	20.	US-2003/0113713	06-19-2003	Glezer et al.	
	21.	US-2005/0026188	02-03-2005	Van Kessel et al.	
	22.	US-2005/0048580	03-03-2005	Labaer et al.	
	23.	US-2006/0003394	01-05-2006	Song	
	24.	US-2006/0216721	09-28-2006	Kozlov et al.	
	25.	US-2006/0216775	09-28-2006	Burkart et al.	
	26.	US-2007/0014810	01-18-2007	Baker et al.	
	27.	US-2007/0020625	01-25-2007	Duchaud et al.	
	28.	US-2007/0020669	01-25-2007	Ericsson	
	29.	US-2007/0026430	02-01-2007	Andersen et al.	
	30.	US-2008/0071071	03-20-2008	LaBaer et al.	
	31.	US-2008/0108804	05-08-2008	Hayashizaki et al.	
	32.	US-2008/0220981	09-11-2008	McGregor	
	33.	US-2008/0293591	11-27-2008	Taussig et al.	
	34.	US-2009/0280487	11-12-2009	Hung et al.	
	35.	US-2010/0069263	03-18-2010	Shendure et al.	
	36.	US-2010/0113302	05-06-2010	Williams	
	37.	US-2010/0173384	07-08-2010	Johnsson et al.	
	38.	US-2011/0245101	10-06-2011	Chee et al.	
	39.	US-2012/0065081	03-15-2012	Chee	
	40.	US-2012/0129248	05-24-2012	Chee et al.	
	41.	US-2012/0258871	10-11-2012	Kozlov et al.	
	42.	US-2012/0270748	10-25-2012	Chee et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 5

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	MERKLING, SALLY ANNE
Attorney Docket Number	699932000200

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	43.	EP-1712623	10-18-2006			
	44.	WO-2003/010176	02-06-2003			
	45.	WO-2005/026387	03-24-2005			
	46.	WO-2007/041689	04-12-2007			
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	48.	WO-2007/076726	07-12-2007			
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	50.	WO-2009/032167	03-12-2009			
	51.	WO-2010/127186	11-04-2010			
	52.	WO-2011/014879	02-03-2011			
	53.	WO-2011/071943	06-16-2011			
	54.	WO-2011/127006	10-13-2011			
	55.	WO-2011/127099	10-13-2011			
	56.	WO-2012/139110	10-11-2012			

Examiner Signature		Date Considered	

*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	57.	Office Action for US 13/266,568, mailed 29 March, 2013.	
	58.	Response to Office Action for US 13/266,568, filed 29 August 2013.	
	59.	Office Action for US 13/388,229, mailed 24 December 2012.	
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	62.	International Search Report and Written Opinion for PCT/US2010/044134, mailed 18 March 2011.	
	63.	International Preliminary Report on Patentability Chapter I for PCT/US2010/044134, issued 31 January 2012.	
	64.	Communication Pursuant to Art. 94(3) EPC for EP 10747097.3-1405, issued 26 July 2013.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 5

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	MERKLING, SALLY ANNE
Attorney Docket Number	699932000200

	65.	Restriction Requirement for US 13/514,045, mailed 23 November 2012.	
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	69.	Response to Office Action for US 13/514,045, filed 27 June 2013.	
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	79.	Voluntary Amendment and Observation for CN 201180017696.3, filed 25 July 2013.	
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	84.	Restriction Requirement for US 13/442,637, mailed 17 May 2012.	
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	91.	Advisory Action for US 13/442,637, mailed 1 April 2013.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 5

Complete if Known	
Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	MERKLING, SALLY ANNE
Attorney Docket Number	699932000200

	98.	ANGENENDT et al.,"Generation of High Density Protein Microarrays by Cell-free in Situ Expression of Unpurified PCR Products," Molecular and Cellular Proteomics, (2006) Ch. 5.9, pp. 1658-66.	
	99.	ATKINSON, Overview of Translation: Lecture Manuscript, U of Texas (2000) pp. 6.1-6.8.	
	100.	BURNS et al., "Well-less, gel-permeation formats for ultra-HTS," DDT (2001) 6(12):S40-S47.	
	101.	CARLSON et al., "Formylglycine-generating Enzyme," J. of Biological Chemistry (2008) 283(29):20117-125.	
	102.	CHA and TILLY, "Specificity, Efficiency and Fidelity of PCR," Genome Res. (1993) 3:518-29.	
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	107.	FU et al., "Counting individual DNA molecules by the stochastic attachment of diverse labels," PNAS (2011) 108:9026-9031.	
	108.	HE et al., "In situ synthesis of protein arrays," Current Opinion in Biotechnology (2008) 19:4-9.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 5 of 5

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	MERKLING, SALLY ANNE
Attorney Docket Number	699932000200

	122.	ROBERTS and SZOSTAK, "RNA-peptide fusions for the in vitro selection of peptides and proteins," PNAS USA (1997) 94:12297-302.	
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	125.	RUSH and BERTOZZI, "New Aldehyde Tag Sequences Identified by Screening Formylglycine Generating Enzymes in Vitro and in Vivo," J. of American Chemical Society (2008) 130: 12240-41 (2008) Supplement.	
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Examiner Signature		Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
PGNS002PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2010/033064	29/04/2010	30/04/2009
Applicant		
PROGNOSYS BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/033064

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, COMPENDEX, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/073171 A2 (KEYGENE NV [NL]; VAN EIJK MICHAEL JOSEPHUS THER [NL]) 28 June 2007 (2007-06-28) the whole document, in particular p. 25, last paragraph, p.29-30 and claims, especially claims 7 and 13-14	1-29
X	WO 2007/076726 A1 (LOK SI [CN]) 12 July 2007 (2007-07-12) the whole document	1-29
A	XIAO MING ET AL: "Direct determination of haplotypes from single DNA molecules" NATURE METHODS, vol. 6, no. 3, March 2009 (2009-03), pages 199-201, XP002591312 ISSN: 1548-7091 cited in the application	1-29

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 2010	30/07/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bassias, Ioannis

Form PCT/ISA/210 (second sheet) (April 2005)

Curio EX1012-p. 132
Curio v Prognosys

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/033064

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/032167 A1 (ILLUMINA CAMBRIDGE [GB]; BIGNELL HELEN [GB]; GORMLEY NIALL ANTHONY [GB) 12 March 2009 (2009-03-12)	1-29
A	WO 2007/145612 A1 (454 LIFE SCIENCES CORP [US]; BERKA JAN [US]; CHEN ZHOUTAO [US]; EGHOLM) 21 December 2007 (2007-12-21)	1-29

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

Curio EX1012-p. 133
Curio v Prognosys

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/033064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007073171 A2	28-06-2007	CN 101365803 A	11-02-2009
		EP 1966394 A2	10-09-2008
		JP 2009520500 T	28-05-2009
		US 2009247415 A1	01-10-2009
WO 2007076726 A1	12-07-2007	EP 1969146 A1	17-09-2008
WO 2009032167 A1	12-03-2009	EP 2191011 A1	02-06-2010
		US 2009093378 A1	09-04-2009
WO 2007145612 A1	21-12-2007	CA 2615323 A1	21-12-2007
		EP 1910537 A1	16-04-2008

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2010/033064	29.04.2010	30.04.2009

International Patent Classification (IPC) or both national classification and IPC
INV. C12Q1/68

Applicant
PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Bassias, Ioannis Telephone No. +49 89 2399-8106

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V:

1 The present application relates to nucleic acid contructs which comprise a region of interest (ROI), at least of unique identifier and at least one amplification site. Said contructs are used in methods for determining the sequence of nucleic acids, for identifying nucleic acids having a desired sequence and in methods for selecting nucleic acids having a desired sequence.

2 Reference is made to the following documents:

D1 WO 2007/073171 A2 (KEYGENE NV [NL]; VAN EIJK MICHAEL JOSEPHUS THER [NL]) 28 June 2007 (2007-06-28)

D2 WO 2007/076726 A1 (LOK SI [CN]) 12 July 2007 (2007-07-12)

3 The application is drafted in a very broad manner. The terms used, "region of interest", "unique identifier", etc. are very undefined and open for interpretation in various directions. Consequently, the claims need to be interpreted in the broadest possible sense. This approach leads to objections under Articles 33(2) and (3) in view of the teaching of D1 and/or D2.

3.1 D1 describes methods for transcript profiling using high throughput sequencing techniques where adaptors are used that can be used as a template for PCR oligonucleotide primers and for sequencing. The constructs can be immobilized on a solid support such as beads. The adaptors may comprise identifier sequences that can be unique and can vary in the length. Any nucleic acid to be analyzed in D1 represents the region of interest (ROI). The unique identifiers are not further characterized in the application. Hence, the unique identifiers of D1 fully fall into the scope of this expression. These unique identifiers can vary in the length. Consequently, any ROI can be attached to different identifiers and thus the concept of having the same ROI with different unique identifiers is fulfilled. The adaptors represent the amplification site since they are used as a template for PCR oligonucleotide primers and for sequencing. Restrictions sites within the constructs are mentioned. Sequencing of the constructs anticipates the method as described in claims 11-17. The determination of the sequence and further analysis for transcript profiling requires the identification of nucleic acids with desired sequences and also the selection thereof. Consequently, the subject-matter of all claims (1-29) is anticipated by the teaching of D1 (Article 33(2) PCT).

3.2 In D2 methods are described for nucleic acid mapping and identification of fine-structural variations in nucleic acids wherein so called "Genomic Variations Tags" (GVTs) are produced that bind to target nucleic acids. Said GVTs comprise one or more restriction endonucleases sites. They can be used as unique genomic positional identifiers. Different restriction endonucleases sites can be used in the GVTs which are tagged to the ROIs. Hence, the same ROI can have different unique identifiers. Amplification and sequencing via these tags is described. Immobilisation on solid support is not specifically mentioned in this prior art document. However, this is not considered something special which would not be within the ordinary skills of a person in the art.

Consequently, claims 1-6, 9-25, 28, and 29 are not in accordance with Article 33(2) PCT in view of D2. Claims 7, 8, 26, and 27 contravene the requirements of Article 33(3) PCT in view of the teaching of D2 combined with general knowledge.

4 Claim 28 lacks clarity (Article 6 PCT) apparently due to a wrong syntax.

5 Expressions like "incorporated herein/hereby by reference" used in the description (e.g. on pages 12 and 24) render the true scope of the application unclear and are thus not in accordance with Article 6 PCT.

The same applies for the use of expressions like "spirit of the invention" (see e.g. on pages 30, 42, 43).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PGNS002PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2010/033064	International filing date *(day/month/year)* 29 April 2010 (29.04.2010)	Priority date *(day/month/year)* 30 April 2009 (30.04.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PROGNOSYS BIOSCIENCES, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 01 November 2011 (01.11.2011)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2010/033064	29.04.2010	30.04.2009

International Patent Classification (IPC) or both national classification and IPC
INV. C12Q1/68

Applicant
PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Bassias, Ioannis Telephone No. +49 89 2399-8106

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V:

1 The present application relates to nucleic acid contructs which comprise a region of interest (ROI), at least of unique identifier and at least one amplification site. Said contructs are used in methods for determining the sequence of nucleic acids, for identifying nucleic acids having a desired sequence and in methods for selecting nucleic acids having a desired sequence.

2 Reference is made to the following documents:

D1 WO 2007/073171 A2 (KEYGENE NV [NL]; VAN EIJK MICHAEL JOSEPHUS THER [NL]) 28 June 2007 (2007-06-28)

D2 WO 2007/076726 A1 (LOK SI [CN]) 12 July 2007 (2007-07-12)

3 The application is drafted in a very broad manner. The terms used, "region of interest", "unique identifier", etc. are very undefined and open for interpretation in various directions. Consequently, the claims need to be interpreted in the broadest possible sense. This approach leads to objections under Articles 33(2) and (3) in view of the teaching of D1 and/or D2.

3.1 D1 describes methods for transcript profiling using high throughput sequencing techniques where adaptors are used that can be used as a template for PCR oligonucleotide primers and for sequencing. The constructs can be immobilized on a solid support such as beads. The adaptors may comprise identifier sequences that can be unique and can vary in the length. Any nucleic acid to be analyzed in D1 represents the region of interest (ROI). The unique identifiers are not further characterized in the application. Hence, the unique identifiers of D1 fully fall into the scope of this expression. These unique identifiers can vary in the length. Consequently, any ROI can be attached to different identifiers and thus the concept of having the same ROI with different unique identifiers is fulfilled. The adaptors represent the amplification site since they are used as a template for PCR oligonucleotide primers and for sequencing. Restrictions sites within the constructs are mentioned. Sequencing of the constructs anticipates the method as described in claims 11-17. The determination of the sequence and further analysis for transcript profiling requires the identification of nucleic acids with desired sequences and also the selection thereof. Consequently, the subject-matter of all claims (1-29) is anticipated by the teaching of D1 (Article 33(2) PCT).

3.2 In D2 methods are described for nucleic acid mapping and identification of fine-structural variations in nucleic acids wherein so called "Genomic Variations Tags" (GVTs) are produced that bind to target nucleic acids. Said GVTs comprise one or more restriction endonucleases sites. They can be used as unique genomic positional identifiers. Different restriction endonucleases sites can be used in the GVTs which are tagged to the ROIs. Hence, the same ROI can have different unique identifiers. Amplification and sequencing via these tags is described. Immobilisation on solid support is not specifically mentioned in this prior art document. However, this is not considered something special which would not be within the ordinary skills of a person in the art.

Consequently, claims 1-6, 9-25, 28, and 29 are not in accordance with Article 33(2) PCT in view of D2. Claims 7, 8, 26, and 27 contravene the requirements of Article 33(3) PCT in view of the teaching of D2 combined with general knowledge.

4 Claim 28 lacks clarity (Article 6 PCT) apparently due to a wrong syntax.

5 Expressions like "incorporated herein/hereby by reference" used in the description (e.g. on pages 12 and 24) render the true scope of the application unclear and are thus not in accordance with Article 6 PCT.

The same applies for the use of expressions like "spirit of the invention" (see e.g. on pages 30, 42, 43).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
PGNS003PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2010/044134	02/08/2010	31/07/2009
Applicant		
PROGNOSYS BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   ☐ the text is approved as submitted by the applicant
   ☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      ☒ as suggested by the applicant
      ☐ as selected by this Authority, because the applicant failed to suggest a figure
      ☐ as selected by this Authority, because this figure better characterizes the invention
   b. ☐ none of the figures is to be published with the abstract

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention provides assay tools for the detection of biological or chemical activity in a sample. The assay tools of the invention provide direct detection using a positive signal generated on a surface of the assay tool. These assay tools provide improved methods for detection and/or identification of multiple agents (e.g., enzymes) in a sample, analysis of substrate specificity of such agents, and binding affinities and specificities of such agents.
Upon activity a component is released from a first immobilised construct and then captured by a capture surface. At least two different immobilised constructs are used.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/044134

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044134

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/573 C12Q1/34 C12Q1/37 G01N33/543

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, COMPENDEX, EMBASE, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/003394 A1 (SONG XUEDONG [US]) 5 January 2006 (2006-01-05) the whole document in particular: paragraphs [0004] - [0006], [0015], [0018], [0020], [0030], [0060], [0061] figure 3 claim 24 -----	1-6
X	WO 2007/060599 A1 (KONINKL PHILIPS ELECTRONICS NV [NL]; VOSSENAAR ERIK R [NL]; PRINS MENN) 31 May 2007 (2007-05-31) the whole document in particular: figures 5,6,9,10 paragraphs [0042], [0060] - [0067], [0080], [0089] -----	1-6

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2011	18/03/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Tuynman, Antonin

6

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/044134

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006003394 A1	05-01-2006	CN 1977167 A	06-06-2007
		EP 1782069 A1	09-05-2007
		KR 20070026691 A	08-03-2007
		WO 2006006961 A1	19-01-2006
WO 2007060599 A1	31-05-2007	CN 101313218 A	26-11-2008
		EP 1957979 A1	20-08-2008
		JP 2009517651 T	30-04-2009
		US 2008311598 A1	18-12-2008

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6

   An assay tool for detecting biological or chemical activity in a sample.

   ---

2. claims: 7-9, 19

   An assay tool for detecting activity in a sample involving constructs with cleavage agent substrate region, affinity region and detectable marker.

   ---

3. claims: 10-18, 34

   An assay tool for detecting cleavage agent activity in a sample involving constructs with cleavage agent substrate and detectable marker.

   ---

4. claims: 20-33, 41

   An assay tool and method for detecting activity of a cleavage agent in a sample wherein the proximity of first and second surface allow for the detection of the positive signal.

   ---

5. claim: 35

   An assay tool for detecting activity of a cleavage agent in a sample, wherein association of a first released component of a combined detectable marker with a second component thereof on the capture surface creates a positive signal though interaction of first and second components of the combined detectable marker

   ---

6. claims: 36, 37, 42, 43

   An assay tool and methods for detecting competitive binding of a molecule in a sample.

   ---

7. claims: 38, 39

   An assay tool for detecting activity of an enzyme.

   ---

8. claim: 40

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method for detecting cleavage agent activity in a sample involving a surface with releasable component constructs and capture agents.

---

9. claims: 44-47

A method for detecting a modulator of enzyme activity

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2010/044134	02.08.2010	31.07.2009

International Patent Classification (IPC) or both national classification and IPC
INV. G01N33/573 C12Q1/34 C12Q1/37 G01N33/543

Applicant
PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Tuynman, Antonin Telephone No. +31 70 340-3741

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 7-47

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 7-47

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-6

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-6
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6
Industrial applicability (IA)	Yes:	Claims	1-6
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

The problem to be solved in the present application (PA) relates to the detection of biological and/or chemical activity in a sample. The single general concept which can be identified a priori as linking the various claimed inventions and which forms a solution to the above mentioned problem relates to "the notion that an assay tool comprising a set of two or more immobilised constructs comprising a releasable component and a capture surface, wherein release of the component allows for the detection of a positive signal"

However, US2006/003394 A (hereinafter referred to as D1, relevant passages as cited in the search report) and WO2007/060599 A (hereinafter referred to as D2, relevant passages as cited in the search report) disclose such a notion.

In the light of D1 and D2, each document if taken alone, the above identified single general concept is not novel and inventive and can thus not be the single general inventive concept as required by Rule 13.1 PCT. The present application is therefore considered not to fulfill the requirement of unity as laid down in Rule 13.1 PCT.

Consequently the groups of inventions are split up as follows:

1) An assay tool for detecting biological or chemical activity in a sample (claims 1-6)

2) An assay tool for detecting activity in a sample involving constructs with cleavage agent substrate region, affinity region and detectable marker (claims 7-9,19)

3) An assay tool for detecting cleavage agent activity in a sample involving constructs with cleavage agent substrate and detectable marker (claims 10-18,34)

4) An assay tool and method for detecting activity of a cleavage agent in a sample wherein the proximity of first and second surface allow for the detection of the positive signal (claims 20-33 and 41)

5) An assay tool for detecting activity of a cleavage agent in a sample, wherein association of a first released component of a combined detectable marker with a second component thereof on the capture surface creates a positive signal though interaction of first and second components of the combined detectable marker (claim 35)

6) An assay tool and methods for detecting competitive binding of a molecule in a sample (claims 36,37,42 and 43)

7) An assay tool for detecting activity of an enzyme (claims 38 and 39)

8) A method for detecting cleavage agent activity in a sample involving a surface with releasable component constructs and capture agents (claim 40)

9) A method for detecting a modulator of enzyme activity (claims 44-47)

No other technical features could be identified that form a technical relationship among each of the separate inventions claimed and which could be considered as special technical feature within the meaning of Rule 13.2 PCT. As no additional search fees have been paid upon invitation, the present opinion is limited to group of inventions 1 (claims 1-6).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 US 2006/003394 A1 (SONG XUEDONG [US]) 5 January 2006 (2006-01-05)

D2 WO 2007/060599 A1 (KONINKL PHILIPS ELECTRONICS NV [NL]; VOSSENAAR ERIK R [NL]; PRINS MENN) 31 May 2007 (2007-05-31)

1 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of independent claim 1 is not new.

D1 discloses : An assay tool (Figure 3, claim 24, pars. 4-6,15,18,20,30,60 and 61) for detecting biological or chemical activity in a sample, comprising: a set of at least two different immobilized constructs (e.g. Figure 3 items 47 and 49: immobilised on particle 43), wherein the constructs comprises a releasable component (item 45, figure 3); and a capture surface (Figure 3, item 31); wherein the exposure of the immobilized constructs to a biological or chemical activity may result in release of a releasable component from one or more of the immobilized constructs, and wherein the interaction of a releasable component with the capture surface directly or indirectly enables the generation of a positive signal (claim 24).

2 The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of independent claim 1 does not involve an inventive step.

2.1 As claim 1 is not novel (see point 1) it cannot be inventive either.

2.2 Also in view of D2 alone claim 1 is not inventive: D2 discloses a similar assay tool for detecting biological or chemical activity in a sample as described in detail under point 1 (see D2, figures 5-10) which differs from presently claimed assay tool in that there is only one type of immobilised construct. The effect thereof is that the tool does not allow for multiplexing assays.

The problem to be solved by the present invention may therefore be regarded as how to provide an assay tool so as to allow multiplexing assays.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: D2 already suggests that different labels can be used (par. 89) in the methods, systems and devices disclosed therein. If this solution is applied to the embodiments involving the label as part of the substrate to be cleaved as well as part of the product (pars. 60-67; figures 5-10), a tool is provided which falls within the scope of present claim 1.

3 Dependent claims 2-6 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see D1 and/or D2 (relevant passages as cited in the search report). The incorporation of the features of claims 2-6 into independent claim 1 is either known or obvious from D1-D2 or falls within the knowledge and ability of a person skilled in the art.

Re Item VII

Certain defects in the international application

4 The phrase " incorporated by reference" on several pages of the description should be deleted. According to the PCT Guidelines, II, 4.26, the patent specification should be self contained i.e. capable of being understood without reference to any other document.

5 The statement which refers to the extent of protection being expanded to cover the spirit of the invention on several pages of the description should be deleted (PCT Guidelines II, 5.30).

Re Item VIII

Certain observations on the international application

6 The application does not meet the requirements of Article 6 PCT, because claim 1 is not clear.

6.1 The phrase "constructs comprises" is unclear as it is not clear whether it was intended that only one of the constructs comprises a releasable component or whether both comprise a releasable component.

6.2 Claim 2 is unclear as only the releasable component can bind to the capture surface and not the complete immobilised constructs comprising a releasable component as the claim presently suggests.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PGNS003PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2010/044134	International filing date *(day/month/year)* 02 August 2010 (02.08.2010)	Priority date *(day/month/year)* 31 July 2009 (31.07.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PROGNOSYS BIOSCIENCES, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 31 January 2012 (31.01.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Agnès Wittmann-Regis e-mail: pt06.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2010/044134	02.08.2010	31.07.2009

International Patent Classification (IPC) or both national classification and IPC
INV. G01N33/573 C12Q1/34 C12Q1/37 G01N33/543

Applicant
PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Tuynman, Antonin Telephone No. +31 70 340-3741

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 7-47

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 7-47

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-6

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-6
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6
Industrial applicability (IA)	Yes:	Claims	1-6
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV

Lack of unity of invention

The problem to be solved in the present application (PA) relates to the detection of biological and/or chemical activity in a sample. The single general concept which can be identified a priori as linking the various claimed inventions and which forms a solution to the above mentioned problem relates to "the notion that an assay tool comprising a set of two or more immobilised constructs comprising a releasable component and a capture surface, wherein release of the component allows for the detection of a positive signal"

However, US2006/003394 A (hereinafter referred to as D1, relevant passages as cited in the search report) and WO2007/060599 A (hereinafter referred to as D2, relevant passages as cited in the search report) disclose such a notion.

In the light of D1 and D2, each document if taken alone, the above identified single general concept is not novel and inventive and can thus not be the single general inventive concept as required by Rule 13.1 PCT. The present application is therefore considered not to fulfill the requirement of unity as laid down in Rule 13.1 PCT.

Consequently the groups of inventions are split up as follows:

1) An assay tool for detecting biological or chemical activity in a sample (claims 1-6)

2) An assay tool for detecting activity in a sample involving constructs with cleavage agent substrate region, affinity region and detectable marker (claims 7-9,19)

3) An assay tool for detecting cleavage agent activity in a sample involving constructs with cleavage agent substrate and detectable marker (claims 10-18,34)

4) An assay tool and method for detecting activity of a cleavage agent in a sample wherein the proximity of first and second surface allow for the detection of the positive signal (claims 20-33 and 41)

5) An assay tool for detecting activity of a cleavage agent in a sample, wherein association of a first released component of a combined detectable marker with a second component thereof on the capture surface creates a positive signal though interaction of first and second components of the combined detectable marker (claim 35)

6) An assay tool and methods for detecting competitive binding of a molecule in a sample (claims 36,37,42 and 43)

7) An assay tool for detecting activity of an enzyme (claims 38 and 39)

8) A method for detecting cleavage agent activity in a sample involving a surface with releasable component constructs and capture agents (claim 40)

9) A method for detecting a modulator of enzyme activity (claims 44-47)

No other technical features could be identified that form a technical relationship among each of the separate inventions claimed and which could be considered as special technical feature within the meaning of Rule 13.2 PCT. As no additional search fees have been paid upon invitation, the present opinion is limited to group of inventions 1 (claims 1-6).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 US 2006/003394 A1 (SONG XUEDONG [US]) 5 January 2006 (2006-01-05)

D2 WO 2007/060599 A1 (KONINKL PHILIPS ELECTRONICS NV [NL]; VOSSENAAR ERIK R [NL]; PRINS MENN) 31 May 2007 (2007-05-31)

1 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of independent claim 1 is not new.

D1 discloses : An assay tool (Figure 3, claim 24, pars. 4-6,15,18,20,30,60 and 61) for detecting biological or chemical activity in a sample, comprising: a set of at least two different immobilized constructs (e.g. Figure 3 items 47 and 49: immobilised on particle 43), wherein the constructs comprises a releasable component (item 45, figure 3); and a capture surface (Figure 3, item 31); wherein the exposure of the immobilized constructs to a biological or chemical activity may result in release of a releasable component from one or more of the immobilized constructs, and wherein the interaction of a releasable component with the capture surface directly or indirectly enables the generation of a positive signal (claim 24).

2 The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of independent claim 1 does not involve an inventive step.

2.1 As claim 1 is not novel (see point 1) it cannot be inventive either.

2.2 Also in view of D2 alone claim 1 is not inventive: D2 discloses a similar assay tool for detecting biological or chemical activity in a sample as described in detail under point 1 (see D2, figures 5-10) which differs from presently claimed assay tool in that there is only one type of immobilised construct. The effect thereof is that the tool does not allow for multiplexing assays.

The problem to be solved by the present invention may therefore be regarded as how to provide an assay tool so as to allow multiplexing assays.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: D2 already suggests that different labels can be used (par. 89) in the methods, systems and devices disclosed therein. If this solution is applied to the embodiments involving the label as part of the substrate to be cleaved as well as part of the product (pars. 60-67; figures 5-10), a tool is provided which falls within the scope of present claim 1.

3 Dependent claims 2-6 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see D1 and/or D2 (relevant passages as cited in the search report). The incorporation of the features of claims 2-6 into independent claim 1 is either known or obvious from D1-D2 or falls within the knowledge and ability of a person skilled in the art.

Re Item VII

Certain defects in the international application

4 The phrase " incorporated by reference" on several pages of the description should be deleted. According to the PCT Guidelines, II, 4.26, the patent specification should be self contained i.e. capable of being understood without reference to any other document.

5 The statement which refers to the extent of protection being expanded to cover the spirit of the invention on several pages of the description should be deleted (PCT Guidelines II, 5.30).

Re Item VIII

Certain observations on the international application

6 The application does not meet the requirements of Article 6 PCT, because claim 1 is not clear.

6.1 The phrase "constructs comprises" is unclear as it is not clear whether it was intended that only one of the constructs comprises a releasable component or whether both comprise a releasable component.

6.2 Claim 2 is unclear as only the releasable component can bind to the capture surface and not the complete immobilised constructs comprising a releasable component as the claim presently suggests.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PGNS005PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2010/059327	International filing date *(day/month/year)* 07 December 2010 (07.12.2010)	Priority date *(day/month/year)* 07 December 2009 (07.12.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PROGNOSYS BIOSCIENCES, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 12 June 2012 (12.06.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yolaine Cussac e-mail: pt05.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: DIANNA L. DEVORE
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* 29 MAR 2011
Applicant's or agent's file reference PGNS005PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/59327	07 December 2010 (07.12.2010)	07 December 2009 (07.12.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68; G01N 33/50 (2011.01)
USPC - 435/6, 435/7.1

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	14 March 2011 (14.03.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2-21,23,30	YES
	Claims	1,22,24-29,31-35	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-35	NO
Industrial applicability (IA)	Claims	1-35	YES
	Claims	NONE	NO

2. Citations and explanations:

Claim 1 lacks novelty under PCT Article 33(2) as being anticipated by US 2008/0312103 A1 to NEMOTO et al. (hereinafter "Nemoto").

As to claim 1, Nemoto teaches an array comprising a substrate having a surface;
two or more individual constructs associated on the surface of the substrate (para [0020]; "An mRNA chip comprising a plurality of the immobilized mRNA-puromycin conjugates described"), wherein the individual constructs comprise: an oligonucleotide encoding a peptide of interest (para [0020] mRNA); and the peptide of interest (para [0039]; "synthesizing a protein by adding the mRNA-PM conjugate immobilized on a solid phase to a translation system"); wherein the oligonucleotide is associated with the substrate surface (para [0008]; "a solid phase binding site for binding an mRNA-puromycin conjugate"; sheet 1 fig 1a, b), and the peptide is associated with the oligonucleotide (para [0039]; "synthesizing a protein by adding the mRNA-PM conjugate immobilized on a solid phase to a translation system. Namely, when a conjugate in which puromycin is ligated to mRNA through the linker is contacted with a translation system, an in vitro virus virion is known to be formed in which the mRNA is ligated with a translated protein through the puromycin"; sheet 1 fig 1a, b).

Claims 22, 24-29, 31-35 lack novelty under PCT Article 33(2) as being anticipated by US 2005/0260653 A1 (LABAER et al.) (hereinafter "LaBaer").

As to claim 22, LaBaer teaches a method for constructing an array (abstract; "Arrays of polypeptides can be generated by translation of nucleic acid sequences encoding the polypeptides at individual addresses on the array") comprising:
a) synthesizing a set of nucleic acid sequences of known sequence on a solid substrate (para [0005]; " In one aspect, the invention features a method that includes: disposing, on a substrate, one or more nucleic acids that include a coding region and an anchoring agent, maintaining the substrate under conditions which enable the anchoring agent of each disposed nucleic acid to stably attached to the substrate"; para [0015]; " In one embodiment, the coding region encodes a polypeptide that includes a first amino acid sequence, e.g., an amino acid sequence of interest").
b) attaching one or more additional nucleic acid regions to the nucleic acids on the solid substrate to provide extended nucleic acids on the substrate (para [0445-0446]; "[0445] Capture Probes. The substrate can include an attached nucleic acid capture probe at each address. In one aspect, capture probes can be used to create a self-assembling array. A unique capture probe at each address selectively hybridizes to a nucleic acid encoding a test amino acid sequence, thereby organizing each encoding nucleic acid to a unique address. The capture nucleic acid can be covalently attached or bound, e.g., to a polycationic surface on the substrate. [0446] The capture probe can itself be synthesized in situ, e.g. by a light-directed method ..., or by being spotted or disposed at the addresses. The capture probe can hybridize to the nucleic acid encoding the test polypeptide. In a preferred embodiment, the capture probe anneals to the T7 promoter region of a single stranded nucleic acid encoding the test amino acid sequence. In another embodiment, the capture probe is ligated to the encoding nucleic acid sequence")
c) performing in vitro transcription and translation utilizing the extended nucleic acids as a template for production of peptides (para [0458]; " The fusion proteins will be generated with commercially available in vitro transcription/translation kits such as the Promega TNT Coupled Reticulocyte Lysate Systems or TNT Coupled Wheat Germ Extract Systems"; para [0022]); and
d) attaching the produced peptides on known locations on the solid substrate (para [0015]; " In one embodiment, the coding region encodes a polypeptide that includes a first amino acid sequence, e.g., an amino acid sequence of interest, and an affinity tag. The affinity tag binds to a binding agent. The method can also include disposing the binding agent on the substrate. In some cases, it is useful to prepare a solution that includes the nucleic acid and the binding agent, and to dispose the solution onto the substrate"; sheet 1 fig 1).

----------continued in Supplemental Box----------

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
No valid CRF was filed in response to the ISA/225 of 10 December 2010, therefore no sequence information was available for the ISR.

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V-2 (Citations and Explanations)

As to claim 24, LaBaer further teaches that the nucleic acids are chemically synthesized directly on the solid substrate (para [0446]; "The capture probe can itself be synthesized in situ, e.g., by a light-directed method").

As to claim 25, LaBaer further teaches that the additional nucleic acids in step b) are attached via enzymatic ligation (para [0446]; "In another embodiment, the capture probe is ligated to the encoding nucleic acid sequence").

As to claim 26, LaBaer further teaches that the set of nucleic acids comprises at least 1,000 nucleic acid sequences on the substrate (para [0367]; For example, a single array containing 10,000 arrayed elements, for example, can be sufficient to yield 10,000 results (e.g., quantitative results)").

As to claim 27, LaBaer further teaches that the set of nucleic acids comprises at least 5,000 nucleic acid sequences on the substrate (para [0367]).

As to claim 28, LaBaer further teaches that the set of nucleic acids comprises at least 10,000 nucleic acid sequences on the substrate (para [0367]).

As to claim 29, LaBaer teaches a method for constructing a peptide array (abstract), comprising:
a) manufacturing a nucleic acid microarray comprising a set of chemicall synthesized oligonucleotides encoding amino acid sequences (para [0005], [0015]);
b) attaching one or more additional nucleic acid regions to the nucleic acids on the solid substrate to provide extended nucleic acids on the substrate (para [0446]);
c) performing in vitro transcription and translation utilizing the extended nucleic acids as a template for production of peptides (para [0458], [0022]) ; and
d) attaching the produced peptides on the solid substrate (para [0015]; sheet 1 fig 1).

As to claim 31, LaBaer further teaches that the nucleic acids are chemically synthesized directly on the solid substrate (para [0446]; "The capture probe can itself be synthesized in situ, e.g., by a light-directed method").

As to claim 32, LaBaer further teaches that the additional nucleic acids in step b) are attached via enzymatic ligation (para [0446]; "In another embodiment, the capture probe is ligated to the encoding nucleic acid sequence").

As to claim 33, LaBaer further teaches that the set of nucleic acids comprises at least 1,000 nucleic acid sequences on the substrate (para [0367]; For example, a single array containing 10,000 arrayed elements, for example, can be sufficient to yield 10,000 results (e.g., quantitative results)").

As to claim 34, LaBaer further teaches that the set of nucleic acids comprises at least 5,000 nucleic acid sequences on the substrate (para [0367]).

As to claim 35, LaBaer further teaches that the set of nucleic acids comprises at least 10,000 nucleic acid sequences on the substrate (para [0367]).

Claims 2-10, 12-15, 23,30 lack an inventive step under PCT Article 33(3) as being obvious over US 2005/0260653 A1 (LABAER et al.) (hereinafter "LaBaer") in view of the publication titled " The developments of semisynthetic DNA.protein conjugates" By NIEMEYER et al. (hereinafter "Niemeyer").

As to claim 2, LaBaer teaches a substrate having a surface; two or more individual constructs associated on the surface of the substrate, wherein the individual constructs comprise: an oligonucleotide comprising a region encoding a peptide of interest, a region encoding an affinity tag and an untranslated region (para [0005]; " In one aspect, the invention features a method that includes: disposing, on a substrate, one or more nucleic acids that include a coding region and an anchoring agent, maintaining the substrate under conditions which enable the anchoring agent of each disposed nucleic acid to stably attached to the substrate"; para [0015]; " In one embodiment, the coding region encodes a polypeptide that includes a first amino acid sequence, e.g., an amino acid sequence of interest, and an affinity tag. The affinity tag binds to a binding agent"; para [0056]; "The nucleic acid can further include one or more of: a transcription promoter; a transcription regulatory sequence; a untranslated leader sequence; a sequence encoding a cleavage site; a recombination site; a 3' untranslated sequence") the peptide of interest and an affinity tag (para [0022]; " In one embodiment, the step of contacting the substrate with a translation effector includes disposing or flowing the translation effector onto the surface, for example, using a single dispensing action or multiple dispensing actions. In one embodiment, the substrate is also contacted with a transcription effector"); and a capture agent that selectively binds to the affinity tag (para [0046]; " In another aspect, the invention features a method that includes: contemporaneously providing (e.g., depositing)----------continued in next Supplemental Box----------

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous Supplemental Box

(claim 2 continued): (i) a binding agent that can interact with a tag and (ii) a nucleic acid that can be stably attached to a substrate and that includes a sequence encoding a first amino acid sequence and the tag onto a substrate"; sheet 1 fig 1) wherein the oligonucleotide is associated with the substrate surface (para [0005]). LaBaer does not teach that the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Consequently it would have been obvious to one of ordinary skill in the art to combine an oligonucleotide comprising a region encoding a peptide of interest, a region encoding an affinity tag and an untranslated region, as taught by LaBaer, with the peptide of interest and an affinity tag, again as taught by LaBaer, with a capture agent that selectively binds to the affinity tag, again as taught by LaBaer, with the oligonucleotide is associated with the substrate surface, again as taught by LaBaer, with the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent, as taught by Niemeyer, because it would have enabled construction of a oligonucleotide-peptide microarray.

As to claim 3, LaBaer further teaches that the untranslated region comprises a transcriptional start site and a ribosomal binding site (para [0115]; " The nucleic acid can further include one or more of: a transcription promoter; a transcription regulatory sequence; a untranslated leader sequence; a transcriptional terminator; and an internal ribosome entry site").

As to claim 4, Niemeyer further teaches that the capture agent is associated with the oligonucleotide (pg 400 fig 6).

As to claim 5, LaBaer teaches that the oligonucleotide is associated with the substrate surface via a linker (para [0040]; " In another aspect, the invention features a method that includes: providing a substrate that includes a plurality of addresses, each addresses including a nucleic acid that includes a coding region and an anchoring agent that stably attaches the nucleic acid to the substrate").

As to claim 6, LaBaer further teaches that the capture agent is associated with the linker (para [0129]; " "The binding agent can be attached to the substrate. For example, the substrate can be derivatized and the binding agent covalent attached thereto").

As to claim 7, LaBaer further teaches that the substrate is a planar support (para [0008]; " The substrate can be planar, e.g., have a horizontal plane in which the addresses are located at different discrete locations. The surface of the substrate can be flat (e.g., a glass slide) ").

As to claim 8, LaBaer further teaches that the substrate is a bead (para [0088]; " In yet another embodiment, an insoluble substrate (e.g., a bead or particle), is disposed at each address of the plurality, and the binding agent is attached to the insoluble substrate").

As to claim 9, LaBaer further teaches that the oligonucleotide is double-stranded (para [0055]; "The nucleic acid can be a RNA, or a DNA (e.g., a single-stranded DNA, or a double stranded DNA").

As to claim 10, Niemeyer further teaches that the oligonucleotide further comprises a region used for introduction of the capture agent to the oligonucleotide (pg 400 fig 6; A microarray of capture oligonucleotides is used as the immobilization matrix. Note that owing to the specificity of Watson.Crick base pairing, many different compounds can be sites pecifically immobilized simultaneously in a single step").

As to claim 12, LaBaer teaches a method of constructing an array (abstract), comprising the steps of:
(a) providing a surface comprising two or more constructs, the constructs
comprising a single-stranded oligonucleotide region encoding a peptide of interest
and an affinity tag (para [0005], [0015]; [0055]-" (para [0055]; "The nucleic acid can be a RNA, or a DNA (e.g., a single-stranded DNA, or a double stranded DNA");
(d) subjecting the double-stranded oligonucleotide region to a transcription
and translation event to produce a peptide comprising the peptide of interest and
the affinity tag (para [0458]; [0022]) wherein the protein produced in step (d) is captured by the capture agent of the construct following translation, thereby forming individual constructs
comprising the peptide associated with a substrate encoding the peptide (sheet 1 fig 1; para [0015]). LaBaer does not teach that the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). In addition, LaBaer does not teach (b) converting the single-stranded oligonucleotide region into a double stranded oligonucleotide region.---------claim continued in next Supplemental Box----------

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous Supplemental Box

(continuation of claim 12)-----However, an artisan of ordinary skill in the art would have readily appreciated that sequence specific regulators of eukaryotic gene expression (e.g. transcription binding, recognition and promoter sites), axiomatically, act through double stranded DNA targets only. Consequently, it would have been obvious that single-stranded oligonucleotides would have had to have been converted to a double stranded oligonucleotide before initiating transcription/translation. Furthermore, LaBaer does not teach (c); introducing an untranslated region comprising a ribosomal start site to the 5' end of the double-stranded oligonucleotide region, wherein the untranslated region is associated with a capture agent with the ability to form a binding pair with the affinity tag. However, LaBaer does teach modular construction of the oligonucleotide microarray involving hybridization, possible extension, and ligation of 2 separate oligonucleotides at each addressable position on the microarray (para [0445-0446]. An artisan of ordinary skill in the art would have readily appreciated that such universal elements as ribosomal binding sites and/or an untranslated region for attachment of a capture agent with the ability to form a binding pair with the affinity tag could have been engineered into the modular second oligonucleotide. Indeed, Niemeyer teaches association of an oligonucleotide attached to a capture agent through hybridization to the microarray attached oligonucleotide (pg 400 fig 6). Consequently, it would have been obvious to one of ordinary skill in the art to combine claim limitations (a), (b) and (d), as taught by LaBaer, with claim limitation (c), as taught by LaBaer in view of the observations of an artisan of ordinary skill in the art concerning introducing modular elements such as a ribosomal binding site into a microarray by way of a two oligonucleotide ligation at each addressable position of the microarray, with oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent, as taught by Niemeyer, because it would have enabled construction of a supramolecular array that would function as a protein biochip.

As to claim 13, LaBaer teaches a method of constructing an array (abstract), comprising the steps of:
(a) providing a substrate comprising a surface with two or more constructs associated on the surface , the constructs comprising a single-stranded oligonucleotide encoding a peptide of interest and an affinity tag (para [0005], [0015], [0055]);
(e) subjecting the double-stranded oligonucleotide to a transcription and translation event to produce a peptide from the double-stranded oligonucleotide; wherein the protein produced in step (e) is captured by the capture agent of the construct; and wherein the resulting array comprises discrete units comprising a nucleic acid associated with substrate and the peptide encoded by the nucleotide also associated with the substrate through a capture agent (sheet 1 fig 1; para [0015]). LaBaer does not specifically teach the peptide encoded by the nucleic acid is associated by the nucleic acid. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). In addition, LaBaer does not teach (d) converting the single-stranded oligonucleotide region into a double stranded oligonucleotide region. However, an artisan of ordinary skill in the art would have readily appreciated that sequence specific regulators of eukaryotic gene expression (e.g. transcription binding, recognition and promoter sites), axiomatically, act through double stranded DNA targets only. Consequently, it would have been obvious that single-stranded oligonucleotides would have had to have been converted to a double stranded oligonucleotide before initiating transcription/translation (i.e. claim limitation (e)). Furthermore, LaBaer does not teach (b) ligating a second, universal oligonucleotide to the oligonucleotides of the constructs, wherein the universal oligonucleotide comprises an untranslated region comprising a ribosomal binding site. However, LaBaer does teach modular construction of the oligonucleotide microarray involving hybridization, possible extension, and ligation of 2 separate oligonucleotides at each addressable position on the microarray (para [0445-0446]. An artisan of ordinary skill in the art would have readily appreciated that such universal elements as ribosomal binding sites and/or an untranslated region for attachment of a capture agent with the ability to form a binding pair with the affinity tag could have been engineered into the modular second oligonucleotide. Indeed, Niemeyer teaches association of an oligonucleotide attached to a capture agent through hybridization to the microarray attached oligonucleotide (pg 400 fig 6), thus fulfilling claim limitation (c). Consequently, it would have been obvious to one of ordinary skill in the art to combine claim limitations (a), (d) and (e), as taught by LaBaer, with claim limitation (b), as taught by LaBaer, in view of the observations of an artisan of ordinary skill in the art concerning introducing modular elements such as a ribosomal binding site into a two oligonucleotide ligation of a microarray, with claim limitation (c), as taught by Niemeyer, because it would have enabled construction of a supramolecular array that would function as a protein biochip.

As to claim 14, LaBaer teaches method of constructing an array (abstract), comprising the steps of:
(a) providing a surface comprising two or more constructs, the constructs comprising a single-stranded oligonucleotide region (para [0055]) having a sequence that is the sequence encoding a peptide of interest and an affinity tag (para [0005], [0015]); LaBaer does not teach the single stranded nucleotide is a reverse complement sequence encoding the peptide of interest. However, an artisan of ordinary skill in the art would have readily appreciated that a reverse complement sequence could have readily hybridized with a mRNA molecule and could have utilized it to hybridize with mRNA introduced to the microRNA. Furthermore, LaBaer does not teach (b) converting the single-stranded oligonucleotide region into a double stranded oligonucleotide region. However, an artisan of ordinary skill in the art would have readily appreciated that sequence specific regulators of eukaryotic gene expression (e.g. transcription binding, recognition and promoter sites), axiomatically, act through double stranded DNA targets only. Consequently, it would have been obvious that single-stranded oligonucleotides would have had to have been converted to a double stranded oligonucleotide before initiating transcription/translation (i.e. claim limitation (d)). LaBaer further teaches (d) subjecting the double-stranded oligonucleotide region to a transcription and translation event to produce a peptide comprising the peptide of interest and the affinity tag wherein the protein produced in step (d) is captured by the capture agent of the construct following translation, thereby forming individual constructs comprising the peptide associated with the substrate and an oligonucleotide encoding the peptide associated with the substrate. LaBaer does not specifically teach the peptide encoded by the nucleic acid is associated with the nucleic acid. ----------claim continued in next Supplemental Box----------

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous Supplemental Box

(continuation of claim 14)----------However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). LaBaer does not teach (c); introducing an untranslated region comprising a ribosomal start site to the 5' end of the double-stranded oligonucleotide region, wherein the untranslated region is associated with a capture agent with the ability to form a binding pair with the affinity tag. However, LaBaer does teach modular construction of the oligonucleotide microarray involving hybridization, possible extension, and ligation of 2 separate oligonucleotides at each addressable position on the microarray (para [0445-0446]. An artisan of ordinary skill in the art would have readily appreciated that such universal elements as ribosomal binding sites and/or an untranslated region for attachment of a capture agent with the ability to form a binding pair with the affinity tag could have been engineered into the modular second oligonucleotide. Indeed, Niemeyer teaches association of an oligonucleotide attached to a capture agent through hybridization to the microarray attached oligonucleotide (pg 400 fig 6). Consequently, it would have been obvious to one of ordinary skill in the art to combine claim limitations (a), (b) and (d), as taught by LaBaer, in view of the observations of an artisan of ordinary skill, with claim limitation (c), as taught by LaBaer, in view of the observations of an artisan of ordinary skill in the art concerning introducing modular elements such as a ribosomal binding site into a microarray by way of a two oligonucleotide ligation step of the microarray, with attachment of a peptide of interest to an oligonucleotide encoding the peptide via a capture agent, as taught by Niemeyer, because it would have enabled construction of a supramolecular array that would function as a protein biochip.

As to claim 15, LaBaer teaches a method of constructing an array (abstract), comprising the steps of: (a) providing a surface comprising two or more constructs, the constructs
comprising a single-stranded oligonucleotide region (para [0055]) having a sequence that is the
sequence encoding a peptide of interest and an affinity tag (para [0005], [0015]); LaBaer does not teach the single stranded nucleotide is a reverse complement sequence encoding the peptide of interest. However, an artisan of ordinary skill in the art would have readily appreciated that a reverse complement sequence could have readily hybridized with a mRNA molecule and could have utilized it to hybridize with mRNA introduced to the microRNA. LaBaer further does not teach (d) converting the single-stranded oligonucleotide regions of the constructs into double-stranded oligonucleotide regions. However, an artisan of ordinary skill in the art would have readily appreciated that sequence specific regulators of eukaryotic gene expression (e.g. transcription binding, recognition and promoter sites), axiomatically, act through double stranded DNA targets only. Consequently, it would have been obvious that single-stranded oligonucleotides would have had to have been converted to a double stranded oligonucleotide before initiating transcription/translation (i.e. claim limitation (e)). LaBaer further teaches (e) subjecting the double-stranded oligonucleotide region to a transcription and translation event to produce a peptide comprising the peptide of interest and the affinity tag wherein the protein produced in step (e) is captured by the capture agent of the construct following translation, thereby forming individual constructs comprising the peptide associated with the substrate and an oligonucleotide encoding the peptide associated with the substrate. LaBaer does not specifically teach the peptide encoded by the nucleic acid is associated by the nucleic acid. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Furthermore, LaBaer does not teach (b) ligating a second, universal oligonucleotide to the oligonucleotides of the constructs, wherein the universal oligonucleotide comprises an untranslated region comprising a ribosomal binding site. However, LaBaer does teach modular construction of the oligonucleotide microarray involving hybridization, possible extension, and ligation of 2 separate oligonucleotides at each addressable position on the microarray (para [0445-0446]. An artisan of ordinary skill in the art would have readily appreciated that such universal elements as ribosomal binding sites and/or an untranslated region for attachment of a capture agent with the ability to form a binding pair with the affinity tag could have been engineered into the modular second oligonucleotide. Indeed, Niemeyer teaches association of an oligonucleotide attached to a capture agent through hybridization to the microarray attached oligonucleotide (pg 400 fig 6), thus fulfilling claim limitation (c). Consequently, it would have been obvious to one of ordinary skill in the art to combine claim limitations (a), (d) and (e), as taught by LaBaer, with claim limitation (b), as taught by LaBaer, in view of the observations of an artisan of ordinary skill in the art concerning introducing modular elements such as a ribosomal binding site into a two oligonucleotide ligation of a microarray, with claim limitation (c), as taught by Niemeyer, because it would have enabled construction of a supramolecular array that would function as a protein biochip.

As to claim 23 and 30, LaBaer teaches that the produced peptides are bound to the substrate (para [0015], sheet 1 fig 1). LaBaer does not teach that the produced peptides are attached to their respective nucleic acid substrates. However, Niemeyer teaches that the produced peptides are attached to their respective nucleic acid substrates (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Consequently it would have been obvious to one of ordinary skill in the art to combine peptides produced by in vitro transcription/translation of an array, as taught by LaBaer, with the produced peptides are attached to their respective nucleic acid substrates, as taught by Niemeyer, because it would have enabled construction of a protein array where the produced peptides are at discrete spatially addressable locations on the array.
----------continued in next Supplemental Box----------

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
previous Supplemental Box

Claim 11 lacks an inventive step under PCT Article 33(3) as being obvious over LaBaer, in view of Niemeyer, in further view of the publication titled " High sensitivity multianalyte immunoassay using covalent DNA-labeled antibodies and polymerase chain reaction" by HENDERSON et al. (hereinafter "Henderson").

As to claim 11, Niemeyer teaches association of capture agent with substrate attached oligonucleotide by DNA annealing (pg 400 fig 6). Neither Niemeyer nor LaBaer teaches that the region is associated to the oligonucleotide via a linker molecule. However, Henderson teaches a region is associated to the oligonucleotide via a linker molecule (pg 523 fig 2; "Design of DNA-antibody reporter conjugates--chemical crosslinker). An artisan of ordinary skill in the art would have readily appreciated that a linker region was well known in the art for covalently linking DNA directly to a protein molecule such as an antibody (i.e. capture agent). Consequently, it would have been obvious to one of ordinary skill in the art to combine association of capture agent with substrate attached oligonucleotide, as taught by Niemeyer, with region of association is a linker, as taught by Henderson, because it would have enabled attaching the capture agent directly to the oligonucleotide.

Claims 16-21 lack an inventive step under PCT Article 33(3) as being obvious over LaBaer, in view of Niemeyer, in further view of the publication titled " Next-generation high-density self-assembling functional protein arrays" by RAMACHANDRAN et al. (hereinafter "Ramachandran").

As to claim 16, LaBaer teaches a method of identifying an agent that binds to a peptide of interest, comprising: providing an array (abstract) comprising:
a substrate having a surface (para [0005]);
two or more individual constructs associated on the surface of the substrate, wherein the individual constructs comprise:
(i) an oligonucleotide encoding a peptide of interest (para [0005], [0015]) and
(ii) the peptide of interest (para [0022]; wherein the oligonucleotide is associated with the substrate surface (para [0005]). LaBaer does not teach that the peptide is associated with the oligonucleotide. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Furthermore, LaBaer does not specifically teach exposing the array to an agent; and detecting the presence or absence of binding of the agent to the peptide of interest. However, Ramachandran teaches exposing the array to an agent; and detecting the presence or absence of binding of the agent to the peptide of interest (pg 537 left col para 1; " To confirm protein function on high-density arrays, we printed an array expressing 647 unique genes in duplicate, including 449 genes that we had not previously tested (Fig. 3a and Supplementary Table 3 online). We tested for binary interactions between several well characterized interacting pairs including Jun-Fos and p53-MDM2 (Fig. 3b). We co-expressed the query protein along with the arrayed proteins by adding the appropriate cDNA clone (without a GST tag) to the cell-free expression lysate. After protein expression and washing, we treated the arrays with protein-specific antibodies to detect the query protein, revealing the positions where it bound. Using Jun, Fos and MDM2 as queries, we detected selective binding to their appropriate interacting partners"; pg 538 fig 3B). An artisan of ordinary skill in the art would have readily appreciated that binding of a protein through protein-protein interaction was well known in the art at the time of the invention. Consequently, it would have been obvious to one of ordinary skill in the art to combine an oligonucleotide bound to a substrate encoding a protein of interest, as taught by LaBaer, with a peptide of interest associated with an array, also taught by LaBaer, with peptide is associated with the oligonucleotide, as taught by Niemeyer, with detecting the presence or absence of binding of an agent to the peptide of interest, as taught by Ramachandran, because it would have enabled a functional protein biochip that identifies an agent that binds to a peptide of interest.

As to claim 17, Ramachandran further teaches the agent is provided in a sample, and wherein presence of binding to the peptide of interest indicates the presence of the agent in a sample (pg 537 left col para 1; pg 538 fig 3B).

As to claim 18, Ramachandran further teaches that the agent is provided in a sample, and wherein absence of binding to the peptide of interest indicates an absence of the agent in a sample (pg 537 left col para 1; pg 538 fig 3B).
----------continued in next Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/59327

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous Supplemental Box

As to claim 19, LaBaer teaches a method of identifying an agent that binds to a peptide of interest, comprising:
providing an array (abstract) comprising:
a substrate having a surface (para [0005]); two or more individual constructs associated on the surface of the substrate, wherein the individual constructs comprise:
(i) an oligonucleotide comprising a region encoding a peptide of interest, a region encoding an affinity tag, and an untranslated region (para [0005], [0015], [0056])
(ii) a peptide comprising the peptide of interest and an affinity tag (para [0022]); and
(iii) a capture agent that selectively binds to the affinity tag (para [0046]); wherein the oligonucleotide is associated with the substrate surface (para [0005]). LaBaer does not teach that the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent. However, Niemeyer teaches oligonucleotide-antibody array where the peptide is associated with the oligonucleotide through binding of the affinity tag to the capture agent (pg 400 fig 6; antibody microarray where antibody is the capture agent). An artisan of ordinary skill in the art would have readily appreciated that the capture agent could have been attached to the oligonucleotide directly, as taught by Niemeyer, or attached directly to the substrate, as taught by LaBaer (sheet 1 fig 1). Furthermore, LaBaer does not teach exposing the array to an agent; and detecting the presence or absence of binding of the agent to the peptide of interest. However, Ramachandran teaches exposing the array to an agent (pg 537 left col para 1); and detecting the presence or absence of binding of the agent to the peptide of interest (pg 537 left col para 1, pg 538 fig 3B). An artisan of ordinary skill in the art would have readily appreciated that binding of a protein through protein-protein interaction was well known in the art at the time of the invention. Consequently, it would have been obvious to one of ordinary skill in the art to combine an oligonucleotide bound to a substrate encoding a protein of interest, as taught by LaBaer, with a peptide of interest associated with an array, also taught by LaBaer, with capture agent that selectively binds to affinity tag, also as taught by LaBaer, with peptide is associated with the oligonucleotide, as taught by Niemeyer, with detecting the presence or absence of binding of an agent to the peptide of interest, as taught by Ramachandran, because it would have enabled a functional protein biochip that identifies an agent that binds to a peptide of interest.

As to claim 20, Ramachandran further teaches that the agent is provided in a sample (pg 537 left col para 1), and wherein the presence of binding to the peptide of interest indicates the presence of the agent in a sample (pg 538 fig 3B).

As to claim 21, Ramachandran the agent is provided in a sample (pg 537 left col para 1), and wherein absence of binding to the peptide of interest indicates an absence of the agent in a sample (pg 538 fig 3B).

Claims 1-35 have industrial applicability as defined in PCT Article 33(4) because the subject matter can be made or used by industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PGNS007PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2011/031308	International filing date *(day/month/year)* 05 April 2011 (05.04.2011)	Priority date *(day/month/year)* 05 April 2010 (05.04.2010)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PROGNOSYS BIOSCIENCES, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 09 October 2012 (09.10.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Lingfei Bai e-mail: pt02.pct@wipo.int

Form PCT/IB/373 (January 2004)

From the
INTERNATIONAL SEARCHING AUTHORITY

To: SARAH BRASHEARS
CONVERGENT LAW GROUP LLP
475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 JUN 2011
Applicant's or agent's file reference: PGNS007PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 11/31308	05 April 2011 (05.04.2011)	05 April 2010 (05.04.2010)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68 (2011.01)
USPC - 435/6

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	25 May 2011 (25.05.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31308

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31308

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	4, 5, 38, 56	YES
	Claims	1-3, 6-37, 39-55, 57	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-57	NO
Industrial applicability (IA)	Claims	1-57	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-3, 6-37, 39-55 and 57 lack novelty under PCT Article 33(2) as being anticipated by US 2006/0046313 A1, Roth et al., (hereinafter Roth).

Regarding claim 1, Roth teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (para [0032] and [0140]), wherein the assay system performs the following steps:
providing a sample affixed to a support (para [0033] - 'The invention reverse phase protein assay includes forming one or more arrays of cell lysates obtained from one or more tissue samples from a patient. For example, individual cells of a cell population obtained from a patient tissue sample may be lysed and extracted 310 to form an array. If cell lysates are obtained from more than one tissue sample, two or more arrays may be formed, with an array containing the cell lysates from a particular tissue sample of the patient In an array of defined locations 320 on a substrate, a mixture of extracted cell proteins 330, 331, 332 is immobilized at (for example, spotted onto) individual defined locations,');
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 (para [0033] - 'Then the cell lysate spots at the defined locations are contacted with a mixture of COIN-labeled probes 330, 332 under conditions suitable to form analyte-COIN complexes 341, 342, 343 as the probes bind individual protein in the spots through both specific and degenerate binding.', and para [0097]);
allowing the encoded probes to interact with the biological targets (para [0033]);
separating encoded probes that interact with the biological targets from encoded probes that do not interact with the biological targets (para [0033] - 'After removal of unbound COIN-labeled probes from the array');
determining all or a portion of a sequence of the encoded probes (para [0104] and [0122]), and
associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample (para [0033] - 'the array 350 may be scanned 340 to detect SERS signals at the defined locations 320 so as to identify and compile data regarding the presence of the known analytes in the tissue sample.').

Regarding claim 27, Roth teaches an assay system to determine spatial patterns of abundance or activity or both of multiple nucleic acid targets at multiple sites in a sample (para [0032] and [0140]), wherein the assay system performs the following steps:
providing a sample affixed to a support (para [0033]);
delivering oligonucleotide probes for multiple nucleic acid targets to the multiple sites in the sample in a known spatial pattern (para [0033] and [0097]);
allowing the oligonucleotide probes to hybridize with the nucleic acid targets (para [0033] and [0102]-[0103]);
washing unhybridized encoded oligonucleotide probes from the sample (para [0033] and [0102]-[0103]);
delivering one or more encoding agents to locations of the multiple sites in the sample according to a known spatial pattern, wherein the combination of encoding agents delivered to each site is different (para [0086] and [0097] - encoding agents are 'Raman-active organic compounds');
coupling the encoding agents and the oligonucleotide probes to form encoded probes (para [0086]);
determining all or a portion of a sequence of the encoded probes using high throughput sequencing (para [0104] and [0122]), and
associating the abundance or activity or both of multiple biological targets to the locations of multiple sites in the sample (para [0033], [0104] and [0122]).

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31308

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
citations and explanations from box V.2

Regarding claim 40, Roth teaches an assay system to determine spatial patterns of abundance or activity or both of multiple protein targets at multiple sites in a sample (para [0032] and [0140]), wherein the assay system performs the following steps:
providing a sample affixed to a support (para [0033]);
delivering encoded probes for the multiple protein targets to the multiple sites in the sample in a known spatial pattern, wherein 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 (para [0033], [0092] and [0097]);
allowing the encoded probes to interact with the protein targets (para [0033]);
separating encoded probes that interact with the protein targets from encoded probes that do not interact with the protein targets (para [0033]);
determining all or a portion of a sequence of the encoded probes by high throughput sequencing (para [0104] and [0122]), and
associating the abundance or activity or both of the multiple protein targets to the locations of the multiple sites in the sample (para [0033]).

Regarding claim 2, Roth teaches the biological targets are nucleic acids and the encoded probes are oligonucleotides (para [0102]-[0103]).

Regarding claim 3, Roth teaches there are two encoded probes for each of the multiple nucleic acid targets (para [0047] and [0091]).

Regarding claim 6, Roth teaches probe regions of the encoded probes comprise antibodies (para [0069]).

Regarding claim 7, Roth teaches the probe regions of the encoded probes are aptamers (para [0069]).

Regarding claim 8, Roth teaches the probe regions of the encoded probes are small molecules (para [0069]).

Regarding claims 9, 39 and 50, Roth teaches an amplification step between the separating step and the determining step (para [0105]).

Regarding claim 10, Roth teaches the determining step is performed by nucleic acid sequencing (para [0104] and [0122]).

Regarding claim 11, Roth teaches the sequencing is high-throughput digital nucleic acid sequencing (para [0039], [0122]-[0124]).

Regarding claims 12-19, 28-33, 41-46, Roth teaches the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000,000 (para [0097]-[0098] and [0138]).

Regarding claims 20-22, 34, 35, 47-49, Roth teaches the sequence of at least one million encoding probes are determined in parallel (para [0097]-[0098], [0104] and [0138]).

Regarding claim 23, Roth teaches the known spatial pattern is determined by histological features of the sample (para [0036] and [0038]).

Regarding claim 24, Roth teaches software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step and the associating step (para [0123]-[0124]).

Regarding claim 25, Roth teaches the probe regions of the encoded probes are proteins (para [0092]), and the separating step is accomplished by encoded probes that interact with the biological targets being captured by an affinity capture agent (para [0027] - 'contacting a biological sample 110 with a substrate 100 having a set of capture antibodies 120 that bind specifically to different proteins attached at defined locations on the substrate 100 to allow formation of antibody-protein complexes 130. The antibody-protein complexes are then contacted with a set of COIN-labeled probes 140 comprising a probe moiety 150 that binds specifically to a known protein analyte').

Regarding claim 26, Roth teaches the probe regions of the encoding probes are nucleic acids and the separating step is accomplished by a washing of the sample (para [0084]-[0085]).

Regarding claim 36, Roth teaches two oligonucleotide probes are delivered for each of the multiple nucleic acid targets (para [0083] - 'the term "oligonucleotide" is used herein to refer to a polynucleotide that is used as a primer or a probe. Generally, an oligonucleotide useful as a probe or primer that selectively hybridizes to a selected nucleotide sequence is at least 6 nucleotides to about 9 nucleotides in length.' --oligonucleotide probes are used as primers; later amplification would require the primers are in pairs).

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US 11/31308

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous supplemental box

Regarding claim 37, Roth teaches the coupling step is performed by ligation (para [0083] - 'Polynucleotide probes used in the invention methods are useful for detecting and hybridizing under suitable conditions to complementary polynucleotides in a biological sample by pairing a known polynucleotide probe with a known Raman-active COIN comprising one or more Raman-active organic compounds, as described herein. A covalent phosphodiester bond generally ligates the nucleotides of a polynucleotide sequence. However, the covalent bond also may be any of numerous other bonds, including a thiodiester bond, a phosphorothioate bond, a peptide-like amide bond or any other bond known to those in the art as useful for linking nucleotides to produce synthetic polynucleotides').

Regarding claim 51, Roth teaches the protein targets are enzymes (para [0090]), and the probe regions of the encoded probes are substrates, putative substrates of both for the enzymes (para [0069] and [0090]).

Regarding claim 52, Roth teaches the probe regions of the encoded probes are affinity capture agents (para [0043]).

Regarding claim 53, Roth teaches the probe regions of the encoded probes are antibodies (para [0069]).

Regarding claim 54, Roth teaches the probe regions of the encoded probes are aptamers (para [0069]).

Regarding claim 55, Roth teaches separating encoded probes that interact with the protein targets from encoded probes that do not interact with the protein targets is accomplished by an affinity capture agent that distinguishes encoded probes that interact with the protein targets from encoded probes that do not interact with the protein targets (para [0027] and [0042]-[0043]).

Regarding claim 57, Roth teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (para [0032] and [0140]), wherein the assay system performs the following steps:
providing a sample affixed to a support (para [0033]);
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 and identifies the biological target (para [0033], [0092] and [0097]);
allowing the encoded probes to interact with the biological targets (para [0033]);
determining all or a portion of a sequence of the encoded probes (para [0104] and [0122]), and
associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample (para [0033]).

Claims 4, 5, 38 and 56 lack an inventive step under PCT Article 33(3) as being obvious over Roth in view of US 6,344,316 B1, Lockhart et al., (hereinafter Lockhart).

Regarding claim 4, Roth teaches the multiple biological targets are proteins (para [0069]), the probe regions of the encoding probes are proteins (para [0073]). Roth does not specifically teach the coding tags comprise oligonucleotides. However, Roth does teach the coding tags are unique and florescent for scanning based detection (para [0031] and [0055]). Lockhart teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (abstract), comprising encoded probes for the multiple biological targets (abstract), wherein the coding tags comprise oligonucleotides (abstract and col. 24, ln 8-30). It would have been obvious to one of ordinary skill in the art to have prepared 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 coding tags comprise oligonucleotides, in view of Roth teaching the coding tags are unique and florescent for scanning based detection (para [0031] and [0055]), and in light of Lockhart teaching unique and florescent coding tags comprising oligonucleotides (col. 24, ln 37-61), since a skilled artisan would have readily appreciated use of the labeling methods taught by Lockhart applied to the probes taught by Roth, since they can be detected in a microarray.

Regarding claim 5, Roth teaches the multiple biological targets comprise enzymes (para [0090]).

Regarding claim 38, Roth does not specifically teach the coupling step is performed by extension followed by ligation. Lockhart teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (abstract), comprising coupling the one or more encoding agents and one or more oligonucleotide probes to form encoded probes (abstract and col. 24, ln 8-30), wherein the coupling step is performed by extension followed by ligation (col. 24, ln 8-30). It would have been obvious to one of ordinary skill in the art to have prepared 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 coupling step is performed by extension followed by ligation, in view of Roth teaching the probe is coupled to the encoding agents by various methods including ligation (para [0083]), and in light of Lockhart teaching coupling of one or more encoding agents and one or more oligonucleotide probes to form encoded probes (col. 24, ln 8-30), wherein the coupling step is performed by extension followed by ligation (col. 24, ln 8-30), since a skilled artisan would have readily appreciated use of the coupling methods taught by Lockhart applied to the probes taught by Roth, since they are both polynucleotide based probes, and could therefore be coupled via extension.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31308

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous supplemental box

Regarding claim 56, Roth does not specifically teach the coding tags are oligonucleotides. However, Roth does teach the coding tags are unique and florescent for scanning based detection (para [0031] and [0055]). Lockhart teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (abstract), comprising encoded probes for the multiple biological targets (abstract), wherein the coding tags comprise oligonucleotides (abstract and col. 24, ln 8-30). It would have been obvious to one of ordinary skill in the art to have prepared 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 coding tags comprise oligonucleotides, in view of Roth teaching the coding tags are unique and florescent for scanning based detection (para [0031] and [0055]), and in light of Lockhart teaching unique and florescent coding tags comprising oligonucleotides (col. 24, ln 37-61), since a skilled artisan would have readily appreciated use of the labeling methods taught by Lockhart applied to the probes taught by Roth, since they can be detected in a microarray.

Claims 1-57 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in the industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PGNS008PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2011/031163	International filing date *(day/month/year)* 05 April 2011 (05.04.2011)	Priority date *(day/month/year)* 05 April 2010 (05.04.2010)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PROGNOSYS BIOSCIENCES, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 09 October 2012 (09.10.2012)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: SARAH BRASHEARS
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475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	23 MAY 2011
Applicant's or agent's file reference PGNS008PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 11/31163	05 April 2011 (05.04.2011)	05 April 2010 (05.04.2010)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68 (2011.01)
USPC - 435/6, 287.2, 7.1, 91.2

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	16 May 2011 (16.05.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/31163

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-37	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-37	NO
Industrial applicability (IA)	Claims	1-37	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-12 and 16-29 lack an inventive step under PCT Article 33(3) as being obvious over US 2006/0134669 A1 (Casasanta), in view of US 2003/0224419 A1 to Corcoran et al. (hereinafter "Corcoran").

As to claim 1, Casasanta teaches a method for identifying binding agents that form a binding pair, comprising:
a) providing a first set of binding constructs immobilized on a support surface, wherein each binding construct of the first set of binding constructs comprises a first binding agent and a first nucleic acid tag unique to the first binding agent (para [0014]...first component of the binding pair is immobilized on a spot of the microarray and the second component is bound to a protein...binding pairs can include...complementary strands of DNA or RNA);
b) providing a second set of binding constructs in solution, wherein each binding construct of the second set of binding constructs comprises a second binding agent and a second nucleic acid tag unique to the second binding agent, and wherein either or both of the first and second sets of binding constructs comprises at least ten different binding agents (para [0014]...second component of the binding pair is introduced to the microarray by...solution flooding);
c) combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs, thereby co-locating the first nucleic acid tags and the second nucleic acid tags (para [0014]...complementary strands of DNA or RNA are bound together, therefore are co-located);
d) creating binding event identifiers from the co-located first and second nucleic acid tags (para [0012]...spectral shifts can be measured for respective molecular binding events).

Casasanta does not specify what Corcoran does in an alternative ligation-based sequencing scheme (para [0022]), namely:
e) determining a sequence of each binding event identifier, wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair (para [0002]...massively parallel signature sequencing).

Neither Casasanta nor Corcoran specify at least ten different binding agents. Casasanta does teach testing a variety of binding pair types (para [0014]...antigen/antibody, peptide/peptide, complementary DNA/RNA), discriminating between different spots (para [0018]) and testing up to 1000 spots (para [0013]). It would have been obvious to one skilled in the art to use at least ten different binding agents, for greater economy of testing scale. Further, it would have been obvious to one skilled in the art to combine the binding pair sequence of Corcoran with the method of Casasanta to enable more specific detection of binding events between a variety of biological molecules.

As to claim 2, Corcoran further teaches wherein the sequence of the binding event identifier is determined by digital readout 36, 38 (Fig 3...display controller, display device).

As to claim 3, Corcoran further teaches wherein the sequence of the binding event identifier is determined by high throughput digital sequencing (para [0022]...massively parallel signature sequencing...identify simultaneously signatures of very large numbers of DNAs attached to microbeads disposed in closely packed arrays).

As to claims 4-7, Casasanta and Corcoran make obvious the method of claim 1. Neither specifies wherein either or both of the first and second sets of binding constructs comprises at least twenty-five, one hundred, one thousand or at least five thousand different binding agents, respectively. Casasanta teaches a 36x28 microarray having 1008 spots (para [0013]) and that the binding pairs may comprise complementary strands of DNA or RNA (para [0014]). Corcoran teaches each binding pair has a unique signature (para [0002]...massively parallel signature sequencing; [0021]...element-to-element differences within microarrays; [0022]...ligation-based sequencing scheme). It would have been obvious to one skilled in the art to use the Corcoran digital sequencing method of an array of any number of spots, to uniquely identify the sequences that are bound.

As to claims 8, Corcoran further teaches wherein the sequences of the binding event identifiers are determined in parallel (para [0002]...massively parallel signature sequencing)

As to claims 9-10, Casasanta and Corcoran make obvious the method of claim 8. Casasanta teaches microarrays having 1008 spots (para [0013]). Corcoran teaches identifying in parallel (para [0002]) sequences of binding pairs on a microarray (para [0002]; [0083]...microbead array display). Neither specifies the sequence of 100,000 binding events determined in parallel. However, it would have been obvious to one skilled in the art that the technique of Corcoran could be applied to microarrays of any dimension.

Please continue to the supplemental page

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Citations and Explanations, Box V(2):

As to claim 11, Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches wherein the binding event identifier is created by coupling the first and second nucleic acid tags (Fig 5...note the sticky ends and the two ligation steps).

As to claim 12, Casasanta and Corcoran make obvious the method of claim 10. Corcoran further teaches wherein the coupling of the first and second tags is accomplished by ligation (Fig 5...note the sticky ends and the two ligation steps).

As to claim 16, Casasanta and Corcoran make obvious the method of claim 1. Casasanta further teaches wherein at least one of the first and second binding agents is a peptide (para [0006]...peptide-peptide pair).

As to claim 17, Casasanta and Corcoran make obvious the method of claim 16. Casasanta further teaches wherein the first and second binding agents are peptides (para [0006]...peptide-peptide pair).

As to claim 18, Casasanta and Corcoran make obvious the method of claim 16. Casasanta further teaches wherein the second binding agent is an antibody (para [0006]...hapten-antibody pair, antigen-antibody pair).

As to claim 19, Casasanta and Corcoran make obvious the method of claim 16, wherein the second binding agent is a small molecule (para [0006]...peptides can be small molecules; avidin and biotin are small molecules).

As to claim 20, Casasanta and Corcoran make obvious the method of claim 1. Casasanta further teaches wherein the first or second binding agent is an aptamer (para [0014]...biotin, antigen, antibody, oligonucleotides are all aptamers).

As to claim 21, Casasanta and Corcoran make obvious the method of claim 20. Casasanta further teaches wherein the first binding agent is a peptide and the second binding agent is an aptamer (para [0014]...first component immobilized on a spot in the microarray...second component introduced by solution flooding...combinations can include antigen/antibody, peptide/peptide, or complementary strands of DNA or RNA...all of these potential components of the binding pair can function as aptamers).

As to claim 22, Casasanta and Corcoran make obvious the method of claim 1. Casasanta further teaches wherein the support is a microarray 8 (para [0012]).

As to claim 23, Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches wherein the support is a bead (Fig 5...see 'image microbeads').

As to claim 24, Casasanta and Corcoran make obvious the method of claim 1. Casasanta further teaches the step of adding a third binding agent in the combining step (para [0014]...third chemical component can bind the complex of the first component and the second component).

As to claim 25, Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches the step of identifying binding agents that bind promiscuously (para [0096]...optical measurements were adjusted for system background noise, which can result from nonspecific binding of probes...or incomplete ligation).

As to claim 26, Casasanta and Corcoran make obvious the method of claim 25. Corcoran further teaches wherein data from promiscuous binding agents is subtracted from binder identifier results of the determining step (para [0096]...optical measurements were adjusted for system background noise, which can result from nonspecific binding of probes...or incomplete ligation).

As to claim 27, Casasanta and Corcoran make obvious the method of claim 25. Corcoran further teaches wherein a quantitative metric can be derived for the extent of promiscuity of promiscuous binding agents (para [0096]...computing the background noise for each signal set...and subtracting that computed value from each of the four fluorescence values...).

As to claim 28. Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches wherein false positives are identified within the binding event identifiers and data from the false positives subtracted from binder identifier results of the determining step (para [0096]...computing the background noise for each signal set...and subtracting that computed value from each of the four fluorescence values...).

As to claim 29, Casasanta and Corcoran make obvious the method of claim 1. Corcoran further teaches the step of determining the number of each binding event identifier sequenced (para [0021]...counting of tags or signatures of DNA fragments).

Claims 13-15 and 30-37 lack an inventive step under PCT Article 33(3) as being obvious over Casasanta, in view of Corcoran and further in view of US 7,378,242 B2 (Hurt).

As to claim 13, Casasanta and Corcoran make obvious the method of claim 10. Neither specifies wherein the coupling of the first and second tags is accomplished by primer extension. Hurt teaches coupling strands of DNA by primer extension (col 3, ln 64-col 4, ln 16). It would have been obvious to one skilled in the art to couple the first and second tags by primer extension, as taught by Hurt, with the method of Casasanta and Corcoran, to more precisely control the nucleotide sequence.

Please continue

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Citations and Explanations, Box V(2):

As to claim 14, Casasanta and Corcoran make obvious the method of claim 1. Neither teaches wherein one or both of the first and second binding constructs comprise a primer sequence. Hurt teaches binding two pieces of DNA by primer extension (col 3, ln 64-col 4, ln 16). It would have been obvious to one skilled in the art to couple the first and second tags by primer extension, as taught by Hurt, with the method of Casasanta and Corcoran, to more precisely control the nucleotide sequence.

As to claim 15, Casasanta, Corcoran and Hurt make obvious the method of claim 13. Hurt further teaches the step of amplifying the binding event identifier after the creating step and before the determining step (col 6, ln 55-60...multiple temperature cycles can be used to amplify the extension product...different temperatures can be used for the three steps: association of the primer to the template, extension, and separation of the LPE product from the template).

As to claim 30, Casasanta teaches a method for identifying binding agents that form a binding pair, comprising:

a) providing a first set of binding constructs immobilized on a support surface, wherein each binding construct of the first set of binding constructs comprises a first binding agent, and a first nucleic acid tag unique to the first binding agent (para [0014]...first component of the binding pair is immobilized on a spot of the microarray and the second component is bound to a protein...binding pairs can include...complementary strands of DNA or RNA);
b) providing a second set of binding constructs in solution, wherein each binding construct of the second set of binding constructs comprises a second binding agent, and a second nucleic acid tag unique to the second binding agent, and wherein either or both of the first and second sets of binding constructs comprises at least ten different binding agents (para [0014]...second component of the binding pair is introduced to the microarray by...solution flooding);
c) combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs, thereby co-locating the first nucleic acid tags and the second nucleic acid tags (para [0014]...complementary strands of DNA or RNA are bound together, therefore are co-located);
d) creating binding event identifiers from the co-located first and second nucleic acid tags (para [0012]...spectral shifts can be measured for respective molecular binding events).

Casasanta does not specify:
wherein the first set of binding constructs also comprises a first primer region,
wherein the second set of binding constructs comprises a second primer region, or
e) determining a sequence of at least one thousand binding event identifiers, wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair; and
f) determining the frequency of each binding event identifier sequenced.

Casasanta teaches a 36x28 microarray having 1008 spots (para [0013]) and that the binding pairs may comprise complementary strands of DNA or RNA (para [0014]). Corcoran teaches each binding pair has a unique signature (para [0002]...massively parallel signature sequencing; [0021]...element-to-element differences within microarrays; [0022]...ligation-based sequencing scheme). It would have been obvious to one skilled in the art to use the Corcoran digital sequencing method of an array of any number of spots, to uniquely identify the sequences that are bound. Corcoran further teaches the step of determining the number of each binding event identifier sequenced (para [0021]...counting of tags or signatures of DNA fragments). It would have been obvious to one skilled in the art to determine the frequency of each binding event identifier sequences, to enable analysis of broader trends in binding events.

Hurt teaches coupling strands of DNA by primer extension (col 3, ln 64-col 4, ln 16). It would have been obvious to one skilled in the art to couple the first and second tags by primer extension, as taught by Hurt, with the method of Casasanta and Corcoran, to more precisely control the nucleotide sequence.

As to claim 31, Casasanta, Corcoran and Hurt make obvious the method of claim 30. Corcoran further teaches wherein the sequences of the binding event identifiers are determined in parallel (para [0002]...massively parallel signature sequencing).

As to claims 32-33, Casasanta, Corcoran, and Hurt make obvious the method of claim 31. None specifies wherein the sequence of at least 1,000 or 100,000 binding event identifiers, respectively, are determined in parallel. Casasanta teaches a 36x28 microarray having 1008 spots (para [0013]) and that the binding pairs may comprise complementary strands of DNA or RNA (para [0014]). Corcoran teaches determining the sequences of the binding event identifiers in parallel (para [0002]...massively parallel signature sequencing; [0021]...element-to-element differences within microarrays; [0022]...ligation-based sequencing scheme). It would have been obvious to one skilled in the art to use the Corcoran digital sequencing method of an array of any number of spots, to uniquely identify the sequences that are bound.

Please continue

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Citations and Explanations, Box V(2):

As to claim 34, Casasanta teaches a method for characterizing the specificity of binding between binding agents that form a binding pair, comprising:
a) providing a first set of binding constructs immobilized on a support surface, wherein each binding construct of the first set of binding constructs comprises a first binding agent, and a first nucleic acid tag unique to the first binding agent (para [0014]...first component of the binding pair is immobilized on a spot of the microarray and the second component is bound to a protein...binding pairs can include...complementary strands of DNA or RNA);
b) providing a second set of binding constructs in solution, wherein each binding construct of the second set of binding constructs comprises a second binding agent, and a second nucleic acid tag unique to the second binding agent, and wherein either or both of the first and second sets of binding constructs comprises at least ten different binding agents (para [0014]...second component of the binding pair is introduced to the microarray by...solution flooding);
c) combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs, thereby co-locating the first nucleic acid tags and the second nucleic acid tags (para [0014]...complementary strands of DNA or RNA are bound together, therefore are co-located);
d) creating binding event identifiers from the co-located first and second nucleic acid tags (para [0012]...spectral shifts can be measured for respective molecular binding events).

Casasanta does not specify what Corcoran does in an alternative ligation-based sequencing scheme (para [0022]), namely:
e) determining a sequence of each binding event identifier, wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair (para [0002]...massively parallel signature sequencing). It would have been obvious to one skilled in the art to determine the frequency of each binding event identifier sequences, to enable analysis of broader trends in binding events.

Neither Casasanta nor Corcoran specifies:
wherein the first set of binding constructs also comprises a first primer region,
wherein the second set of binding constructs comprises a second primer region. Hurt teaches coupling strands of DNA by primer extension (col 3, ln 64-col 4, ln 16). It would have been obvious to one skilled in the art to couple the first and second tags by primer extension, as taught by Hurt, with the method of Casasanta and Corcoran, to more precisely control and track the nucleotide sequence.

As to claims 35-36, Casasanta, Corcoran and Hurt make obvious the method of claim 34, but do not specify wherein the sequence of at least 1,000 or 100,000 binding event identifiers, respectively, are determined in parallel. Casasanta teaches a 36x28 microarray having 1008 spots (para [0013]) and that the binding pairs may comprise complementary strands of DNA or RNA (para [0014]). Corcoran teaches determining the sequences of the binding event identifiers in parallel (para [0002]...massively parallel signature sequencing; [0021]...element-to-element differences within microarrays; [0022]...ligation-based sequencing scheme). It would have been obvious to one skilled in the art to use the Corcoran digital sequencing method of an array of any number of spots, to uniquely identify the sequences that are bound.

As to claim 37, Casasanta, Corcoran and Hurt make obvious the method of claim 34. Hurt further teaches the step of amplifying the binding event identifier after the creating step and before the determining step (col 6, ln 55-60...multiple temperature cycles can be used to amplify the extension product...different temperatures can be used for the three steps: association of the primer to the template, extension, and separation of the LPE product from the template).

Claims 1-37 have industrial applicability as defined by PCT Article 33(4) because the subject can be made or used in industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: SARAH J. BRASHEARS
CONVERGENT LAW GROUP LLP
475 WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE

(PCT Article 17(3)(a) and Rules 40.1 and 40.2(e))

Applicant's or agent's file reference PGNS009PCT	Date of mailing *(day/month/year)* 16 JUL 2012 **PAYMENT DUE** within **ONE MONTH** from the above date of mailing
International application No. PCT/US 12/32759	International filing date *(day/month/year)* 09 April 2012 (09.04.2012)
Applicant PROGNOSYS BIOSCIENCES, INC.	

1. This International Searching Authority

(i) considers that there are 3+ *(number of)* inventions claimed in the international application covered by the claims indicated below/on an extra sheet:
**********Please See the Extra Sheet**********

(ii) therefore considers that **the international application does not comply with the requirement of unity of invention** (Rules 13.1, 13.2 and 13.3) for the reasons indicated below/on an extra sheet:
**********Please See the Extra Sheet**********

(iii) ☐ has carried out a partial international search (see Annex) ☒ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
1-3, 6-8

(iv) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid.

2. Consequently, the applicant is hereby **invited to pay**, within the time limit indicated above, additional fees in the amount indicated below:

$2080	x	2+	=	$4160+
Fee per additional invention		number of additional inventions		total amount of additional fees/currency

3. The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fees may be made under protest**, that is, a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fees is excessive, where applicable, subject to the payment of a protest fee.

Where the applicant pays additional fees under protest, the applicant is hereby invited, within the time limit indicated above, to pay a protest fee (Rule 40.2(e)) in the amount of _____ *(amount/currency)*

Where the applicant has not, within the time limit indicated above, paid the required protest fee, the protest will be considered not to have been made and the International Searching Authority will so declare.

4. ☐ Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/206 (April 2005)

INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE

International application No.
PCT/US 12/32759

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+, claims 1-8, drawn to a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism. The first named invention (claims 1-3, 6-8), is limited to wherein the species are eukaryotic species. Applicant is invited to elect an additional limitations including: wherein the species are bacterial species or human pathogens (claims 4-5), to be searched by paying additional fee for each election.

Group II, claims 9-14, drawn to a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed such that the peptide sequence diversity is no less than 1 % of the encoding oligonucleotide sequence diversity.

Group III, claims 15-20 drawn to a method for analyzing a sample using a set of peptide constructs, each peptide construct comprising a custom-designed peptide portion and an identifying nucleic acid portion, comprising the steps of: a. performing an assay on the set of peptide constructs, where some of the peptide constructs are acted upon by assay agents, b. separating the peptide constructs that are acted upon by the assay agents from the peptide constructs that are not acted upon by the assay agents, and c. determining the identities of substantially all of the peptide constructs of either the peptide constructs that were acted upon by the assay agents or the peptide constructs that were not acted upon by the assay agents by analyzing the nucleic acid portion of the peptide constructs.

The inventions listed as Groups I+-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I+- II do not include the inventive concept of analyzing a sample using a set of peptide constructs, comprising the steps of: a. performing an assay on the set of peptide constructs, b. separating the peptide constructs that are acted upon by the assay agents from the peptide constructs that are not acted upon by the assay agents, and c. determining the identities of substantially all of the peptide constructs, as required by Group III.

Groups II-III do not include the inventive concept of a set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism, as required by Groups I+.

Furthermore, among Group I+, identifying oligonucleotide sequence from eukaryotic species (claims 2-3) are structurally different from identifying oligonucleotide sequence from bacterial species or human pathogens (claims 4-5) and are collected in different databases.

The inventions of Groups I+ and III share the technical feature of a set of peptide constructs, each peptide construct comprising a custom -designed peptide portion and an identifying nucleic acid portion; and Group I+ and II further share the technical feature of a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2003/0235852 A1 to ROBERTS et al. (hereinafter 'Roberts') as follows:

Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090] - 'libraries of molecules having a diversity of at least about 10.sup.9 different molecules', wherein '10.sup.9 different molecules' comprising at least 5,000 distinct peptide constructs; para [0008] - 'a library of nucleic acid-peptide fusion molecules'; para [0127] - the starting library contained approximately 3.times.10.sup.12 different peptides')
--- each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide', wherein 'an encoding nucleic acid' is 'an identifying oligonucleotide portion'; para [0005] - 'it is easier to determine a nucleotide sequence of a nucleic acid molecule encoding a peptide than it is to determine the amino acid sequence of a peptide,... prepare peptide libraries, wherein the encoding nucleic acid molecule remains physically associated with the peptide. Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide')
---that are custom-designed (para [0004] - 'Libraries of peptides ... be prepared based on a known peptide', wherein 'be prepared based on a known peptide' is 'custom-designed'). Without a shared special technical feature, the inventions lack unity with one another.

The inventions of Groups I+ further share the technical feature of a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism. However, this shared technical feature does not represent a contribution over prior art as being obvious over Roberts, in view of US 2009/0280487 A1 to HUNG et al. (hereinafter 'Hung') as follow:

**********Continued in the next extra sheet**********

INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE

International application No.
PCT/US 12/32759

Continuation of:
The previous extra sheet

Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090]; para [0008]; para [0127], as discussed above)
— each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009]; para [0005], as discussed above)
—that are custom-designed (para [0004],as discussed above)
— so that the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids (para [0065] - 'the nucleic acid-peptide fusion molecules can include any number of amino acid resides...at least... 15, 20, 25, 30, or more amino acid residues').

Although Roberts does not specifically teach wherein the peptide sequences of at least 12 amino acids are at least 10% of the set of peptide that have more than 80% amino acid identity to the protein sequences of interest, one of ordinary skill in the art at the time the invention was made would have known to do so, because Roberts teaches based on the detection of a desired activity of a peptide for identifying the peptide sequence associated with the activity (para [0005] - 'Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide'), which requires the peptide having enough amino acids and requires enough percentage of peptides to have enough amino acids, including to have at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids to include a functional group that have more than 80% amino acid identity to the protein sequences of interest. And furthermore, it is a common practice to include peptides with known sequences in consensus regions that have at least 80% amino acid identity to the same proteins from different species when preparing a library (please see US 2007/0020625 A1 to DUCHAUD et al.: para [0253] - 'a DNA library prepared from the genome of a bacterium belonging to... species different from the Photorhabdus strain used to construct the DNA library'; para [0093] - 'The expression "polypeptide exhibiting a certain percentage identity with another", ... "homologous polypeptide" will also be used... the amino acid sequence exhibits at least 80%, preferably 85%, 90%, 95%, 98% or 99%, identity'; please also see US 2005/0026188 A1 to van KESSEL et al.: para [0029] - 'developing a library of nucleotide sequences ... corresponding to variable regions of the cpn60 gene'; para [0060] - 'a "cnp60-like" sequence ... encoding a protein ... has a biological function similar to that of cpn60, ... homology of at least 70%, 80% or 90% may be used'; para [0062]- 'performs substantially the same role ... the homology will be at least about 80%, 85%, 90% or 95%').

Roberts does not specifically teach wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism. Hung discloses a peptide library comprising G-protein coupled receptor polypeptides from up to 100 different species (para [0062] - 'a library contains a plurality of members, ...up to about 1000 or more olfactory GPCR polypeptides.... derived from a plurality of species'; para para [0019] - '"G-protein coupled receptors", or "GPCRs" are polypeptides'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal', wherein 'up to about 100...species of animal' is 'up to 100 different species of organism'; para [0129] - 'producing a library ... up to about 1000 or more...different olfactory GPCRs'; para [0056]; para [0058]) for activity determination and modulator identification (para [0096] - 'screening for olfactory GPCR modulators'; para [0103] - 'GPCR activity may be measured by assessing a reporter signal').

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Roberts and Hung, to obtain a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences of interest, based on the teaching of Roberts and the common practice, wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism, based on the combination of Hung and Roberts, in order to include protein of interests in the same family from different species for facilitating identifying the peptide sequence associated with activity for characterization of protein of interest. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PGNS009PCT	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 12/32759	International filing date *(day/month/year)* 09 April 2012 (09.04.2012)	(Earliest) Priority Date *(day/month/year)* 08 April 2011 (08.04.2011)
Applicant PROGNOSYS BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☐ the text is approved as submitted by the applicant.

   ☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32759

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+, claims 1-8, drawn to a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism. The first named invention (claims 1-3, 6-8), is limited to wherein the species are eukaryotic species. Applicant is invited to elect an additional limitations including: wherein the species are bacterial species or human pathogens (claims 4-5), to be searched by paying additional fee for each election.

**********Continued in the extra sheet**********

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 6-8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32759

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The disclosure provides methods for constructing peptide construct sets and methods of use of these peptide construct sets in assay systems for peptide analysis, and in particular for use in high throughput peptide analysis. The methods allow for analysis of large sets of peptide constructs in a cost-effective manner, employing molecular biological techniques that are both robust and easily parallelized. Thus, the methods allow for the construction of peptide construct sets encompassing, e.g., the human proteome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32759

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C40B 40/08; C40B 40/10; C40B 50/06 (2012.01)
USPC - 506/17; 506/18; 506/26
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C40B 40/08; C40B 40/10; C40B 50/06; A61K 38/00; A61K 38/04; G01N 33/566 (2012.01)
USPC - 506/17; 506/18; 506/26; 530/300; 530/324, 530/325, 530/326; 530/327; 436/501

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - C40B 40/08; C40B 40/10; C40B 50/06; A61K 38/00; A61K 38/04; G01N 33/566 (2012.01) - see keyword below
USPC - 506/17; 506/18; 506/26; 530/300; 530/324, 530/325, 530/326; 530/327; 436/501 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google: peptide, nucleotide, encoding, fusion, conjugate, library, translation, ribosome, collection, array, micro-array, distinct, diversity, different, construct, identical, species, organism, eukaryotic, mammalian, human, overlapping, amino acid, length, 5000,10000, in-frame, stop codon, elongation, relea

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/0235852 A1 (ROBERTS et al.) 25 December 2003 (25.12.2003), para [0004], [0005], [0008], [0009], [0057], [0059], [0065], [0066], [0083], [0090], [0092], [0094], and [0127]	1-3, 6-8
Y	US 2009/0280487 A1 (HUNG et al.) 12 November 2009 (12.11.2009), para [0019],[0039], [0056], [0058], [0062], [0066], [0073], [0091], [0096], [0103], and [0129]	1-3, 6-8
Y	US 2007/0014810 A1 (BAKER et al.) 18 January 2007 (18.01.2007), para [0359], and [0361]	6
A	US 2007/0020625 A1 (DUCHAUD et al.) 25 January 2007 (25.01.2007), para [0093], and [0253]	1-3, 6-8
A	US 2005/0026188 A1 (VAN KESSEL et al.) 03 February 2005 (03.02.2005), para [0029], [0060], and [0062]	1-3, 6-8
A	Atkinson, Insert Overview of Translation here 2 pages, Between sections 5 and 6, University of Texas, Lecture manuscript, 2000, [online]. [Retrieved on 2012.09.11]. Retrieved from the Internet: <URL: http://www.sbs.utexas.edu/herrin/bio344/lectures/lecturespdf/Background/gSection%206.pdf> Entire documentation, especially pg 6.5, Elongation; and pg 6.6, Translocation and Termination	1-3, 6-8
A	US 2010/0113302 A1 (Williams) 06 May 2010 (06.05.2010), para [0008], [0014], [0018], [0024], [0046], [0054], and [0056]	1-3, 6-8
A	US 2008/0220981 A1 (McGregor) 11 September 2008 (11.09.2008), Abstract, para [0009], [0011], and [0022]	1-3, 6-8

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2012 (12.09.2012)	28 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32759

Continuation of:
Box No III (unity of invention is lacking)

Group II, claims 9-14, drawn to a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed such that the peptide sequence diversity is no less than 1 % of the encoding oligonucleotide sequence diversity.

Group III, claims 15-20 drawn to a method for analyzing a sample using a set of peptide constructs, each peptide construct comprising a custom-designed peptide portion and an identifying nucleic acid portion, comprising the steps of: a. performing an assay on the set of peptide constructs, where some of the peptide constructs are acted upon by assay agents, b. separating the peptide constructs that are acted upon by the assay agents from the peptide constructs that are not acted upon by the assay agents, and c. determining the identities of substantially all of the peptide constructs of either the peptide constructs that were acted upon by the assay agents or the peptide constructs that were not acted upon by the assay agents by analyzing the nucleic acid portion of the peptide constructs.

The inventions listed as Groups I+-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I+- II do not include the inventive concept of analyzing a sample using a set of peptide constructs, comprising the steps of: a. performing an assay on the set of peptide constructs, b. separating the peptide constructs that are acted upon by the assay agents from the peptide constructs that are not acted upon by the assay agents, and c. determining the identities of substantially all of the peptide constructs, as required by Group III.

Groups II-III do not include the inventive concept of a set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism, as required by Groups I+.

Furthermore, among Group I+, identifying oligonucleotide sequence from eukaryotic species (claims 2-3) are structurally different from identifying oligonucleotide sequence from bacterial species or human pathogens (claims 4-5) and are collected in different databases.

The inventions of Groups I+ and III share the technical feature of a set of peptide constructs, each peptide construct comprising a custom-designed peptide portion and an identifying nucleic acid portion; and Group I+ and II further share the technical feature of a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2003/0235852 A1 to ROBERTS et al. (hereinafter 'Roberts') as follows:

Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090] - 'libraries of molecules having a diversity of at least about 10.sup.9 different molecules', wherein '10.sup.9 different molecules' comprising at least 5,000 distinct peptide constructs; para [0008] - 'a library of nucleic acid-peptide fusion molecules'; para [0127] - the starting library contained approximately 3.times.10.sup.12 different peptides')
--- each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide', wherein 'an encoding nucleic acid' is 'an identifying oligonucleotide portion'; para [0005] - 'it is easier to determine a nucleotide sequence of a nucleic acid molecule encoding a peptide than it is to determine the amino acid sequence of a peptide,... prepare peptide libraries, wherein the encoding nucleic acid molecule remains physically associated with the peptide. Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide')
---that are custom-designed (para [0004] - 'Libraries of peptides ... be prepared based on a known peptide', wherein 'be prepared based on a known peptide' is 'custom-designed'). Without a shared special technical feature, the inventions lack unity with one another.

The inventions of Groups I+ further share the technical feature of a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set
of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism. However, this shared technical feature does not represent a contribution over prior art as being obvious over Roberts, in view of US 2009/0280487 A1 to HUNG et al. (hereinafter 'Hung') as follow:

**********Continued in the next extra sheet**********

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32759

Continuation of:
The previous extra sheet - Box No III (unity of invention is lacking)

Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090]; para [0008]; para [0127], as discussed above)
--- each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009]; para [0005], as discussed above)
---that are custom-designed (para [0004],as discussed above)
--- so that the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids (para [0065] - 'the nucleic acid-peptide fusion molecules can include any number of amino acid resides...at least... 15, 20, 25, 30, or more amino acid residues').

Although Roberts does not specifically teach wherein the peptide sequences of at least 12 amino acids are at least 10% of the set of peptide that have more than 80% amino acid identity to the protein sequences of interest, one of ordinary skill in the art at the time the invention was made would have known to do so, because Roberts teaches detecting a desired activity of a peptide for identifying the peptide sequence associated with the activity (para [0005] - 'Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide'), which requires the peptide having enough amino acids and requires enough percentage of peptides to have enough amino acids, including to have at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids to include a functional group that have more than 80% amino acid identity to the protein sequences of interest. And furthermore, it is a common practice to include peptides with known sequences in consensus regions that have at least 80% amino acid identity to the same proteins from different species when preparing a library (please see US 2007/0020625 A1 to DUCHAUD et al.: para [0253] - 'a DNA library prepared from the genome of a bacterium belonging to... species different from the Photorhabdus strain used to construct the DNA library'; para [0093] - 'The expression "polypeptide exhibiting a certain percentage identity with another", ... "homologous polypeptide" will also be used... the amino acid sequence exhibits at least 80%, preferably 85%, 90%, 95%, 98% or 99%, identity'; please also see US 2005/0026188 A1 to van KESSEL et al.: para [0029] - 'developing a library of nucleotide sequences ... corresponding to variable regions of the cpn60 gene'; para [0060] - 'a "cnp60-like" sequence ... encoding a protein ... has a biological function similar to that of cpn60, ... homology of at least 70%, 80% or 90% may be used'; para [0062]- 'performs substantially the same role ... the homology will be at least about 80%, 85%, 90% or 95%').

Roberts does not specifically teach wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism. Hung discloses a peptide library comprising G-protein coupled receptor polypeptides from up to 100 different species (para [0062] - 'a library contains a plurality of members, ...up to about 1000 or more olfactory GPCR polypeptides.... derived from a plurality of species'; para para [0019] - '"G-protein coupled receptors", or "GPCRs" are polypeptides'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal', wherein 'up to about 100...species of animal' is 'up to 100 different species of organism'; para [0129] - 'producing a library ... up to about 1000 or more...different olfactory GPCRs'; para [0056]; para [0058]) for activity determination and modulator identification (para [0096] - 'screening for olfactory GPCR modulators'; para [0103] - 'GPCR activity may be measured by assessing a reporter signal').

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Roberts and Hung, to obtain a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences of interest, based on the teaching of Roberts and the common practice, wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism, based on the combination of Hung and Roberts, in order to include protein of interests in the same family from different species for facilitating identifying the peptide sequence associated with activity for characterization of protein of interest. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: SARAH J. BRASHEARS
CONVERGENT LAW GROUP LLP
475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	28 SEP 2012
Applicant's or agent's file reference PGNS009PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 12/32759	09 April 2012 (09.04.2012)	08 April 2011 (08.04.2011)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C40B 40/08; C40B 40/10; C40B 50/06 (2012.01)
USPC - 506/17; 506/18; 506/26

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	12 September 2012 (12.09.2012)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+, claims 1-8, drawn to a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism. The first named invention (claims 1-3, 6-8), is limited to wherein the species are eukaryotic species. Applicant is invited to elect an additional limitations including: wherein the species are bacterial species or human pathogens (claims 4-5), to be searched by paying additional fee for each election.

Group II, claims 9-14, drawn to a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed such that the peptide sequence diversity is no less than 1 % of the encoding oligonucleotide sequence diversity.

Group III, claims 15-20 drawn to a method for analyzing a sample using a set of peptide constructs, each peptide construct comprising a custom-designed peptide portion and an identifying nucleic acid portion, comprising the steps of: a. performing an assay on the set of peptide constructs, where some of the peptide constructs are acted upon by assay agents, b. separating the peptide constructs that are acted upon by the assay agents from the peptide constructs that are not acted upon by the assay agents, and c. determining the identities of substantially all of the peptide constructs of either the peptide constructs that were acted upon by the assay agents or the peptide constructs that were not acted upon by the assay agents by analyzing the nucleic acid portion of the peptide constructs.

The inventions listed as Groups I+-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I+- II do not include the inventive concept of analyzing a sample using a set of peptide constructs, comprising the steps of: a. performing an assay on the set of peptide constructs, b. separating the peptide constructs that are acted upon by the assay agents from the peptide constructs that are not acted upon by the assay agents, and c. determining the identities of substantially all of the peptide constructs, as required by Group III.

Groups II-III do not include the inventive concept of a set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism, as required by Groups I+.

Furthermore, among Group I+, identifying oligonucleotide sequence from eukaryotic species (claims 2-3) are structurally different from identifying oligonucleotide sequence from bacterial species or human pathogens (claims 4-5) and are collected in different databases.

The inventions of Groups I+ and III share the technical feature of a set of peptide constructs, each peptide construct comprising a custom -designed peptide portion and an identifying nucleic acid portion; and Group I+ and II further share the technical feature of a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2003/0235852 A1 to ROBERTS et al. (hereinafter 'Roberts') as follows:

**********Continued in the supplmental box**********

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts
   - ☒ the parts relating to claims Nos. 1-3, 6-8

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-3, 6-8	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-3, 6-8	NO
Industrial applicability (IA)	Claims	1-3, 6-8	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-3 and 7-8 lack an inventive step under PCT Article 33(3) as being obvious over US 2003/0235852 A1 to ROBERTS et al. (hereinafter 'Roberts'), in view of US 2009/0280487 A1 to HUNG et al. (hereinafter 'Hung').

Regarding claim 1, Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090] - 'libraries of molecules having a diversity of at least about 10.sup.9 different molecules', wherein '10.sup.9 different molecules' comprising at least 5,000 distinct peptide constructs; para [0008] - 'a library of nucleic acid-peptide fusion molecules'; para [0127] - the starting library contained approximately 3.times.10.sup.12 different peptides')
--- each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide', wherein 'an encoding nucleic acid' is 'an identifying oligonucleotide portion'; para [0005] - 'it is easier to determine a nucleotide sequence of a nucleic acid molecule encoding a peptide than it is to determine the amino acid sequence of a peptide,... prepare peptide libraries, wherein the encoding nucleic acid molecule remains physically associated with the peptide. Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide')
---that are custom-designed (para [0004] - 'Libraries of peptides ... be prepared based on a known peptide', wherein 'be prepared based on a known peptide' is 'custom-designed')
--- so that the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids (para [0065] - 'the nucleic acid-peptide fusion molecules can include any number of amino acid resides...at least... 15, 20, 25, 30, or more amino acid residues').

Although Roberts does not specifically teach wherein the peptide sequences of at least 12 amino acids are at least 10% of the set of peptide that have more than 80% amino acid identity to the protein sequences of interest, one of ordinary skill in the art at the time the invention was made would have known to do so, because Roberts teaches detecting a desired activity of a peptide for identifying the peptide sequence associated with the activity (para [0005] - 'Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide'), which requires the peptide having enough amino acids and requires enough percentage of peptides to have enough amino acids, including to have at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids to include a functional group that have more than 80% amino acid identity to the protein sequences of interest. And furthermore, it is a common practice to include peptides with known sequences in consensus regions that have at least 80% amino acid identity to the same proteins from different species when preparing a library (please see US 2007/0020625 A1 to DUCHAUD et al.: para [0253] - 'a DNA library prepared from the genome of a bacterium belonging to... species different from the Photorhabdus strain used to construct the DNA library'; para [0093] - 'The expression "polypeptide exhibiting a certain percentage identity with another", ... "homologous polypeptide" will also be used... the amino acid sequence exhibits at least 80%, preferably 85%, 90%, 95%, 98% or 99%, identity'; please also see US 2005/0026188 A1 to van KESSEL et al.: para [0029] - 'developing a library of nucleotide sequences ... corresponding to variable regions of the cpn60 gene'; para [0060] - 'a "cnp60-like" sequence ... encoding a protein ... has a biological function similar to that of cpn60, ... homology of at least 70%, 80% or 90% may be used'; para [0062]- 'performs substantially the same role ... the homology will be at least about 80%, 85%, 90% or 95%').

Roberts does not specifically teach wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism. Hung discloses a peptide library comprising G-protein coupled receptor polypeptides from up to 100 different species (para [0062] - 'a library contains a plurality of members, ...up to about 1000 or more olfactory GPCR polypeptides.... derived from a plurality of species'; para [0019] - '"G-protein coupled receptors", or "GPCRs" are polypeptides'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal', wherein 'up to about 100... species of animal' is 'up to 100 different species of organism'; para [0129] - 'producing a library ... up to about 1000 or more...different olfactory GPCRs'; para [0056]; para [0058]) for activity determination and modulator identification (para [0096] - 'screening for olfactory GPCR modulators'; para [0103] - 'GPCR activity may be measured by assessing a reporter signal').

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Roberts and Hung, to obtain a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences of interest, based on the teaching of Roberts and common practice, wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism, based on the combination of Hung and Roberts, in order to include protein of interests in the same family from different species for facilitating identifying the peptide sequence associated with activity for characterization of protein of interest.

**********Continued in the supplemental box**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fu lly supported by the description, are made:

For dependent claims 2-6, 10-14, 16, 19-20, the word 'where' in each claim is assumed to read as 'wherein'.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No IV (Lack of unity of invention)

Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090] - 'libraries of molecules having a diversity of at least about 10.sup.9 different molecules', wherein '10.sup.9 different molecules' comprising at least 5,000 distinct peptide constructs; para [0008] - 'a library of nucleic acid-peptide fusion molecules'; para [0127] - the starting library contained approximately 3.times.10.sup.12 different peptides')
--- each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide', wherein 'an encoding nucleic acid' is 'an identifying oligonucleotide portion'; para [0005] - 'it is easier to determine a nucleotide sequence of a nucleic acid molecule encoding a peptide than it is to determine the amino acid sequence of a peptide,... prepare peptide libraries, wherein the encoding nucleic acid molecule remains physically associated with the peptide. Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide')
---that are custom-designed (para [0004] - 'Libraries of peptides ... be prepared based on a known peptide', wherein 'be prepared based on a known peptide' is 'custom-designed'). Without a shared special technical feature, the inventions lack unity with one another.

The inventions of Groups I+ further share the technical feature of a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set
of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism. However, this shared technical feature does not represent a contribution over prior art as being obvious over Roberts, in view of US 2009/0280487 A1 to HUNG et al. (hereinafter 'Hung') as follow:

Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090]; para [0008]; para [0127], as discussed above)
--- each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009]; para [0005], as discussed above)
---that are custom-designed (para [0004],as discussed above)
--- so that the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids (para [0065] - 'the nucleic acid-peptide fusion molecules can include any number of amino acid resides...at least... 15, 20, 25, 30, or more amino acid residues').
Although Roberts does not specifically teach wherein the peptide sequences of at least 12 amino acids are at least 10% of the set of peptide that have more than 80% amino acid identity to the protein sequences of interest, one of ordinary skill in the art at the time the invention was made would have known to do so, because Roberts teaches detecting a desired activity of a peptide for identifying the peptide sequence associated with the activity (para [0005] - 'Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide'), which requires the peptide having enough amino acids and requires enough percentage of peptides to have enough amino acids, including to have at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids to include a functional group that have more than 80% amino acid identity to the protein sequences of interest. And furthermore, it is a common practice to include peptides with known sequences in consensus regions that have at least 80% amino acid identity to the same proteins from different species when preparing a library (please see US 2007/0020625 A1 to DUCHAUD et al.: para [0253] - 'a DNA library prepared from the genome of a bacterium belonging to... species different from the Photorhabdus strain used to construct the DNA library'; para [0093] - 'The expression "polypeptide exhibiting a certain percentage identity with another", ... "homologous polypeptide" will also be used... the amino acid sequence exhibits at least 80%, preferably 85%, 90%, 95%, 98% or 99%, identity'; please also see US 2005/0026188 A1 to van KESSEL et al.: para [0029] - 'developing a library of nucleotide sequences ... corresponding to variable regions of the cpn60 gene'; para [0060] - 'a "cnp60-like" sequence ... encoding a protein ... has a biological function similar to that of cpn60, ... homology of at least 70%, 80% or 90% may be used'; para [0062]- 'performs substantially the same role ... the homology will be at least about 80%, 85%, 90% or 95%').
Roberts does not specifically teach wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism. Hung discloses a peptide library comprising G-protein coupled receptor polypeptides from up to 100 different species (para [0062] - 'a library contains a plurality of members, ...up to about 1000 or more olfactory GPCR polypeptides.... derived from a plurality of species'; para para [0019] - '"G-protein coupled receptors", or "GPCRs" are polypeptides'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal', wherein 'up to about 100...species of animal' is 'up to 100 different species of organism'; para [0129] - 'producing a library ... up to about 1000 or more...different olfactory GPCRs'; para [0056]; para [0058]) for activity determination and modulator identification (para [0096] - 'screening for olfactory GPCR modulators'; para [0103] - 'GPCR activity may be measured by assessing a reporter signal').
It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Roberts and Hung, to obtain a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences of interest, based on the teaching of Roberts and the common practice, wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism, based on the combination of Hung and Roberts, in order to include protein of interests in the same family from different species for facilitating identifying the peptide sequence associated with activity for characterization of protein of interest. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V No 2 (citations and explanations)

Regarding claim 2, the combination of Roberts and Hung discloses the set of peptide constructs from claim 1, and the said combination further discloses wherein the species are eukaryotic species (Roberts: para [0066] - 'nucleic acid-peptide fusion molecules, ...the initiator AUG codon in eukaryotic systems', wherein 'the initiator AUG codon in eukaryotic systems' indicating the peptide constructs are for eukaryotic species; para [0083] - 'RNA-peptide fusions then are generated using an in vitro or in situ translation system. ... eukaryotic systems are preferred'; Hung: para [0056] - 'the olfactory GPCR may be of human origin or of non-human animal origin... may be a mouse, a rat, a dog, or any other non-human animal'; para [0066] - 'a particular species, particularly a mammalian, e.g., human or mouse species'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal').

Regarding claim 3, the combination of Roberts and Hung discloses the set of peptide constructs from claim 2, and Hung further discloses wherein the species are mammalian species (para [0056] - 'the olfactory GPCR may be of human origin or of non-human animal origin... may be a mouse, a rat, a dog, or any other non-human animal'; para [0066] - 'a particular species, particularly a mammalian, e.g., human or mouse species'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal').

Regarding claim 7, the combination of Roberts and Hung discloses the set of peptides from claim 1, and Roberts further discloses wherein the peptide portion is dissociated from the ribosome before being linked to the identifying nucleic acid (para [0009] - 'The encoding nucleic acid is translationally linked at or near its 3' terminus to the C-terminus of its encoded peptide, ... via a peptide acceptor such as puromycin'; para [0057]; para [0059] - 'puromycin acts as a universal inhibitor of protein synthesis by binding the translation complex A site, accepting the growing peptide chain, and falling off the ribosome ...methods for translationally linking an encoding nucleic acid and encoded peptide ... effecting the joining using a peptide acceptor such as puromycin, which can be linked at or near the 3' terminus of the encoding nucleic acid such that it can enter the ribosome complex during translation and be incorporated at the C-terminus of the growing (nascent) peptide, thereby terminating translation and linking the encoding nucleic acid and encoded peptide', wherein ' puromycin ... falling off the ribosome... terminating translation and linking the encoding nucleic acid and encoded peptide' indicates 'wherein the peptide portion is dissociated from the ribosome before being linked to the identifying nucleic acid'; Please see Alkinson for the translation steps: Entire documentation, especially pg 6.5, Elongation; and pg 6.6, Translocation and Termination).

Regarding claim 8, the combination of Roberts and Hung discloses the set of peptide constructs from claim 1, and the said combination further obviates wherein the set of peptide constructs comprises at least 100,000 distinct peptide constructs (Roberts: para [0090] - 'libraries of molecules having a diversity of at least about 10.sup.9 different molecules'; para [0008] - 'a library of nucleic acid-peptide fusion molecules'; para [0127] - the starting library contained approximately 3.times.10.sup.12 different peptides')
---each comprising a peptide portion of at least 10 amino acids and an identifying oligonucleotide portion (Roberts: para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide', wherein 'an encoding nucleic acid' is 'an identifying oligonucleotide portion'; para [0005] - 'it is easier to determine a nucleotide sequence of a nucleic acid molecule encoding a peptide than it is to determine the amino acid sequence of a peptide,...Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide'; para [0065] - 'the nucleic acid-peptide fusion molecules can include any number of amino acid resides...at least... 15, 20, 25, 30, or more amino acid residues')
---wherein the peptide portions are encoded within oligonucleotide sequences that are custom designed (Roberts: para [0004] - 'Libraries of peptides ... be prepared based on a known peptide', wherein 'be prepared based on a known peptide' is 'custom-designed'; para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide').
----such that at least 90% of the sequences contain no more than one in-frame codon that can function as a stop codon in the translation system used to make the peptide constructs (Roberts: para [0092] - 'the orthogonal aminoacylated tRNA, which is charged with an unnatural amino acid residue, recognizes a stop codon... a start codon operably linked to a protein coding sequence, and each of which is linked to a peptide acceptor at the 3'-end of the peptide coding sequence, which includes or can include one or a series of stop codons, ... to produce a population of RNA-peptide fusion molecules comprising peptides', wherein additional stop codons are used for translating unatural amino acids, one of ordinary skill in the art at the time the invention was made would have known to include no more than one in-frame codon that can function as a stop codon in the translation system used to make the peptide constructs because is the basic principle for successful protein translation; para [0094] - 'an amber suppressor tRNA, which recognizes a UAG stop codon. ...other unnatural residues such as N-methyl glycine and N--(S)-phenylethyl glycine similarly can be used'; Hung: para [0073] - 'a fusion protein may contain a heterologous N-terminal domain (e.g. an epitope tag) fused in-frame with a GPCR that has had its N-terminal methionine residue either deleted or substituted with an alternative amino acid', wherein 'fused in-frame' is the basic practice including 'in-frame codon that can function as a stop codon' for protein translation; para [0039] - 'The boundaries of the coding sequence are typically determined by a start codon at the 5' (amino) terminus and a translation stop codon at the 3' (carboxy) terminus', wherein 'a translation stop codon at the 3' (carboxy) terminus' indicates each conding sequence having 'one in-frame codon that can function as a stop codon in the translation system used to make the peptide constructs', one of ordinary skill in the art at the time the invention was made would have known to have ' at least 90% of the sequences contain no more than one in-frame codon that can function as a stop codon in the translation system used to make the peptide constructs' for producing sufficient amount of distinct peptides, but not high percentage of premature peptides due to the presence of undesired stop codon).

**********Continued in the next supplemental box**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
The previous supplemental box - Box V No 2 (citations and explanations)

Claim 6 lacks an inventive step under PCT Article 33(3) as being obvious over Roberts, in view of Hung, as above, and further in view of US 2007/0014810 A1 to BAKER et al. (hereinafter 'Baker').

Regarding claim 6, the combination of Roberts and Hung discloses a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism, as discussed in the discussion of claim 1. Roberts further discloses using the set of peptide constructs for detecting a desired activity of a peptide for identifying the peptide sequence associated with the activity (para [0005] - 'Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide').

Said combination does not specifically teach wherein the peptide sequences are grouped into one or more sets of partially overlapping sequences. Baker discloses a method for identifying ligand binding domains of a sequence of interest, the method comprising producing a set of peptide sequences that are partially overlapping sequences that cover the entire sequence of the sequence of interest for identifying ligand binding domains (para [0359] - 'The identification of motifs and/or super motifs that correlate with high and intermediate affinity binding ... identification of immunogenic peptide epitopes ... all possible peptides of 9 amino acids in length and overlapping by eight amino acids ... which cover the entire sequence of the ... proteins ...were evaluated for binding to five allele-specific HLA molecules'; para [0361] - 'a large fraction of HLA class I and class II molecules can be classified into a relatively few supertypes, each characterized by largely overlapping peptide binding repertoires, and consensus structures of the main peptide binding pockets'). Although Baker does not specifically teach the peptide sequences are grouped into one or more sets of partially overlapping sequences, one of ordinary skill in the art at the time the invention was made would have known to do so by grouping partially overlapping sequences generated from the same protein in the same group for facilitating characterization of the protein function associated with the peptide fragments in the protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Roberts and Hung with that of Baker, to obtain a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism, based on the combination of Roberts and Hung, and further wherein the peptide sequences are grouped into one or more sets of partially overlapping sequences, based on the combination of Baker, Roberts and Hung, in order to obtain a set of distinct peptide constructs that include all factional fragments of the targeted protein sequences for facilitating characterization of the functional domain of the targeted protein sequences in different species of organism.

Claims 1-3 and 6-8 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PGNS009PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2012/032759	International filing date *(day/month/year)* 09 April 2012 (09.04.2012)	Priority date *(day/month/year)* 08 April 2011 (08.04.2011)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PROGNOSYS BIOSCIENCES, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 08 October 2013 (08.10.2013)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Mineko Mohri e-mail: pt08.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: SARAH J. BRASHEARS
CONVERGENT LAW GROUP LLP
475 N. WHISMAN ROAD, SUITE 400
MOUNTAIN VIEW, CA 94043

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	28 SEP 2012
Applicant's or agent's file reference PGNS009PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 12/32759	09 April 2012 (09.04.2012)	08 April 2011 (08.04.2011)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C40B 40/08; C40B 40/10; C40B 50/06 (2012.01)
USPC - 506/17; 506/18; 506/26

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	12 September 2012 (12.09.2012)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+, claims 1-8, drawn to a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism. The first named invention (claims 1-3, 6-8), is limited to wherein the species are eukaryotic species. Applicant is invited to elect an additional limitations including: wherein the species are bacterial species or human pathogens (claims 4-5), to be searched by paying additional fee for each election.

Group II, claims 9-14, drawn to a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed such that the peptide sequence diversity is no less than 1 % of the encoding oligonucleotide sequence diversity.

Group III, claims 15-20 drawn to a method for analyzing a sample using a set of peptide constructs, each peptide construct comprising a custom-designed peptide portion and an identifying nucleic acid portion, comprising the steps of: a. performing an assay on the set of peptide constructs, where some of the peptide constructs are acted upon by assay agents, b. separating the peptide constructs that are acted upon by the assay agents from the peptide constructs that are not acted upon by the assay agents, and c. determining the identities of substantially all of the peptide constructs of either the peptide constructs that were acted upon by the assay agents or the peptide constructs that were not acted upon by the assay agents by analyzing the nucleic acid portion of the peptide constructs.

The inventions listed as Groups I+-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I+- II do not include the inventive concept of analyzing a sample using a set of peptide constructs, comprising the steps of: a. performing an assay on the set of peptide constructs, b. separating the peptide constructs that are acted upon by the assay agents from the peptide constructs that are not acted upon by the assay agents, and c. determining the identities of substantially all of the peptide constructs, as required by Group III.

Groups II-III do not include the inventive concept of a set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism, as required by Groups I+.

Furthermore, among Group I+, identifying oligonucleotide sequence from eukaryotic species (claims 2-3) are structurally different from identifying oligonucleotide sequence from bacterial species or human pathogens (claims 4-5) and are collected in different databases.

The inventions of Groups I+ and III share the technical feature of a set of peptide constructs, each peptide construct comprising a custom -designed peptide portion and an identifying nucleic acid portion; and Group I+ and II further share the technical feature of a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2003/0235852 A1 to ROBERTS et al. (hereinafter 'Roberts') as follows:

**********Continued in the supplmental box**********

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts
   - ☒ the parts relating to claims Nos. 1-3, 6-8

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-3, 6-8	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-3, 6-8	NO
Industrial applicability (IA)	Claims	1-3, 6-8	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-3 and 7-8 lack an inventive step under PCT Article 33(3) as being obvious over US 2003/0235852 A1 to ROBERTS et al. (hereinafter 'Roberts'), in view of US 2009/0280487 A1 to HUNG et al. (hereinafter 'Hung').

Regarding claim 1, Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090] - 'libraries of molecules having a diversity of at least about 10.sup.9 different molecules', wherein '10.sup.9 different molecules' comprising at least 5,000 distinct peptide constructs; para [0008] - 'a library of nucleic acid-peptide fusion molecules'; para [0127] - the starting library contained approximately 3.times.10.sup.12 different peptides')
--- each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide', wherein 'an encoding nucleic acid' is 'an identifying oligonucleotide portion'; para [0005] - 'it is easier to determine a nucleotide sequence of a nucleic acid molecule encoding a peptide than it is to determine the amino acid sequence of a peptide,... prepare peptide libraries, wherein the encoding nucleic acid molecule remains physically associated with the peptide. Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide')
---that are custom-designed (para [0004] - 'Libraries of peptides ... be prepared based on a known peptide', wherein 'be prepared based on a known peptide' is 'custom-designed')
--- so that the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids (para [0065] - 'the nucleic acid-peptide fusion molecules can include any number of amino acid resides...at least... 15, 20, 25, 30, or more amino acid residues').

Although Roberts does not specifically teach wherein the peptide sequences of at least 12 amino acids are at least 10% of the set of peptide that have more than 80% amino acid identity to the protein sequences of interest, one of ordinary skill in the art at the time the invention was made would have known to do so, because Roberts teaches detecting a desired activity of a peptide for identifying the peptide sequence associated with the activity (para [0005] - 'Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide'), which requires the peptide having enough amino acids and requires enough percentage of peptides to have enough amino acids, including to have at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids to include a functional group that have more than 80% amino acid identity to the protein sequences of interest. And furthermore, it is a common practice to include peptides with known sequences in consensus regions that have at least 80% amino acid identity to the same proteins from different species when preparing a library (please see US 2007/0020625 A1 to DUCHAUD et al.: para [0253] - 'a DNA library prepared from the genome of a bacterium belonging to... species different from the Photorhabdus strain used to construct the DNA library'; para [0093] - 'The expression "polypeptide exhibiting a certain percentage identity with another", ... "homologous polypeptide" will also be used... the amino acid sequence exhibits at least 80%, preferably 85%, 90%, 95%, 98% or 99%, identity'; please also see US 2005/0026188 A1 to van KESSEL et al.: para [0029] - 'developing a library of nucleotide sequences ... corresponding to variable regions of the cpn60 gene'; para [0060] - 'a "cnp60-like" sequence ... encoding a protein ... has a biological function similar to that of cpn60, ... homology of at least 70%, 80% or 90% may be used'; para [0062]- 'performs substantially the same role ... the homology will be at least about 80%, 85%, 90% or 95%').

Roberts does not specifically teach wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism. Hung discloses a peptide library comprising G-protein coupled receptor polypeptides from up to 100 different species (para [0062] - 'a library contains a plurality of members, ...up to about 1000 or more olfactory GPCR polypeptides.... derived from a plurality of species'; para [0019] - '"G-protein coupled receptors", or "GPCRs" are polypeptides'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal', wherein 'up to about 100... species of animal' is 'up to 100 different species of organism'; para [0129] - 'producing a library ... up to about 1000 or more...different olfactory GPCRs'; para [0056]; para [0058]) for activity determination and modulator identification (para [0096] - 'screening for olfactory GPCR modulators'; para [0103] - 'GPCR activity may be measured by assessing a reporter signal').

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Roberts and Hung, to obtain a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences of interest, based on the teaching of Roberts and common practice, wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism, based on the combination of Hung and Roberts, in order to include protein of interests in the same family from different species for facilitating identifying the peptide sequence associated with activity for characterization of protein of interest.

**********Continued in the supplemental box**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fu lly supported by the description, are made:

For dependent claims 2-6, 10-14, 16, 19-20, the word 'where' in each claim is assumed to read as 'wherein'.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No IV (Lack of unity of invention)

Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090] - 'libraries of molecules having a diversity of at least about 10.sup.9 different molecules', wherein '10.sup.9 different molecules' comprising at least 5,000 distinct peptide constructs; para [0008] - 'a library of nucleic acid-peptide fusion molecules'; para [0127] - the starting library contained approximately 3.times.10.sup.12 different peptides')
--- each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide', wherein 'an encoding nucleic acid' is 'an identifying oligonucleotide portion'; para [0005] - 'it is easier to determine a nucleotide sequence of a nucleic acid molecule encoding a peptide than it is to determine the amino acid sequence of a peptide,... prepare peptide libraries, wherein the encoding nucleic acid molecule remains physically associated with the peptide. Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide')
---that are custom-designed (para [0004] - 'Libraries of peptides ... be prepared based on a known peptide', wherein 'be prepared based on a known peptide' is 'custom-designed'). Without a shared special technical feature, the inventions lack unity with one another.

The inventions of Groups I+ further share the technical feature of a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set
of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism. However, this shared technical feature does not represent a contribution over prior art as being obvious over Roberts, in view of US 2009/0280487 A1 to HUNG et al. (hereinafter 'Hung') as follow:

Roberts discloses a set of at least 5,000 distinct peptide constructs (para [0090]; para [0008]; para [0127], as discussed above)
--- each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences (para [0009]; para [0005], as discussed above)
---that are custom-designed (para [0004],as discussed above)
--- so that the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids (para [0065] - 'the nucleic acid-peptide fusion molecules can include any number of amino acid resides...at least... 15, 20, 25, 30, or more amino acid residues').
Although Roberts does not specifically teach wherein the peptide sequences of at least 12 amino acids are at least 10% of the set of peptide that have more than 80% amino acid identity to the protein sequences of interest, one of ordinary skill in the art at the time the invention was made would have known to do so, because Roberts teaches detecting a desired activity of a peptide for identifying the peptide sequence associated with the activity (para [0005] - 'Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide'), which requires the peptide having enough amino acids and requires enough percentage of peptides to have enough amino acids, including to have at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids to include a functional group that have more than 80% amino acid identity to the protein sequences of interest. And furthermore, it is a common practice to include peptides with known sequences in consensus regions that have at least 80% amino acid identity to the same proteins from different species when preparing a library (please see US 2007/0020625 A1 to DUCHAUD et al.: para [0253] - 'a DNA library prepared from the genome of a bacterium belonging to... species different from the Photorhabdus strain used to construct the DNA library'; para [0093] - 'The expression "polypeptide exhibiting a certain percentage identity with another", ... "homologous polypeptide" will also be used... the amino acid sequence exhibits at least 80%, preferably 85%, 90%, 95%, 98% or 99%, identity'; please also see US 2005/0026188 A1 to van KESSEL et al.: para [0029] - 'developing a library of nucleotide sequences ... corresponding to variable regions of the cpn60 gene'; para [0060] - 'a "cnp60-like" sequence ... encoding a protein ... has a biological function similar to that of cpn60, ... homology of at least 70%, 80% or 90% may be used'; para [0062]- 'performs substantially the same role ... the homology will be at least about 80%, 85%, 90% or 95%').
Roberts does not specifically teach wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism. Hung discloses a peptide library comprising G-protein coupled receptor polypeptides from up to 100 different species (para [0062] - 'a library contains a plurality of members, ...up to about 1000 or more olfactory GPCR polypeptides.... derived from a plurality of species'; para para [0019] - '"G-protein coupled receptors", or "GPCRs" are polypeptides'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal', wherein 'up to about 100...species of animal' is 'up to 100 different species of organism'; para [0129] - 'producing a library ... up to about 1000 or more...different olfactory GPCRs'; para [0056]; para [0058]) for activity determination and modulator identification (para [0096] - 'screening for olfactory GPCR modulators'; para [0103] - 'GPCR activity may be measured by assessing a reporter signal').
It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Roberts and Hung, to obtain a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences of interest, based on the teaching of Roberts and the common practice, wherein the peptides of interest are protein sequences encoded by up to 100 different species of organism, based on the combination of Hung and Roberts, in order to include protein of interests in the same family from different species for facilitating identifying the peptide sequence associated with activity for characterization of protein of interest. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V No 2 (citations and explanations)

Regarding claim 2, the combination of Roberts and Hung discloses the set of peptide constructs from claim 1, and the said combination further discloses wherein the species are eukaryotic species (Roberts: para [0066] - 'nucleic acid-peptide fusion molecules, ...the initiator AUG codon in eukaryotic systems', wherein 'the initiator AUG codon in eukaryotic systems' indicating the peptide constructs are for eukaryotic species; para [0083] - 'RNA-peptide fusions then are generated using an in vitro or in situ translation system. ... eukaryotic systems are preferred'; Hung: para [0056] - 'the olfactory GPCR may be of human origin or of non-human animal origin... may be a mouse, a rat, a dog, or any other non-human animal'; para [0066] - 'a particular species, particularly a mammalian, e.g., human or mouse species'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal').

Regarding claim 3, the combination of Roberts and Hung discloses the set of peptide constructs from claim 2, and Hung further discloses wherein the species are mammalian species (para [0056] - 'the olfactory GPCR may be of human origin or of non-human animal origin... may be a mouse, a rat, a dog, or any other non-human animal'; para [0066] - 'a particular species, particularly a mammalian, e.g., human or mouse species'; para [0091] - 'The olfactory GPCRs may be of known identity...may be derived from ... up to about 100... species of animal').

Regarding claim 7, the combination of Roberts and Hung discloses the set of peptides from claim 1, and Roberts further discloses wherein the peptide portion is dissociated from the ribosome before being linked to the identifying nucleic acid (para [0009] - 'The encoding nucleic acid is translationally linked at or near its 3' terminus to the C-terminus of its encoded peptide, ... via a peptide acceptor such as puromycin'; para [0057]; para [0059] - 'puromycin acts as a universal inhibitor of protein synthesis by binding the translation complex A site, accepting the growing peptide chain, and falling off the ribosome ...methods for translationally linking an encoding nucleic acid and encoded peptide ... effecting the joining using a peptide acceptor such as puromycin, which can be linked at or near the 3' terminus of the encoding nucleic acid such that it can enter the ribosome complex during translation and be incorporated at the C-terminus of the growing (nascent) peptide, thereby terminating translation and linking the encoding nucleic acid and encoded peptide', wherein ' puromycin ... falling off the ribosome... terminating translation and linking the encoding nucleic acid and encoded peptide' indicates 'wherein the peptide portion is dissociated from the ribosome before being linked to the identifying nucleic acid'; Please see Alkinson for the translation steps: Entire documentation, especially pg 6.5, Elongation; and pg 6.6, Translocation and Termination).

Regarding claim 8, the combination of Roberts and Hung discloses the set of peptide constructs from claim 1, and the said combination further obviates wherein the set of peptide constructs comprises at least 100,000 distinct peptide constructs (Roberts: para [0090] - 'libraries of molecules having a diversity of at least about 10.sup.9 different molecules'; para [0008] - 'a library of nucleic acid-peptide fusion molecules'; para [0127] - the starting library contained approximately 3.times.10.sup.12 different peptides')
---each comprising a peptide portion of at least 10 amino acids and an identifying oligonucleotide portion (Roberts: para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide', wherein 'an encoding nucleic acid' is 'an identifying oligonucleotide portion'; para [0005] - 'it is easier to determine a nucleotide sequence of a nucleic acid molecule encoding a peptide than it is to determine the amino acid sequence of a peptide,...Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide'; para [0065] - 'the nucleic acid-peptide fusion molecules can include any number of amino acid resides...at least... 15, 20, 25, 30, or more amino acid residues')
---wherein the peptide portions are encoded within oligonucleotide sequences that are custom designed (Roberts: para [0004] - 'Libraries of peptides ... be prepared based on a known peptide', wherein 'be prepared based on a known peptide' is 'custom-designed'; para [0009] - 'a library of diverse nucleic acid-peptide fusion molecules, wherein each molecule of the library comprises an encoding nucleic acid ... linked to an encoded peptide').
----such that at least 90% of the sequences contain no more than one in-frame codon that can function as a stop codon in the translation system used to make the peptide constructs (Roberts: para [0092] - 'the orthogonal aminoacylated tRNA, which is charged with an unnatural amino acid residue, recognizes a stop codon... a start codon operably linked to a protein coding sequence, and each of which is linked to a peptide acceptor at the 3'-end of the peptide coding sequence, which includes or can include one or a series of stop codons, ... to produce a population of RNA-peptide fusion molecules comprising peptides', wherein additional stop codons are used for translating unatural amino acids, one of ordinary skill in the art at the time the invention was made would have known to include no more than one in-frame codon that can function as a stop codon in the translation system used to make the peptide constructs because is the basic principle for successful protein translation; para [0094] - 'an amber suppressor tRNA, which recognizes a UAG stop codon. ...other unnatural residues such as N-methyl glycine and N--(S)-phenylethyl glycine similarly can be used'; Hung: para [0073] - 'a fusion protein may contain a heterologous N-terminal domain (e.g. an epitope tag) fused in-frame with a GPCR that has had its N-terminal methionine residue either deleted or substituted with an alternative amino acid', wherein 'fused in-frame' is the basic practice including 'in-frame codon that can function as a stop codon' for protein translation; para [0039] - 'The boundaries of the coding sequence are typically determined by a start codon at the 5' (amino) terminus and a translation stop codon at the 3' (carboxy) terminus', wherein 'a translation stop codon at the 3' (carboxy) terminus' indicates each conding sequence having 'one in-frame codon that can function as a stop codon in the translation system used to make the peptide constructs', one of ordinary skill in the art at the time the invention was made would have known to have ' at least 90% of the sequences contain no more than one in-frame codon that can function as a stop codon in the translation system used to make the peptide constructs' for producing sufficient amount of distinct peptides, but not high percentage of premature peptides due to the presence of undesired stop codon).

**********Continued in the next supplemental box**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/32759

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
The previous supplemental box - Box V No 2 (citations and explanations)

Claim 6 lacks an inventive step under PCT Article 33(3) as being obvious over Roberts, in view of Hung, as above, and further in view of US 2007/0014810 A1 to BAKER et al. (hereinafter 'Baker').

Regarding claim 6, the combination of Roberts and Hung discloses a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism, as discussed in the discussion of claim 1. Roberts further discloses using the set of peptide constructs for detecting a desired activity of a peptide for identifying the peptide sequence associated with the activity (para [0005] - 'Upon identifying a peptide having a desired activity, the sequence of the encoding nucleic acid associated with the peptide can be determined, thus providing information as to the amino acid sequence of the encoded peptide').

Said combination does not specifically teach wherein the peptide sequences are grouped into one or more sets of partially overlapping sequences. Baker discloses a method for identifying ligand binding domains of a sequence of interest, the method comprising producing a set of peptide sequences that are partially overlapping sequences that cover the entire sequence of the sequence of interest for identifying ligand binding domains (para [0359] - 'The identification of motifs and/or super motifs that correlate with high and intermediate affinity binding ... identification of immunogenic peptide epitopes ... all possible peptides of 9 amino acids in length and overlapping by eight amino acids ... which cover the entire sequence of the ... proteins ...were evaluated for binding to five allele-specific HLA molecules'; para [0361] - 'a large fraction of HLA class I and class II molecules can be classified into a relatively few supertypes, each characterized by largely overlapping peptide binding repertoires, and consensus structures of the main peptide binding pockets'). Although Baker does not specifically teach the peptide sequences are grouped into one or more sets of partially overlapping sequences, one of ordinary skill in the art at the time the invention was made would have known to do so by grouping partially overlapping sequences generated from the same protein in the same group for facilitating characterization of the protein function associated with the peptide fragments in the protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Roberts and Hung with that of Baker, to obtain a set of at least 5,000 distinct peptide constructs, each comprising a peptide portion and an identifying oligonucleotide portion, wherein the peptide portions are encoded by oligonucleotide sequences that are custom-designed so that at least 10% of the set of peptide constructs produced contain contiguous peptide sequences of at least 12 amino acids that have more than 80% amino acid identity to protein sequences encoded by up to 100 different species of organism, based on the combination of Roberts and Hung, and further wherein the peptide sequences are grouped into one or more sets of partially overlapping sequences, based on the combination of Baker, Roberts and Hung, in order to obtain a set of distinct peptide constructs that include all factional fragments of the targeted protein sequences for facilitating characterization of the functional domain of the targeted protein sequences in different species of organism.

Claims 1-3 and 6-8 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

Electronic Acknowledgement Receipt

EFS ID:	17216964
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/Diane Blevins
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	24-OCT-2013
Filing Date:	05-APR-2011
Time Stamp:	17:04:46
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	Miscellaneous Incoming Letter	69993-20002_00-Trans_of_IDS.pdf	24966 3ea94cab6a16919fea2416bec6b7bc54e957d756	no	1

Warnings:	
Information:	

2	Transmittal Letter	69993-20002_00_-_SIDS.pdf	24995 b98c93b70524e16204b17104f6bbf99a836b513d	no	3
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	69993-20002_00_-_SB_08.pdf	69666 d8b8aa80cf4d25d061f05942c92dd57060c47985	no	5
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Foreign Reference	43_EP1712623.pdf	3120009 8ed42314b60eba9e8c3fcd20c5172979b6b15d30	no	49
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Information:					
5	Foreign Reference	44_WO2003010176.pdf	1543534 f3863f4ebacebb34bf96386a74890fa874d51d4a	no	26
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24	Non Patent Literature	63_IPRP_PCTUS2010044134_01312012.pdf	355766 e956b499389edce7371ade52f6b01df0fdb84612	no	10
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25	Non Patent Literature	64_COMM_EP107470973_07262013.pdf	702067 fa43b6a0ad93201e3232245fa5ca0757de3126a9	no	5
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28	Non Patent Literature	67_OA_US13514045_02212013.pdf	261525 c7b36f80f7a7c7398d5760197454e73dbf49bd82	no	8

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29	Non Patent Literature	68_RESPOA_US13514045_06172013.pdf	315180 7992cd6eb8e983126ffa3642c036b982a68d2161	no	8
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30	Non Patent Literature	69_RESPOA_13514045_06272013.pdf	142873 6ea56aa86d961a56aae4acdea30634e3b830330f	no	5
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32	Non Patent Literature	71_IPRP_PCTUS2010059327_06122012.pdf	727086 784b610c8bbb23ad52232307b9b6008f4fee7412	no	11
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33	Non Patent Literature	72_PATEXMRPRT_AU2010328226_05092013.pdf	1374467 03d49a3dbaf52553003f7910c11d56bfd04b9907	no	4
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34	Non Patent Literature	73_CNOA_CN2010800553512_07232013.pdf	2242737 aaacba37f6ceb417201a1303e45f12f3a2fa535f	no	22
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36	Non Patent Literature	75_RSPEPSRCHRPRT_EP1083656851403_09102013.pdf	2821289 2978cc7db30563198ba95c1314cc706b269f6bf3	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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	9

Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	S. Merkling
Attorney Docket Number	699932000200

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement (3 pages)
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Form PTO/SB/08A/B (5 pages)
References (93)

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP (Customer No. 25225)		
Signature	/Bu Yin/		
Printed name	Bu Yin		
Date	October 24, 2013	Reg. No.	68,930

I hereby certify that this paper and the accompanying documents listed above are being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: October 24, 2013 Signature: /Diane Blevins/ (Diane Blevins)

sd-628671

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: October 24, 2013
Electronic Signature for Diane Blevins: /Diane Blevins/

Patent
Docket No. 699932000200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mark S. CHEE

Application No.: 13/080,616

Filing Date: April 5, 2011

For: SPATIALLY ENCODED BIOLOGICAL ASSAYS

Examiner: Sally Anne Merkling

Group Art Unit: 1773

Confirmation No.: 2142

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98

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

Dear Madam:

Pursuant to 37 C.F.R. § 1.97 and § 1.98, Applicant submits for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. Copies of U.S. Patent Publications and Patents are not submitted herewith pursuant to 37 C.F.R. § 1.98(a)(2)(ii). Copies of the foreign documents and non-patent literature are submitted herewith. The Examiner is requested to make these documents of record.

sd-627973

This Information Disclosure Statement is submitted:

☐ With the application; accordingly, no fee or separate requirements are required.

☐ With the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required.

☐ Before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☒ Within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☐ After receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance.

- ☐ The required fee is submitted herewith.
- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above; accordingly, no fee is believed to be due.

☐ After mailing of a final Office Action or Notice of Allowance, but before payment of the Issue Fee.

- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above and the required fee is submitted herewith.

Applicant would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

The information contained in this Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

sd-627973

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing Docket No. 699932000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 24, 2013

Respectfully submitted,

Electronic signature: /Bu Yin/
Bu Yin
Registration No.: 68,930
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego, California 92130-2040
(858) 720-7912

sd-627973

Electronic Acknowledgement Receipt

EFS ID:	17217315
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/Diane Blevins
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	24-OCT-2013
Filing Date:	05-APR-2011
Time Stamp:	17:06:58
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	100_BURNS_2001.pdf	777057 5223441517b38b632d68480954cc037fa13a91ef	no	8
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4	Non Patent Literature	104_DARMANIS_2011.pdf	819358 dcddbf15a19fb2d7543f86bb8e2e043338ae84d6	no	10
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13	Non Patent Literature	113_HENDRICKSON_1995.pdf	1792648 6c86b8af42156c1a1047af514cbbd2c60b913410	no	8
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Warnings:					
Information:					
		Total Files Size (in bytes):	69526870		

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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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

25225 7590 12/17/2013

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
MERKLING, SALLY ANNE	
ART UNIT	**PAPER NUMBER**
1773	

NOTIFICATION DATE	DELIVERY MODE
12/17/2013	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):

PatentDocket@mofo.com
EOfficeSD@mofo.com

Office Action Summary	Application No. 13/080,616	Applicant(s) CHEE, MARK S.	
	Examiner SALLY MERKLING	Art Unit 1773	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 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 *4/5/2011*.

☐ 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) *1-57* 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) _____ is/are rejected.

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

9)☒ Claim(s) *1-57* 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 _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

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

4) ☐ Other: _____.

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

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-39 are drawn to an oligonucleotide array device, classified in class 435, subclass 287.2.

II. Claims 40-57 are drawn to a protein based array device classified in class 436, subclass 518.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are directed to related products. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, mode of operation, function or effect because invention I is drawn to a detection and expression device based on polynucleotides whereas invention II is drawn to an apparatus consisting of protein based probes and similar detection and expression schemes. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants and thus the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; the inventions do not overlap in scope, i.e., are mutually exclusive; and the inventions as claimed are not obvious variants.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to

petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A. Sakelaris whose telephone number is 5712726297. The examiner can normally be reached on Monday-Friday 8-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 5712721267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SALLY MERKLING/
Primary Examiner, Art Unit 1773
12/11/2013

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	SALLY MERKLING	1773

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

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

CLAIM		DATE								
Final	Original	12/11/2013								
	1	÷								
	2	÷								
	3	÷								
	4	÷								
	5	÷								
	6	÷								
	7	÷								
	8	÷								
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	35	÷								
	36	÷								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	SALLY MERKLING	1773

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

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

CLAIM		DATE								
Final	Original	12/11/2013								
	37	÷								
	38	÷								
	39	÷								
	40	÷								
	41	÷								
	42	÷								
	43	÷								
	44	÷								
	45	÷								
	46	÷								
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	51	÷								
	52	÷								
	53	÷								
	54	÷								
	55	÷								
	56	÷								
	57	÷								

Docket No.: 699932000200
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Mark S. CHEE	Confirmation No.: 2142
Application No.: 13/080,616	Art Unit: 1773
Filed: April 5, 2011	Examiner: Sally Anne Merkling
For: SPATIALLY ENCODED BIOLOGICAL ASSAYS	

RESPONSE TO RESTRICTION REQUIREMENT

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

Dear Commissioner:

INTRODUCTORY COMMENTS

This is in response to the Restriction Requirement dated December 17, 2013, for which a response is due January 17, 2013. Accordingly, this response is timely filed. Consideration of the pending claims on the merits, as amended, in light of the remarks presented herein is respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 10 of this paper.

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CLAIM AMENDMENT

1. (currently amended): ~~An assay system~~ A method 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~~ comprising the following steps:

providing a sample affixed to a support;

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

2. (currently amended): The ~~assay system~~ method of claim 1, wherein the biological targets are nucleic acids and the encoded probes are oligonucleotides.

3. (currently amended): The ~~assay system~~ method of claim 2, wherein there are two encoded probes for each of the multiple nucleic acid targets.

4. (currently amended): The ~~assay system~~ method of claim 1, wherein the multiple biological targets are proteins, the probe regions of the encoding probes are proteins and the coding tags comprise oligonucleotides.

5. (currently amended): The ~~assay system~~ method of claim 4, wherein the multiple biological targets comprise enzymes.

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6. (currently amended): The ~~assay system~~ method of claim 1, wherein probe regions of the encoded probes comprise antibodies.

7. (currently amended): The ~~assay system~~ method of claim 1, wherein the probe regions of the encoded probes are aptamers.

8. (currently amended): The ~~assay system~~ method of claim 1, wherein the probe regions of the encoded probes are small molecules.

9. (currently amended): The ~~assay system~~ method of claim 1, further comprising an amplification step between the separating step and the determining step.

10. (currently amended): The ~~assay system~~ method of claim 1, wherein the determining step is performed by nucleic acid sequencing or high-throughput sequencing.

11. (currently amended): The ~~assay system~~ method of claim 10, wherein the sequencing is high-throughput digital nucleic acid sequencing.

12. (currently amended): The ~~assay system~~ method of claim 1, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20.

13. (currently amended): The ~~assay system~~ method of claim 12, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 50.

14. (currently amended): The ~~assay system~~ method of claim 13, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 75.

15. (currently amended): The ~~assay system~~ method of claim 14, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 100.

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16. (currently amended): The ~~assay system~~ method of claim 15, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000.

17. (currently amended): The ~~assay system~~ method of claim 16, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 10,000.

18. (currently amended): The ~~assay system~~ method of claim 17, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 100,000.

19. (currently amended): The ~~assay system~~ method of claim 18, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000,000.

20. (currently amended): The ~~assay system~~ method of claim ~~11~~ 1, wherein the sequences of at least one hundred thousand encoding probes are determined in parallel.

21. (currently amended): The ~~assay system~~ method of claim 20, wherein the sequences of at least five hundred thousand encoding probes are determined in parallel.

22. (currently amended): The ~~assay system~~ method of claim 21, wherein the sequences of at least one million encoding probes are determined in parallel.

23. (currently amended): The ~~assay system~~ method of claim 1, wherein the known spatial pattern is determined by histological features of the sample.

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24. (currently amended): The ~~assay system~~ method of claim 1, wherein software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step and the associating step.

25. (currently amended): The ~~assay system~~ method of claim 1, wherein 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.

26. (currently amended): The ~~assay system~~ method of claim 1, wherein the probe regions of the encoding probes are nucleic acids and the separating step is accomplished by ~~a~~ washing ~~of~~ the sample.

27. (currently amended): ~~An assay system~~ A method to determine spatial patterns of abundance or activity or both of multiple nucleic acid targets at multiple sites in a sample, ~~wherein the assay system performs~~ comprising 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, wherein the ~~combination of~~ one or more encoding agents delivered to each site ~~is different~~ identify the location of the site in the sample;

coupling the encoding agents and the oligonucleotide probes delivered to each site 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~~ nucleic acid targets to the locations of the multiple sites in the sample.

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28. (currently amended): The ~~assay system~~ method of claim 27, wherein the product of the multiple ~~biological~~ nucleic acid targets being assayed and the multiple sites in the sample is greater than 20.

29. (currently amended): The ~~assay system~~ method of claim 28, wherein the product of the multiple ~~biological~~ nucleic acid targets being assayed and the multiple sites in the sample is greater than 50.

30. (currently amended): The ~~assay system~~ method of claim 29, wherein the product of the multiple ~~biological~~ nucleic acid targets being assayed and the multiple sites in the sample is greater than 75.

31. (currently amended): The ~~assay system~~ method of claim 30, wherein the product of the multiple ~~biological~~ nucleic acid targets being assayed and the multiple sites in the sample is greater than 10,000.

32. (currently amended): The ~~assay system~~ method of claim 31, wherein the product of the multiple ~~biological~~ nucleic acid targets being assayed and the multiple sites in the sample is greater than 100,000.

33. (currently amended): The ~~assay system~~ method of claim 32, wherein the product of the multiple ~~biological~~ nucleic acid targets being assayed and the multiple sites in the sample is greater than 1,000,000.

34. (currently amended): The ~~assay system~~ method of claim ~~33~~ 27, wherein the sequences of at least one hundred thousand encoding probes are determined in parallel.

35. (currently amended): The ~~assay system~~ method of claim 34, wherein the sequences of at least one million encoding probes are determined in parallel.

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36. (currently amended): The ~~assay system~~ method of claim 27, wherein two oligonucleotide probes are delivered for each of the multiple nucleic acid targets.

37. (currently amended): The ~~assay system~~ method of claim 27, wherein the coupling step is performed by ligation.

38. (currently amended): The ~~assay system~~ method of claim 27, wherein the coupling step is performed by extension followed by ligation.

39. (currently amended): The ~~assay system~~ method of claim 27, further comprising an amplification step between the coupling step and the determining step.

40. (withdrawn): An assay system to determine spatial patterns of abundance or activity or both of multiple protein 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 protein targets to the multiple sites in the sample in a known spatial pattern, wherein 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.

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41. (withdrawn): The assay system of claim 40, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20.

42. (withdrawn): The assay system of claim 41, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 50.

43. (withdrawn): The assay system of claim 42, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 75.

44. (withdrawn): The assay system of claim 43, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 100.

45. (withdrawn): The assay system of claim 44, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 500.

46. (withdrawn): The assay system of claim 45, wherein the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1000.

47. (withdrawn): The assay system of claim 46, wherein the sequence of at least ten thousand encoding probes are determined in parallel.

48. (withdrawn): The assay system of claim 40, wherein the sequence of at least one hundred thousand encoding probes are determined in parallel.

49. (withdrawn): The assay system of claim 48, wherein the sequence of at least one million encoding probes are determined in parallel.

50. (withdrawn): The assay system of claim 40, further comprising an amplification step between the coupling step and the determining step.

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51. (withdrawn): The assay system of claim 40, wherein the protein targets are enzymes, and the probe regions of the encoded probes are substrates, putative substrates of both for the enzymes.

52. (withdrawn): The assay system of claim 40, wherein the probe regions of the encoded probes are affinity capture agents.

53. (withdrawn): The assay system of claim 52, wherein the probe regions of the encoded probes are antibodies.

54. (withdrawn): The assay system of claim 52, wherein the probe regions of the encoded probes are aptamers.

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REMARKS

Claim Status

Claims 1-57 are pending. Claims 40-57 will be withdrawn by virtue of this response. Claims 1-39 are amended, support for which is found throughout the original specification, including in the original claims. No new matter is introduced by way of the amendment. Entry of the amendment and consideration of the claims on the merits are respectfully requested.

Restriction Requirement

Applicant elects, without traverse, to prosecute Group I. Claims 1-39 encompass the elected subject matter. Applicant's election is made without prejudice.

Reservation of Rights

Applicant expressly reserves the right under 35 U.S.C. § 121 to file a divisional application directed to the non-elected subject matter during the pendency of this application, or to pursue the non-elected subject matter in this application or an application claiming priority from this application.

Should anything about this election remain unclear, a telephone call to the undersigned is respectfully requested. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

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In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 699932000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 16, 2014

Respectfully submitted,

Electronic signature: / Bu Yin /

Bu Yin
Registration No.: 68,930
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego, California 92130-2040
Telephone: (858) 720-7912

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: January 16, 2014 Electronic Signature for Jessica Thomas: /Jessica Thomas/

Curio EX1012-p. 257
Curio v Prognosys

Electronic Acknowledgement Receipt

EFS ID:	17938549
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/Peggy Bozym
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	16-JAN-2014
Filing Date:	05-APR-2011
Time Stamp:	19:43:54
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	Miscellaneous Incoming Letter	2014-01-16_Transmittal_699932000200.pdf	24671 f94a8bcddb86774ffbb1c5cf71ce508737fbb23b	no	1

Warnings:	
Information:	

2		2014-01-16_Response_699932000200.pdf	36102 abdca0e0afa96a2ac3e7f56f546f3c5d3d14bd04	yes	11

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Response to Election / Restriction Filed	1	1
Claims	2	9
Applicant Arguments/Remarks Made in an Amendment	10	11

Warnings:	
Information:	
Total Files Size (in bytes):	60773

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	12

Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	S. Merkling
Attorney Docket Number	699932000200

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply (11 pages)
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

Customer No. 25225

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP		
Signature	/Bu Yin/		
Printed name	Bu Yin		
Date	January 16, 2014	Reg. No.	68,930

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: January 16, 2014 Electronic Signature for Jessica Thomas: /Jessica Thomas/

sd-633976

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 13/080,616	Filing Date 04/05/2011	☐ 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 $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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

AMENDMENT **01/16/2014**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 54	Minus	** 57	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***4	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ 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.
** 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 number found in the appropriate box in column 1.

LIE
/TRINA RIDDICK/

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.

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	2

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2010/0099103	04-2010	Hsieh et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	2.	WO-2010/019826	02-2010	Nanostring Technologies, Inc.		

Examiner Signature		Date Considered	

*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	3.	BLOKZIJL et al., "Profiling protein expression and interactions: proximity ligation as a tool for personalized medicine," J Intern Med (2010) 268:232-245	
	4.	CHENG et al., "Sensitive Detection of Small Molecules by Competitive Immunomagnetic-Proximity Ligation Assay," Anal Chem (2012) 84:2129-2132	
	5.	ELLINGTON et al., "Antibody-based protein multiplex platforms: technical and operational challenges," Clin Chem (2010) 56(2):186-193	
	6.	European Search Report for EP 11766613.1, dated 15 January 2014, 5 pages	
	7.	Final Office Action for US 13/266,568, mailed 5 December 2013, 7 pages	
	8.	First Examination Report for CN 201180017696.3, mailed 18 October 2013, 14 pages	
	9.	FLANIGON et al., "Multiplex protein detection with DNA readout via mass spectrometry," N Biotechnol (2013) 30(2):153-158	
	10.	GU et al., "Protein tag-mediated conjugation of oligonucleotides to recombinant affinity binders for proximity ligation," N Biotechnol (2013) 30(2):144-152	
	11.	HAMMOND et al., "Profiling cellular protein complexes by proximity ligation with dual tag microarray readout," (2012) 7(7):e40405	
	12.	MIR et al., "Sequencing by cyclic ligation and cleavage (CycLiC) directly on a microarray captured template," Nucleic Acids Research (2009) 37(1):e5-1	
	13.	LUNDBERG et al., "Multiplexed homogeneous proximity ligation assays for high-throughput protein biomarker research in serological material," Mol Cell Proteomics (2011) 10(4):M110.004978	

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	**13/080,616**
				Filing Date	April 5, 2011
				First Named Inventor	Mark S. CHEE
				Art Unit	1634
				Examiner Name	J. Martinell
Sheet	2	of	2	Attorney Docket Number	699932000200

	14.	Patent Examination Report No. 1 for AU 2010278710, issued 11 July 2013, 3 pages	
	15.	Preliminary Amendment for US 14/068,921, filed 22 November 2013, 10 pages	
	16.	Proseek® Multiplex 96x96 User Manual (2013) Olink Bioscience, Uppsala, Sweden, 20 pages	
	17.	Response to First Examination Report for EP 10836568.5-1403, filed 17 February 2014, 10 pages	
	18.	ZHANG et al., "Assembling DNA through Affinity Binding to Achieve Ultrasensitive Protein Detection," Angew Chem Int Ed (2013) 52:2-10	
	19.	ZHANG et al., "Binding-induced DNA assembly and its application to yoctomole detection of proteins," Anal Chem (2012) 84(2):877-884	

Examiner Signature		Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

sd-636464

Electronic Acknowledgement Receipt

EFS ID:	18339461
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/Lauren Swan
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	28-FEB-2014
Filing Date:	05-APR-2011
Time Stamp:	17:39:33
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	Miscellaneous Incoming Letter	2014-02-28_TRANSMITTAL_699932000200.pdf	24832 d85f26092946d7091f98658ac8fe2e812ba388d6	no	1

Warnings:	
Information:	

2	Transmittal Letter	2014-02-28_sIDS_699932000200.pdf	24951 ccc2e3145a2580b364e28b8b649a1cab36f53648	no	3
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	2014-02-28_SB08_699932000200.pdf	33908 1b38b4d334d53989872a9a45412b13c8a0ca7829	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Foreign Reference	2_WO2010019826.pdf	5473055 0d7d115950b9e6dbf68ef28dd022e700362597b4	no	92
Warnings:					
Information:					
5	Non Patent Literature	3_BLOKZIJL.pdf	756561 1ecfbe9c0fdb48e6d06ca6ea63363b8cf0c2ceb2	no	14
Warnings:					
Information:					
6	Non Patent Literature	4_CHENG.pdf	1933661 932344fd7d604d563b2a9c207dfe83fc8006abec	no	4
Warnings:					
Information:					
7	Non Patent Literature	5_ELLINGTON.pdf	614191 c02516ac5164e0eeee89a0a69fa16a6d1cb9a511	no	8
Warnings:					
Information:					
8	Non Patent Literature	6_EurSrchRpt_EP11766613.pdf	260984 65bc740e440b19600cb38e16760f2e778122c493	no	5
Warnings:					
Information:					
9	Non Patent Literature	7_FinalOA_Dec52013_13266568.pdf	260008 81419d14660f583122d670d1dfaaa2a53fce446a	no	7
Warnings:					
Information:					
10	Non Patent Literature	8_FirstExRpt_CN201180017696 3.pdf	890977 5ee360275950d5ca0eda6e082b95e024b31aee69	no	14

Warnings:					
Information:					
11	Non Patent Literature	9_FLANIGON.pdf	747185 9421da40aa929d937d2a295939af914764c2e23f	no	6
Warnings:					
Information:					
12	Non Patent Literature	10_GU.pdf	875704 a6bca40535adffef2c3202aad84d225acce9a155	no	9
Warnings:					
Information:					
13	Non Patent Literature	11_HAMMOND.pdf	571074 bff852cc06e2256a5d9a17d38a20aef2f1a2f536	no	9
Warnings:					
Information:					
14	Non Patent Literature	12_MIR.pdf	828699 8e26f6d97d755726126b8d3e98900c550e2f1e06	no	8
Warnings:					
Information:					
15	Non Patent Literature	13_LUNDBERG_Multiplexed.pdf	1221764 d7be07bd7a6a2e89b040a57b09fd6b0ad378d2ac	no	10
Warnings:					
Information:					
16	Non Patent Literature	14_ExRpt_AU2010278710.pdf	643403 cdd66f4d374d0b7854cfceb0cce5b05cd05ca97d	no	3
Warnings:					
Information:					
17	Non Patent Literature	15_PrelimAmend_14068921.pdf	332217 02a1403f5692e641bc9a44894d9ddfad5444e036	no	10
Warnings:					
Information:					
18	Non Patent Literature	16_Proseek_Multiplex.pdf	2650723 c9c5d37d3c20ddf91d464ab7ad53b8e5e49ef4e9	no	20
Warnings:					
Information:					
19	Non Patent Literature	17_Response_EP108365685.pdf	202795 2ba439c23a30591b98a3435de3623dbdb139ce19	no	10

Warnings:					
Information:					
20	Non Patent Literature	18_ZHANG_Assembling.pdf	1656840 ded8c2e839589b117084ebb9a6a26f15faf1a125	no	9
Warnings:					
Information:					
21	Non Patent Literature	19_ZHANG_Binding.pdf	1722500 14458285a78770ca61e28a467040f5ded7dfdce1	no	8
Warnings:					
Information:					
		Total Files Size (in bytes):	21726032		

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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.

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	6

Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

PTO/SB/08A/B (2 pages)

References (18)

Remarks

Customer No. 25225

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP		
Signature	/Bu Yin/		
Printed name	Bu Yin		
Date	February 28, 2014	Reg. No.	68,930

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: February 28, 2014 Electronic Signature for Lauren Swan: /Lauren Swan/

sd-636991

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: February 28, 2014
Electronic Signature for Lauren Swan: /Lauren Swan/

Patent
Docket No. 699932000200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mark S. CHEE

Application No.: 13/080,616

Filing Date: April 5, 2011

For: SPATIALLY ENCODED BIOLOGICAL ASSAYS

Examiner: J. Martinell

Group Art Unit: 1634

Confirmation No.: 2142

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98

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

Dear Madam:

Pursuant to 37 C.F.R. § 1.97 and § 1.98, Applicant submits for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. Copies of the foreign document and non-patent literature are submitted herewith. The Examiner is requested to make these documents of record.

sd-636451

This Information Disclosure Statement is submitted:

☐ With the application; accordingly, no fee or separate requirements are required.

☐ With the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required.

☐ Before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☒ Within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☐ After receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance.

- ☐ The required fee is submitted herewith.
- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above; accordingly, no fee is believed to be due.

☐ After mailing of a final Office Action or Notice of Allowance, but before payment of the Issue Fee.

- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above and the required fee is submitted herewith.

Applicant would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

The information contained in this Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

sd-636451

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing Docket No. 699932000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 28, 2014

Respectfully submitted,

Electronic signature: /Bu Yin/
Bu Yin
Registration No.: 68,930
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
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(858) 720-7912

sd-636451

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1.	Response After Final Office Action for 13/266,568, filed 4 March 2014	
	2.	Response to First Examination Report for CN 201180017696.3, filed 3 March 2014	
	3.	Response to Patent Examination Report No. 1 for AU 2011237729, filed 3 March 2014	

Examiner Signature		Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

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Dated: March 17, 2014
Electronic Signature for Jennifer Jung: /Jennifer Jung/

Patent
Docket No. 699932000200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mark S. CHEE

Application No.: 13/080,616

Filing Date: April 5, 2011

For: SPATIALLY ENCODED BIOLOGICAL ASSAYS

Examiner: J. Martinell

Group Art Unit: 1634

Confirmation No.: 2142

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98

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

Dear Commissioner:

Pursuant to 37 C.F.R. § 1.97 and § 1.98, Applicant submits for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. Copies of the documents are submitted herewith. The Examiner is requested to make these documents of record.

sd-637356

This Information Disclosure Statement is submitted:

☐ With the application; accordingly, no fee or separate requirements are required.

☐ With the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required.

☐ Before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☒ Within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☐ After receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance.

- ☐ The required fee is submitted herewith.
- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above; accordingly, no fee is believed to be due.

☐ After mailing of a final Office Action or Notice of Allowance, but before payment of the Issue Fee.

- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above and the required fee is submitted herewith.

Applicant would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

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Dated: March 17, 2014

Respectfully submitted,

Electronic signature: /Bu Yin/
Bu Yin
Registration No.: 68,930
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego, California 92130-2040
(858) 720-7912

sd-637356

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	5

Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement – 3 pages
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosures:
  PTO/SB/08 in 1 page; 3 references

Remarks

Customer No. 25225

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP		
Signature	/Bu Yin/		
Printed name	Bu Yin		
Date	March 17, 2014	Reg. No.	68,930

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: March 17, 2014 Signature: /Jennifer Jung/ (Jennifer Jung)

sd-637938

Electronic Acknowledgement Receipt

EFS ID:	18497041
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/Jennifer Jung
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	17-MAR-2014
Filing Date:	05-APR-2011
Time Stamp:	17:53:46
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	1_RespAF_13266568_030414.pdf	462334 13b0a15406bc9a0e1bf225b23114a64f1867c4ed	no	11

Warnings:	
Information:	

2	Non Patent Literature	2_RespExRpt_CN201180017696 3.pdf	8406200 9c99481fb59d1e8471c3acfddf1f74ed496ea266	no	19
Warnings:					
Information:					
3	Non Patent Literature	3_Resp_AU2011237729.pdf	4946044 f704ce26809793d01e668ffb188a369093135df0	no	25
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	69993_IDS_List.pdf	25121 657ac47df157fd20d9c87ad30c231d633cef3d72	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
5	Transmittal Letter	69993_IDS_Transmittal.pdf	24833 136013f0bd02a1103d1a40e70918861010dcfcea	no	3
Warnings:					
Information:					
6	Transmittal Letter	69993_Transmittal.pdf	24751 579736ae1f9987b69746811a5015be9188a31ba7	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	13889283		

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

25225 7590 04/09/2014

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
MARTINELL, JAMES	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
04/09/2014	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):

PatentDocket@mofo.com
EOfficeSD@mofo.com

Office Action Summary	Application No. 13/080,616	Applicant(s) CHEE, MARK S.	
	Examiner JAMES MARTINELL	Art Unit 1634	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *1/16/14*.

☐ 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) *1-54* is/are pending in the application.

5a) Of the above claim(s) *40-54* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-39* 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 *4/5/11* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *3/17/14; 2/28/14; 10/24/13; 11/30/11*.

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

4) ☐ Other: _____.

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

Applicant's election of Group I, claims 1-39 in the reply filed on January 16, 2014 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 40-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 16, 2014.

References that are crossed out on the Information Disclosure Statements are those that are not in the English language and for which no English language translation is in the file. See MPEP 609.

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: 160, 200, 306, and 550. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) 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 disclosure is objected to because of the following informalities: The Brief Description of the Drawings (paragraph 0004) should mention Figures 4A, 4B, and 4C.

Appropriate correction is required.

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

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

Claims 1-26 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. The claims are vague, indefinite, and incomplete.

(a) The recitation of "determining all or a portion of a sequence" (claim 1) is vague, indefinite, and incomplete because there is no mention of what the sequence is a part of.

(b) The recitation of "wherein the known spatial pattern is determined by histological features of the sample" is vague and indefinite because the term is not clearly defined in the application and because there is no clear and definite art-recognized meaning for the term, "histological features".

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

A person shall be entitled to a patent unless –

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

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-37, and 39 are rejected under pre-AIA 35 U.S.C. 102(b) as being clearly anticipated by Roth et al (U.S. Patent Application Publication 2006/0046313 A1). Roth et al teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (paragraphs 0032 and 0140), wherein the assay system performs the steps of providing a sample affixed to a support (paragraph 0033), delivering encoded probes for the multiple biological targets to the multiple sites in the sample is 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 (paragraph 0033), allowing the encoded probes to interact with the biological targets (paragraph 0033), separating the encoded probes that interact with the biological targets from encoded probes that do not interact with the biological targets (paragraph 0033), determining all or a portion of a sequence of the encoded probes (paragraphs 0104 and 0122), and associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample (paragraph 0033). Roth et al also teach the use of oligonucleotide probes (*e.g.*, paragraphs 0033 and 0102-0103), washing unhybridized probes from the probes bound the targets (paragraphs 0033 and 0102-0103), delivering one or more encoding agents to locations of the multiple sites in the sample according to a known spatial pattern wherein the combination of encoding agents delivered to each site is different (paragraphs 0086 and 0097), coupling the encoding agents and the oligonucleotide probes to form encoded probes (paragraph 0086), determining all or a portion of a sequence of the encoded probes using high throughput sequencing (paragraphs 0104 and 0122) and associating the abundance or activity or both of multiple biological targets to the locations of multiple sites in the sample (paragraphs 0033, 0104, and 0122). Roth et al further teaches the biological targets are nucleic acids and the encoded probes are oligonucleotides (paragraphs 0102-0103), that there are

two encoded probes for each of the multiple nucleic acid targets (paragraphs 0047 and 0091), probe regions of the encoded probes comprise antibodies, the probe regions of the encoded probes are aptamers (paragraph 0069), the probe regions of the encoded probes are small molecules (paragraph 0069), an amplification step between the separating step and the determining step (paragraph 0105), the determining step is performed by nucleic acid sequencing (paragraph 0104 and 0122), sequencing is high throughput digital nucleic acid sequencing (paragraphs 0039 and 0122-0124), the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000,000 (paragraphs 0097-0098 and 0138), the sequences of at least 1,000,000 encoding probes are determined in parallel (paragraphs 0097-0098, 0104, and 0138), the known spatial pattern is determined by histological features of the sample (paragraphs 0036 and 0038), software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step, and the associating step (paragraphs 0123-0124). Roth et al teaches the probe regions of the encoded probes are proteins (paragraph 0092) and the separating step is accomplished by encoded probes that interact with the biological targets being captured by an affinity capture agent (paragraph 0027), Separation of interacting probes and non-interacting probes is by washing (paragraphs 0084-0085). Roth et al also teaches two oligonucleotide probes are delivered for each of the multiple nucleic acid targets (paragraph 0083) and the coupling step is performed by ligation (paragraph 0083).

Claims 4, 5, and 38 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Roth et al (U.S. Patent Application Publication 2006/0046313 A1) in view of Lockhart et al (U.S. Patent No. 6,344,316). The discussion of Roth et al above is incorporated here. Lockhart et al teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (Abstract), comprising encoded probes for the multiple biological targets (Abstract), wherein the coding tags comprise oligonucleotides (Abstract and column 24, lines 8-30). It would have been obvious for one of ordinary skill in the art at the time the invention was made to have prepared 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 coding tags comprise oligonucleotides, in view of Roth et al teaching the coding tags are unique and fluorescent for scanning based detection (paragraphs 0031 and 0055), and in light of Lockhart et al teaching unique and fluorescent tags comprising oligonucleotides (column 24, lines 37-61), one of ordinary skill in the art using the labeling methods taught by Lockhart et al applied to the probes of Roth et al for the known and expected result. It also would have been obvious for one of ordinary skill in the art at the time the invention was made to use extension and ligation as the coupling step (see Lockhart et al, column 24, lines 8-30).

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. 13/080,616	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	Classification
*	A	US-2006/0046313 A1	03-2006	Roth et al.	436/518
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	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
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	SALLY MERKLING	1773

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

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

CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
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	34	÷	✓							
	35	÷	✓							
	36	÷	✓							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
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CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014							
	37	÷	✓							
	38	÷	✓							
	39	÷	✓							
	40	÷	N							
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	45	÷	N							
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	54	÷	N							
	55	÷	N							
	56	÷	N							
	57	÷	N							

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	13/080,616
Filing Date	05-April-2011
First Named Inventor	Mark Chee
Art Unit	1773
Examiner Name	Not Assigned
Attorney Docket Number	PGNS007US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number - Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	6,210,894	04-03-2001	Brennan	
	2	6,344,316	02-05-2002	Lockhart et al.	
	3	6,632,641	10-14-2003	Brennan et al.	
	4	6,878,515	04-12-~~2007~~ 2005	Landegren ~~et al.~~	
	5	7,544,473	06-09-2009	Brenner	
	6	7,378,242	05-27-2008	Hurt, et al.	
	7	2003/0232382	12-18-~~06-23~~-2003	Brennan et al.	
	8	2006/0046313	03-02-2006	Roth et al.	
	9	2003/0224419	12-04-2003	Corcoran et al.	
	10	2005/0164292	07-28-2005	Faroqui et al.	
	11	2005/0255548	11-17-2005	Lipovsek et al.	
	12	2006/0134669	06-22-2006	Casasanta III	
	13	2006/0275799	12-07-2006	Banerjee et al.	
	14	2008/0312103	12-18-2008	Nemoto et al.	
	15	2009/0291854	11-26-2009	Weisinger-Mayr et al.	
	16	2005/0260653	11-24-2005	LaBaer et al.	
	17	2010/0184614	07-22-2010	Ye et al.	

Examiner Signature	/James Martinell/	Date Considered	04/04/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet	2	of	4

Complete if Known	
Application Number	13/080,616
Filing Date	05-April-2011
First Named Inventor	Mark Chee
Art Unit	1773
Examiner Name	Not Assigned
Attorney Docket Number	PGNS007US

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] - Number[4] - Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	18	WO 2007/073171	06-28-2007	Van Elij et al.		

Examiner Signature	/James Martinell/	Date Considered	04/04/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 4

Complete if Known	
Application Number	13/080,616
Filing Date	05-April-2011
First Named Inventor	Mark Chee
Art Unit	1773
Examiner Name	Not Assigned
Attorney Docket Number	PGNS007US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	19	FREDRIKSSON, et al., "Protein detection using proximity-dependent DNA ligation assays," Nature Biotech., 20:473-77 (2002)	
	20	FREDRIKSSON, et al., "Multiplexed protein detection by proximity ligation for cancer detection," Nature Methods, 4(4):327-29 (2007	
	21	KOZLOV ,et al., "A High-Complexity Multiplexed Solution-Phase Assay for Profiling Protease Activity on Microarrays," Comb. Chem. And High Throughput, 11:24-35 (2008)	
	22	NIEMEYER, "The developments of semisynthetic DNA/protein conjugates," Trends Biotechnol, 20(9):395-401(2002)	
	23	CHANDRA, et al., "Cell-free synthesis-based protein microarrays and their applications," Proteomics ePub, 5(6):717-30 (2009)	
	24	RAMACHANDRAN et al., "Next-generation high-density self-assembling functional protein arrays,: Nature Methods, 5(6):535-38 (2008)	
	25	Search Report for PCT/US2010/059327 (PGNS005PCT) (3/29/2011)	
	26	Search Report for PCT/US2011/031308 (PGNS007PCT) (6/7/2011)	
	27	Search Report for PCT/US2011/031163 (PGNS008PCT) (5/23/2011)	

Examiner Signature	/James Martinell/	Date Considered	04/04/2014

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Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
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				Filing Date	05-April-2011
				First Named Inventor	Mark Chee
				Art Unit	1773
				Examiner Name	Not Assigned
Sheet		of		Attorney Docket Number	PGNS007US

Dear Sir/Madam:

The references being cited on this form PTO/SB/08 are being called to the attention of the Examiner. It is respectfully requested that the cited references be considered during the prosecution of this application, and the references be made of record therein and appear among the “references cited” on any patent to issue therefrom.

As provided by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all relevant information.

This Information Disclosure Statement is being filed before the issuance of the first Office Action on the merits; thus, applicants do not believe that any fees are due.

Respectfully submitted,

/SarahBrashears/

Sarah J. Brashears
Registration No. 38,087

Date: 30 November 2011

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 5

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	MERKLING, SALLY ANNE
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-6,258,558	07-10-2001	Szostak et al.	
	2.	US-6,261,804	07-17-2001	Szostak et al.	
	3.	US-6,281,804	08-28-2001	Haller et al.	
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	20.	US-2003/0113713	06-19-2003	Glezer et al.	
	21.	US-2005/0026188	02-03-2005	Van Kessel et al.	
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	23.	US-2006/0003394	01-05-2006	Song	
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	28.	US-2007/0020669	01-25-2007	Ericsson	
	29.	US-2007/0026430	02-01-2007	Andersen et al.	
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	31.	US-2008/0108804	05-08-2008	Hayashizaki et al.	
	32.	US-2008/0220981	09-11-2008	McGregor	
	33.	US-2008/0293591	11-27-2008	Taussig et al.	
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	35.	US-2010/0069263	03-18-2010	Shendure et al.	
	36.	US-2010/0113302	05-06-2010	Williams	
	37.	US-2010/0173384	07-08-2010	Johnsson et al.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 5

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	MERKLING, SALLY ANNE
Attorney Docket Number	699932000200

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Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	43.	EP-1712623	10-18-2006			
	44.	WO-2003/010176	02-06-2003			
	45.	WO-2005/026387	03-24-2005			
	46.	WO-2007/041689	04-12-2007			
	47.	WO-2007/060599	05-31-2007			
	48.	WO-2007/076726	07-12-2007			
	49.	WO-2007/145612	12-21-2007			
	50.	WO-2009/032167	03-12-2009			
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	55.	WO-2011/127099	10-13-2011			
	56.	WO-2012/139110	10-11-2012			

Examiner Signature	/James Martinell/	Date Considered	04/04/2014

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	57.	Office Action for US 13/266,568, mailed 29 March, 2013.	
	58.	Response to Office Action for US 13/266,568, filed 29 August 2013.	
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Sheet 3 of 5

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Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	MERKLING, SALLY ANNE
Attorney Docket Number	699932000200

	65.	Restriction Requirement for US 13/514,045, mailed 23 November 2012.	
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/James Martinell/ 04/04/2014

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Sheet 5 of 5

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Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1773
Examiner Name	MERKLING, SALLY ANNE
Attorney Docket Number	699932000200

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Examiner Signature	/James Martinell/	Date Considered	04/04/2014

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

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sd-627975

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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	Art Unit
	JAMES MARTINELL	1634

CPC- SEARCHED		
Symbol	Date	Examiner
C12Q1/6837, 6874; C12Q2565/501, 513, 50, 514, 518, 519, 525, 531, 537, 543, 549; G01N21/6452, 8903; 33/53	4/3/14	JM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST text search (printout attached)	4/3/14	JM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/JAMES MARTINELL/ Primary Examiner.Art Unit 1634

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	5497	(((high adj density) or (high adj resolution)) near5 (array$ or microarray$)) near10 (dna or (nucleic adj acid) or protein or antibod$)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 18:52
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L3	4255	l1 and l2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 18:53
L4	73229	435/6.$[ccls]	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 18:53
L5	28671	435/7.1[ccls]	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 18:53
L6	93617	l4 or l5	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 18:53
L7	2316	l3 and l6	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 18:53
L8	32464	536/23.1[ccls]	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:17
L9	4639	536/24.31[ccls]	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:17
L10	2778	536/24.32[ccls]	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:17
L11	36292	l8 or l9 or l10	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:17
L12	554	l3 and l11	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:17

L13	182	l12 not l7	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:18
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L15	1446	c12q1/6874.cpc.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:32
L16	1207	c12q2565/501.cpc.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:32
L17	296	c12q2565/513.cpc.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:32
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L20	612	c12q2565/518.cpc.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:33
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L25	198	c12q2565/543.cpc.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:34
L26	69	c12q2565/549.cpc.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:34
L27	2244	g01n21/6452.cpc.	US-PGPUB; USPAT; EPO; JPO;	OR	ON	2014/04/03 20:34

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L29	1218	g01n33/53.cpc.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:34
L30	5645	l14 or l15 or l16 or l17 or l18	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:35
L31	1287	l19 or l20 or l21 or l22 or l23	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:35
L32	3102	l24 or l25 or l26 or l27 or l28	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:35
L33	10050	l29 or l30 or l31 or l32	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:35
L34	6010	l2 and l33	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:35
L35	656	l3 and l33	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:36
L36	163	l35 not l7	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:36
L37	145	l36 not l13	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/03 20:36

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	2

Complete if Known	
Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2010/0099103	04-2010	Hsieh et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	2.	WO-2010/019826	02-2010	Nanostring Technologies, Inc.		

Examiner Signature	/James Martinell/	Date Considered	04/04/2014

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	3.	BLOKZIJL et al., "Profiling protein expression and interactions: proximity ligation as a tool for personalized medicine," J Intern Med (2010) 268:232-245	
	4.	CHENG et al., "Sensitive Detection of Small Molecules by Competitive Immunomagnetic-Proximity Ligation Assay," Anal Chem (2012) 84:2129-2132	
	5.	ELLINGTON et al., "Antibody-based protein multiplex platforms: technical and operational challenges," Clin Chem (2010) 56(2):186-193	
	6.	European Search Report for EP 11766613.1, dated 15 January 2014, 5 pages	
	7.	Final Office Action for US 13/266,568, mailed 5 December 2013, 7 pages	
	8.	First Examination Report for CN 201180017696.3, mailed 18 October 2013, 14 pages	
	9.	FLANIGON et al., "Multiplex protein detection with DNA readout via mass spectrometry," N Biotechnol (2013) 30(2):153-158	
	10.	GU et al., "Protein tag-mediated conjugation of oligonucleotides to recombinant affinity binders for proximity ligation," N Biotechnol (2013) 30(2):144-152	
	11.	HAMMOND et al., "Profiling cellular protein complexes by proximity ligation with dual tag microarray readout," (2012) 7(7):e40405	
	12.	MIR et al., "Sequencing by cyclic ligation and cleavage (CycLiC) directly on a microarray captured template," Nucleic Acids Research (2009) 37(1):e5-1	
	13.	LUNDBERG et al., "Multiplexed homogeneous proximity ligation assays for high-throughput protein biomarker research in serological material," Mol Cell Proteomics (2011) 10(4):M110.004978	

/James Martinell/ 04/04/2014

sd-636464

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

ALTERNATIVE TO PTO/SB/08A/B
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	**13/080,616**
				Filing Date	April 5, 2011
				First Named Inventor	Mark S. CHEE
				Art Unit	1634
				Examiner Name	J. Martinell
Sheet	2	of	2	Attorney Docket Number	699932000200

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	14.	Patent Examination Report No. 1 for AU ~~2010279740~~, issued ~~11~~ July 2013, 3 pages	
	15.	Preliminary Amendment for US 14/068,921, filed 22 November 2013, 10 pages	
	16.	Proseek® Multiplex 96x96 User Manual (2013) Olink Bioscience, Uppsala, Sweden, 20 pages	
	17.	Response to First Examination Report for EP 10836568.5-1403, filed 17 February 2014, 10 pages	
	18.	ZHANG et al., "Assembling DNA through Affinity Binding to Achieve Ultrasensitive Protein Detection," Angew Chem Int Ed (2013) 52:2-10	
	19.	ZHANG et al., "Binding-induced DNA assembly and its application to yoctomole detection of proteins," Anal Chem (2012) 84(2):877-884	

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	13/080,616
				Filing Date	April 5, 2011
				First Named Inventor	Mark S. CHEE
				Art Unit	1634
(Use as many sheets as necessary)				Examiner Name	J. Martinell
Sheet	1	of	1	Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS					
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FOREIGN PATENT DOCUMENTS						
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NON PATENT LITERATURE DOCUMENTS			
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	1.	Response After Final Office Action for 13/266,568, filed 4 March 2014	
	2.	~~Response to First Examination Report for CN 201180017606.2, filed 3 March 2014~~	
	3.	Response to Patent Examination Report No. 1 for AU 2011237729, filed 3 March 2014	

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sd-637355

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 1

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	1.	Notice of Acceptance issued in Australian Patent Application No. AU 2011237729, dated 20 March 2014, 6 pages	
	2.	Examination Report issued in European Patent Application No. 10836568.5, dated 12 March 2014, 3 pages	

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sd-643563

Electronic Patent Application Fee Transmittal

Application Number:	13080616
Filing Date:	05-Apr-2011
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Filer:	Bu Yin/Lauren Swan
Attorney Docket Number:	699932000200

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
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Petition:				
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Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt

EFS ID:	19458635
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin
Filer Authorized By:	
Attorney Docket Number:	699932000200
Receipt Date:	30-JUN-2014
Filing Date:	05-APR-2011
Time Stamp:	19:49:26
Application Type:	Utility under 35 USC 111(a)

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Payment was successfully received in RAM	$90
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	2014-06-30_Transmittal_69993 2000200.pdf	23569 dfbb157a6f3e9a08119956e5a40a3c8ddb9 de351	no	1
Warnings:					
Information:					
2	Transmittal Letter	2014-06-30_IDS_Letter_699932 000200.pdf	24947 4c43af0127f865e9d613446909a18009ddfc 7575	no	3
Warnings:					
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3	Information Disclosure Statement (IDS) Form (SB08)	2014-06-30_IDS_SB08_699932 000200.pdf	27092 7b5c51e2dc5fc573f6f38a073ef97e1d7df96 6b2	no	1
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National Stage of an International Application under 35 U.S.C. 371

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TRANSMITTAL FORM

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Total Number of Pages in This Submission	5

Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
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Examiner Name	J. Martinell
Attorney Docket Number	699932000200

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
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- [ ] Amendment/Reply
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- [x] Information Disclosure Statement (3 pages)
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- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

PTO/SB/08A/B (1 page)

References (2)

Remarks

Customer No. 25225

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP		
Signature	/Bu Yin/		
Printed name	Bu Yin		
Date	June 30, 2014	Reg. No.	68,930

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: June 30, 2014 Electronic Signature for Lauren Swan: / Lauren Swan /

sd-644405

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Electronic Signature for Lauren Swan: _____/ Lauren Swan /_____

Patent
Docket No. 699932000200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mark S. CHEE

Application No.: 13/080,616

Filing Date: April 5, 2011

For: SPATIALLY ENCODED BIOLOGICAL ASSAYS

Examiner: J. Martinell

Group Art Unit: 1634

Confirmation No.: 2142

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98

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

Dear Madam:

Pursuant to 37 C.F.R. § 1.97 and § 1.98, Applicant submits for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. Copies of the documents are submitted herewith. The Examiner is requested to make these documents of record.

sd-643564

This Information Disclosure Statement is submitted:

☐ With the application; accordingly, no fee or separate requirements are required.

☐ With the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required.

☐ Before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☐ Within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☒ After receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance.

- ☒ The required fee is submitted herewith.
- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above; accordingly, no fee is believed to be due.

☐ After mailing of a final Office Action or Notice of Allowance, but before payment of the Issue Fee.

- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above and the required fee is submitted herewith.

Applicant would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

The information contained in this Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing Docket No. (699932000200). However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 30, 2014

Respectfully submitted,

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Bu Yin
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sd-643564

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: August 11, 2014 Electronic Signature: / Jennifer S. Jung / Jennifer S. Jung

Docket No.: 699932000200
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mark S. CHEE

Application No.: 13/080,616

Filed: April 5, 2011

For: SPATIALLY ENCODED BIOLOGICAL ASSAYS

Confirmation No.: 2142

Art Unit: 1634

Examiner: James Martinell

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. 1.111

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

Dear Commissioner:

This is in response to an Office action herein, mailed April 9, 2014, time for response to which was set to expire July 9, 2014. Filed herewith is a Petition and fee for a one-month extension of time, thereby extending the deadline for response to August 11, 2014 (August 9, 2014 being a Saturday). Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 5 of this paper.

Remarks/Arguments begin on page 13 of this paper.

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AMENDMENTS TO THE SPECIFICATION

Under "Description of the Figures," please replace the second full paragraph on page 7 with the following rewritten paragraph:

Figure 4 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 10×10 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.

On page 15, please replace the second full paragraph with the following rewritten paragraph:

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.

Please replace the paragraph bridging pages 15 and 16 with the following rewritten paragraph:

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

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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.

On page 19, please replace the first full paragraph with the following rewritten paragraph:

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.

Please replace the paragraph bridging pages 22 and 23 with the following rewritten paragraph:

The pool of resulting sequences is shown at 540. A sequence readout was obtained for target-specific oligonucleotide 1 only at a4b1, a4b2, a1b3, 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

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at a1b4, 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.

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AMENDMENTS TO THE CLAIMS

1. (currently amended): A method to determine a spatial ~~patterns~~ pattern of abundance or activity or both of ~~multiple~~ a biological target ~~targets at multiple sites~~ in a sample, comprising the following steps:

~~providing a sample affixed to a support;~~

delivering encoded probes for ~~multiple biological targets~~ a biological target ~~in a known spatial pattern~~ to multiple sites in [[the]] a sample affixed to a support, wherein each encoded probe comprises a probe region ~~that interacts with~~ capable of specific binding to the [[a]] biological target and a coding tag comprising an oligonucleotide that identifies [[a]] the location of the site to which the encoded probe is delivered;

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

separating encoded probes ~~that interact with~~ specifically bound to the biological ~~targets~~ target from encoded probes ~~that do not interact with~~ not specifically bound to the biological ~~targets~~ target;

determining ~~all or a portion of~~ a sequence of the encoded probes, wherein the sequence comprises all or a portion of the coding tag oligonucleotide sequence, thereby identifying the location of the site to which the encoded probe is delivered; and

associating the abundance or activity or both of the ~~multiple~~ biological ~~targets~~ target to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the biological target in the sample.

2. (currently amended): The method of claim 1, wherein the biological target is a nucleic acid ~~targets are nucleic acids~~ and the encoded probes are oligonucleotides.

3. (currently amended): The method of claim 2, wherein there are two encoded probes for ~~each of the multiple~~ the nucleic acid ~~targets~~ target at each of the multiple sites in the sample.

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4. (currently amended): The method of claim 1, wherein the ~~multiple~~ biological ~~targets are proteins~~ target is a protein, the probe regions of the ~~encoding~~ encoded probes are proteins, and the coding tags comprise oligonucleotides.

5. (currently amended): The method of claim 4, wherein the ~~multiple~~ biological ~~targets comprise enzymes~~ target comprises an enzyme.

6. (currently amended): The method of claim 1, wherein each of the probe regions of the encoded probes ~~comprise antibodies~~ comprises an antibody, an aptamer, and/or a small molecule that is capable of specific binding to the biological target.

7-8. (canceled)

9. (previously presented): The method of claim 1, further comprising an amplification step between the separating step and the determining step.

10. (currently amended): The method of claim 1, wherein the determining step is performed by nucleic acid sequencing or high-throughput sequencing or high-throughput digital nucleic acid sequencing.

11. (canceled)

12. (currently amended): The method of claim 1, wherein multiple biological targets in the sample are assayed and the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 100, 1,000, 10,000, 100,000, or 1,000,000.

13-19. (canceled)

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20. (currently amended): The method of claim 1, wherein the sequences of at least one hundred thousand, at least five hundred thousand, or at least one million ~~encoding~~ encoded probes are determined in parallel.

21-23. (canceled)

24. (previously presented): The method of claim 1, wherein software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step and the associating step.

25. (currently amended): The method of claim 1, wherein the probe regions of the encoded probes are proteins and the separating step is accomplished by capturing encoded probes ~~that interact with~~ specifically bound to the biological ~~targets being captured by~~ target using an affinity capture agent.

26. (currently amended): The method of claim 1, wherein the probe regions of the ~~encoding~~ encoded probes are nucleic acids and the separating step is accomplished by washing the sample.

27. (currently amended): A method to determine a spatial ~~patterns~~ pattern of abundance or activity or both of ~~multiple~~ a nucleic acid target ~~targets at multiple sites~~ in a sample, comprising the following steps:

~~providing a sample affixed to a support;~~

delivering an oligonucleotide ~~probes~~ probe capable of specific hybridization with a nucleic acid target ~~for multiple nucleic acid targets~~ to multiple sites in [[the]] a sample affixed to a support;

allowing the oligonucleotide ~~probes~~ probe to hybridize with the nucleic acid ~~targets~~ target;

washing unhybridized oligonucleotide ~~probes~~ probe from the sample;

delivering one or more encoding agents to the multiple sites in the sample ~~according to a known spatial pattern~~, wherein the one or more encoding agents delivered to each site comprise an oligonucleotide that identifies ~~identify~~ the location of the site in the sample;

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coupling the one or more encoding agents and the oligonucleotide ~~probes~~ probe delivered to each site to form an encoded ~~probes~~ probe specifically hybridized with the nucleic acid target at the site;

determining ~~all or a portion of~~ a sequence of the encoded probes, wherein the sequence comprises all or a portion of the one or more encoding agent oligonucleotide sequences, thereby identifying the location of the site to which the one or more encoding agents are delivered; and

associating the abundance or activity or both of ~~multiple~~ nucleic acid ~~targets~~ target to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the nucleic acid target in the sample.

28. (currently amended): The method of claim 27, wherein multiple nucleic acid targets in the sample are assayed and the product of the multiple nucleic acid targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 10,000, 100,000, or 1,000,000.

29-33. (canceled)

34. (currently amended): The method of claim 27, wherein the sequences of at least one hundred thousand or at least one million ~~encoding~~ encoded probes are determined in parallel.

35. (canceled)

36. (currently amended): The method of claim 27, wherein two oligonucleotide probes are delivered for ~~each of the multiple~~ the nucleic acid ~~targets~~ target.

37. (previously presented): The method of claim 27, wherein the coupling step is performed by ligation.

38. (previously presented): The method of claim 27, wherein the coupling step is performed by extension followed by ligation.

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39. (previously presented): The method of claim 27, further comprising an amplification step between the coupling step and the determining step.

40-54. (canceled)

55. (new): A method of determining a spatial pattern of abundance or activity or both of a biological target in a sample, comprising:

delivering a probe capable of specific binding to a biological target to multiple sites in a sample affixed to a support;

allowing the probe to interact with the biological target at each of the multiple sites in the sample;

delivering an encoding agent to each of the multiple sites in the sample, wherein the encoding agent delivered to each site comprise an oligonucleotide that identifies the location of the site in the sample;

coupling the encoding agent to the probe delivered to each of the multiple sites to form an encoded probe at each of the multiple sites;

determining a sequence of the encoded probes, wherein the sequence comprises all or a portion of the encoding agent oligonucleotide sequence, thereby identifying the location of the site to which the encoding agent is delivered; and

associating the abundance or activity or both of the biological target at each of the multiple sites to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the biological target in the sample.

56. (new): The method of claim 55, wherein one or more biological targets in the sample are assayed in parallel.

57. (new): The method of claim 56, wherein for each biological target, one or more probes capable of specific binding to the biological target are delivered to the multiple sites in the sample.

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58. (new): The method of claim 55, wherein at least two encoding agents are delivered to each of the multiple sites in the sample and are coupled to the probe delivered to the site to form an encoded probe comprising the at least two encoding agents.

59. (new): The method of claim 55, wherein the biological target comprises a nucleic acid and the probe comprises an oligonucleotide.

60. (new): The method of claim 55, wherein the biological target comprises a protein and the probe comprises a protein.

61. (new): The method of claim 55, wherein the biological target comprises an enzyme, and the probe comprises a substrate or putative substrate for the enzyme.

62. (new): The method of claim 55, wherein the probe comprises an affinity capture agent, antibody, aptamer, or small molecule.

63. (new): The method of claim 55, further comprising amplifying all or a portion of a sequence of the encoded probe.

64. (new): The method of claim 55, wherein the determining step is performed by nucleic acid sequencing or high-throughput sequencing.

65. (new): The method of claim 55, wherein multiple biological targets in the sample are assayed and the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 100, 1,000, 10,000, 100,000, or 1,000,000.

66. (new): The method of claim 55, wherein the sequences of at least one hundred thousand, at least five hundred thousand, or at least one million encoded probes are determined in parallel.

67. (new): The method of claim 55, wherein the probe for the biological target and/or the encoding agent are delivered to the multiple sites in the sample according to a known spatial pattern.

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68. (new): The method of claim 55, wherein software programmed hardware performs at least two steps of the delivering steps, the coupling step, the determining step, and the associating step.

69. (new): The method of claim 55, further comprising separating probes specifically bound to the biological target from probes not specifically bound to the biological target.

70. (new): The method of claim 69, wherein the separating step is accomplished by washing the sample.

71. (new): The method of claim 55, wherein the coupling step is performed by ligation, or performed by extension followed by ligation.

72. (new): The method of claim 55, wherein the biological target is a nucleic acid and the probe is capable of specific hybridization with the nucleic acid target, wherein the probe sequence identifies the nucleic acid target.

73. (new): The method of claim 72, wherein in the determining step, the encoded probe sequence being determined comprises all or a portion of the probe sequence and all or a portion of the encoding agent oligonucleotide sequence.

74. (new): The method of claim 73, further comprising quantification of the encoded probe sequence being determined, wherein:

the determined probe sequence identifies the nucleic acid target;

the determined encoding agent oligonucleotide sequence identifies the location of the site at which the probe specific hybridizes with the nucleic acid target; and

the quantity of the encoded probe sequence indicates the amount of the probe specifically hybridized with the nucleic acid target at the site in the sample, and thereby indicates the abundance or activity of the nucleic acid target at the site in the sample.

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75. (new): The method of claim 55, wherein the biological target is a protein, the probe is capable of specific binding to the protein target and comprises an oligonucleotide sequence that identifies the protein target.

76. (new): The method of claim 75, wherein in the determining step, the encoded probe sequence being determined comprises all or a portion of the probe oligonucleotide sequence and all or a portion of the encoding agent oligonucleotide sequence.

77. (new): The method of claim 76, further comprising quantification of the encoded probe sequence being determined, wherein:

the determined probe oligonucleotide sequence identifies the protein target;

the determined encoding agent oligonucleotide sequence identifies the location of the site at which the probe specific binds to the protein target; and

the quantity of the encoded probe sequence indicates the amount of the probe specifically binds to the protein target at the site in the sample, and thereby indicates the abundance or activity of the protein target at the site in the sample.

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REMARKS

Claim Status and Amendment

Before entry of the claim amendments, claims 1-54 are pending with claims 40-54 withdrawn. Claims 7-8, 11, 13-19, 21-23, 29-33, 35, and 40-54 are canceled without prejudice. Claims 1-6, 10, 12, 20, 25-28, 34, and 36 are amended, and new claims 55-77 are added. Support for the claim amendments can be found throughout the specification as originally filed, including in the original claims.

With respect to all claim amendments, Applicant has not dedicated to the public or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application. No new matter has been added by means of any of the amendments herein. Entry is thus respectfully requested. After entry, claims 1-6, 9-10, 12, 20, 24-28, 34, 36-39, and 55-77 will be pending. Reconsideration and allowance of the claims as amended is respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement is submitted concurrently herewith. Applicants thank the Examiner in advance for review of the cited references and return of the initialed form SB/08. Should any of the references be unavailable, the Examiner is requested to contact the undersigned, and additional copies will be provided.

Amendments to the Specification

The specification is amended to include reference numbers 150, 160, 200, 306, and 550. The brief description of Figure 4 is amended to describe Figures 4A, 4B, and 4C. Support for the amendments can be found throughout the specification as originally filed, for example, at page 21 of the original specification as filed. No new matter is added by way of the amendments, and entry of the amendments is respectfully requested.

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The Objections to the Drawings

The drawings stand objected to for allegedly including reference numbers 160, 200, 306, and 550, which are allegedly not mentioned in the description. It is believed that the amendments to the specification fully address the objections. Withdrawal of the objections is thus respectfully requested.

The Rejections under 35 U.S.C. § 112

Claims 1-26 stand rejected under 35 U.S.C. § 112 as allegedly being indefinite. Specifically, the recitation of "determining all or a portion of a sequence" in claim 1 is allegedly vague, indefinite, and incomplete, because there is allegedly no mention of what the sequence is a part of. Applicant disagrees. The Office is respectfully reminded that before entry of the claim amendments, claim 1 recites "determining all or a portion of a sequence of the encoded probes." Emphasis added. Therefore, it is clear that the sequence is a part of the encoded probes as recited in the claim. Nevertheless, for the sole purpose of advancing prosecution, claim 1 is amended. It is believed the amended claim is clear and definite. Withdrawal of the rejection is requested.

The recitation of "histological feature" in the claims is rejected. Without acquiescing to the propriety of the rejection, the amended claims no longer recite the rejected language. The rejection is therefore rendered moot.

The Rejections under 35 U.S.C. § 102

Claims 1-3, 6-37, and 39 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Roth *et al.*, U.S. Patent Application Publication 2006/0046313 A1 (hereinafter "Roth"). Applicant respectfully traverses the rejection and requests reconsideration.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). There can be no difference between the claimed invention and the cited reference disclosure, as viewed by a person of ordinary skill in the field of the invention, for there to be anticipation. *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984). To establish inherent

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anticipation, the Office must provide some basis to conclude "that the allegedly inherent characteristic necessarily flows" from the teachings of the art, and that this would be recognized by one of ordinary skill. *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990); MPEP § 2112 IV, citing *in re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); *see also in re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *in re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). Inherency may not be established by probabilities or possibilities, or the mere fact that a certain thing may result. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); MPEP § 2163.07(a). "A prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species. MPEP § 2112 IV. Here, the cited art fails to teach each and every claim element and therefore does not anticipate.

Claim 1

Instant claim 1 recites, *inter alia*:

delivering encoded probes for a biological target to multiple sites in a sample affixed to a support, wherein each encoded probe comprises a probe region capable of specific binding to the biological target and a coding tag comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered;

allowing the encoded probes to interact with the biological target;

separating encoded probes specifically bound to the biological target from encoded probes not specifically bound to the biological target;

determining a sequence of the encoded probes, wherein the sequence comprises all or a portion of the coding tag oligonucleotide sequence, thereby identifying the location of the site to which the encoded probe is delivered; and

associating the abundance or activity or both of the biological target to the locations of the multiple sites in the sample to determine the spatial pattern of the abundance or activity or both of the biological target in the sample.

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The cited Roth reference fails to teach each and every claim element, and therefore fails to anticipate. Roth discloses the use of probes labeled with composite organic-inorganic nanoparticles (COINs) for biological assays. COINs are typically clusters of several primary metal crystal particles with Raman-active organic compounds trapped in the junctions of the primary particles or embedded in the metal atoms, and intrinsically produce surface enhanced Raman scattering (SERS) signals upon laser irradiation. *See* Roth at the abstract and at paragraph [0063]. Since most biological targets are not Raman-active, upon binding of a COIN-labeled probe to a biological target, shifts in the Raman spectrum can be used to assay the binding. *Id.* The Office has not identified any teaching in Roth of a COIN comprising any oligonucleotide that identifies the location of the site to which a COIN-labeled probe is delivered, let alone determining all or a portion of the oligonucleotide sequence to identify the location.

For example, the Office cites Roth at paragraphs [0032] and [0140] as allegedly teaching an assay system to determine spatial patterns of abundance or activity or both of biological targets at multiple sites in a sample. Paragraph [0032] of Roth, however, merely teaches that capture probes (labeled with COIN) are attached at different known defined locations on an array. Such disclosure does not amount to any teaching of an encoded probe comprising a probe region and a coding tag comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered, as recited in the present claim. As a first matter, the COIN labels are composite organic-inorganic nanoparticles, which the Office has not shown to comprise any oligonucleotide. Moreover, even assuming Roth's COINs may comprise an oligonucleotide, the Office still has not articulated any teaching of any such oligonucleotide that identifies the location of the site to which a COIN-labeled probe is delivered. In fact, it is the SERS signals, not any oligonucleotide sequence of the COINs, that are collected, associated with the positions to which the probes are attached, and correlated with the specificity of the capture antibodies to characterize the target protein. *See* Roth at paragraph [0032].

Although Roth at paragraph [0140] teaches "a COIN-labeled oligonucleotide that is complementary to the target nucleic acid sequence," such disclosure merely teaches the probe region being an oligonucleotide, and not the COIN (the alleged coding tag) being an oligonucleotide. Furthermore, the Office has not identified any teaching that the oligonucleotide

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portion of Roth's COIN-labeled oligonucleotide probe identifies the location to which the COIN-labeled probe is delivered.

The Office additionally cites Roth at paragraphs [0033], [0104] and [0122] as allegedly teaching the steps of the claimed methods. Applicant respectfully disagrees for at least the following reasons.

First, Roth at paragraph [0033] requires lysing tissue samples in order to form "arrays of cell lysates obtained from one or more tissue samples from a patient." Emphasis added. One of skill in the art would understand that lysing a tissue sample in order to obtain cell lysates would have disrupted the structural integrity of the tissue sample, rendering it impossible to determine the spatial pattern of abundance or activity or both of a biological target in the tissue sample. Thus, the cited Roth disclosure fails to teach (or even suggest, for that matter) the currently claimed methods.

Second, Roth teaches that "a mixture of extracted cell proteins **330**, **331**, **332** is immobilized at (for example, spotted onto) individual defined locations." *See* Roth at paragraph [0033] and Figure 3. The cell lysate spots are then contacted with a mixture of COIN-labeled probes. *Id.* For example, as shown in Figure 3 of Roth, extracted cell proteins **330**, **331**, and **332** identify locations X_1X_1, X_1X_2, and X_2X_2, respectfully. In contrast, since all of the cell lysate spots (*e.g.*, as shown in Figure 3 of Roth) are contacted with the mixture of the COIN-labeled probes, the COIN-labeled probes do not identify the locations to which they are delivered. *Id.* Thus, it is clear that the "defined locations" of Roth are identified by the immobilized extracted cell proteins (*i.e.*, the targets), not by the COIN-labeled probes, let alone by any oligonucleotide sequence of the COIN. Roth thus falls far short of teaching each and every claim element.

Third, COINs intrinsically produce SERS signals upon laser irradiation, and may be used to label any probe for an analyte. *See* Roth at the abstract and paragraph [0092]. As discussed bove, the Office has not provided any teaching that the COINs of Roth are encoded with spatial information of where the COINs or COIN-labeled probes are delivered, much less that the COINs comprise an oligonucleotide that identifies a location to which the COINs or COIN-labeled probes are delivered. For this reason alone, Roth fails to anticipate.

Fourth, even assuming Roth at paragraphs [0104] and [0122] teaches determining all or a portion of a sequence of the COIN-labeled probes, the Office still has not identified any teaching of

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any COIN (the alleged coding tag) in Roth that comprises an oligonucleotide. Furthermore, the Office has not identified any teaching in Roth of an encoded probe comprising a coding tag comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered, as recited in the present claim.

In sum, Roth fails to teach each and every claim element. Accordingly, Roth fails to anticipate instant claim 1 and dependent claims therefrom. Withdrawal of the rejections is respectfully requested.

Claim 27

Instant claim 27 recites, *inter alia*:

delivering an oligonucleotide probe capable of specific hybridization with a nucleic acid target to multiple sites in a sample affixed to a support;

allowing the oligonucleotide probe to hybridize with the nucleic acid target;

washing unhybridized oligonucleotide probe from the sample;

delivering one or more encoding agents to the multiple sites in the sample, wherein the one or more encoding agents delivered to each site comprise an oligonucleotide that identifies the location of the site in the sample;

coupling the one or more encoding agents and the oligonucleotide probe delivered to each site to form an encoded probe specifically hybridized with the nucleic acid target at the site;

determining a sequence of the encoded probes, wherein the sequence comprises all or a portion of the one or more encoding agent oligonucleotide sequences, thereby identifying the location of the site to which the one or more encoding agents are delivered; and

associating the abundance or activity or both of nucleic acid target to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the nucleic acid target in the sample.

As discussed above, Roth discloses COINs (the alleged encoding agent) and the use of COIN-labeled probes (the alleged encoded probes) for biological assays. Applicant's arguments regarding claim 1 as detailed above also apply to instant claim 27. In addition, the Office has not identified any express teaching in Roth that its COIN comprises an oligonucleotide, let alone

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delivering any encoding agent comprising an oligonucleotide to a sample and coupling the encoding agent to any probe. The Office has not argued inherent anticipation. However, the Office is respectfully reminded that inherency may not be established by probabilities or possibilities, or the mere fact that a certain thing may result (*see* MPEP § 2163.07(a)), and that an art reference that discloses a genus still does not inherently disclose all species within that broad category if there is no disclosure of the claimed species (*see* MPEP § 2112 IV). Thus, the mere argument that Roth's COINs may comprise an oligonucleotide falls far short of establishing inherent anticipation. Moreover, even assuming Roth's COINs may comprise an oligonucleotide, the Office still has not articulated any teaching of any such oligonucleotide that identifies the location of the site to which the COIN or COIN-labeled probe is delivered, let alone determining all or a portion of the oligonucleotide sequence to identify the location.

In view of the above, the cited Roth reference fails to teach each and every claim element, and therefore fails to anticipate instant claim 27 and dependent claims therefrom. Withdrawal of the rejections is respectfully requested.

Claim 55

Applicant's arguments regarding claims 1 and 27 as detailed above also apply to new claim 55, which recites, *inter alia*, delivering an encoding agent to the multiple sites in the sample affixed to a support, wherein the encoding agent delivered to each site comprises an oligonucleotide that identifies the location of the site in the sample, and determining all or a portion of the encoding agent oligonucleotide sequence to identify the location of the site to which the encoding agent is delivered. Therefore, the cited Roth reference fails to teach each and every claim element, and therefore fails to anticipate instant claim 55 and dependent claims therefrom.

The Rejections under 35 U.S.C. § 103

Claims 4, 5, and 38 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Roth in view of Lockhart *et al.*, US 6,344,316 (hereinafter "Lockhart"). Applicant respectfully traverses the rejection and requests reconsideration.

The Office bears the initial burden to make a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, (Fed. Cir. 1993); *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

To make a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). There must be shown some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the teachings of the references to arrive at something within the claims, with a reasonable expectation of success. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398; 82 U.S.P.Q.2d 1385; 127 S. Ct. 1727 (2007); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Office must provide some articulated reason why the claimed invention would have been obvious to one of ordinary skill in the art. MPEP § 2142; *KSR*, 82 U.S.P.Q.2d at 1396. The fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEP § 2143.01. Furthermore, if a modification renders a reference unsatisfactory for its intended purpose, or changes the principle of operation of a reference, the teachings of that reference do not render the claimed invention obvious. MPEP § 2143.01. Finally, in the analysis of prior art references, it is improper to exercise hindsight to select bits and pieces from the references to create a motivation to modify that is not found in the references, but only in the applicant's disclosure. *In re Dow Chemical Co.* 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Here, a *prima facie* case of obviousness has not been established.

As discussed above, Roth fails to teach or suggest the coding tag of the encoded probe (as recited in instant claim 1) or the encoding agent (as recited in instant claims 27 and 55), which comprises an oligonucleotide that identifies the location of the site to which the encoded probe or the encoding agent is delivered. Roth further fails to teach or even suggest determining all or a portion of the oligonucleotide sequence to identify the location. The Office has not identified any teaching in Lockhart that cures the deficiencies of Roth. Instead, the Office merely asserts that Lockhart teaches unique and fluorescent tags comprising oligonucleotides, citing Lockhart at column 24, lines 8-30 and 37-61. Even assuming this is the case, the Office still has not shown or even argued that Lockhart's fluorescent tag sequence identifies the location to which the fluorescent tag or a labeled probe is delivered. Moreover, the Office has not articulated any teaching or suggestion of a step of determining all or a portion of the coding tag or encoding agent

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oligonucleotide sequence in order to identify the location to which the encoded probe or encoding agent is delivered. Indeed, the Office merely argues that the combination of cited art teaches fluorescent coding tags for scanning based detection, and fluorescent tags comprising oligonucleotides. The alleged teachings of fluorescence-based assays fall far short of teaching or even suggesting the currently claimed methods, which require determining a sequence of the encoded probes. Moreover, the Office has not articulated any reason why the skilled artisan reading Roth and Lockhart would have arrived at the present claims, with a reasonable expectation of success. In view of the above, Lockhart fails to remedy the deficiencies of Roth, and a *prima facie* case has not been established.

In addition, Lockhart provides a method for identifying differences in nucleic acid abundances (*e.g.*, expression levels) between two or more samples. To this end, Lockhart discloses an array of different oligonucleotide probes "where the sequence and location of each different probe is known," and nucleic acid samples containing the targets are then hybridized to the probe array. *See* Lockhart at the abstract. Thus, the Lockhart assay systems requires probes, not the sample, to be immobilized on an array (*i.e.*, affixed to a support). Such disclosure is fundamentally different from the claimed subject matter, which requires delivering encoded probes or encoding agents to a sample affixed to a support, wherein the encoded probes or encoding agents identify the location to which the encoded probes or encoding agents are delivered in order to determine a spatial pattern of a biological target in the sample. If anything, Lockhart teaches the opposite of what is recited in the present claims. The Office has not provided any reason that the skilled artisan would have deviated from the specific teachings of Lockhart in order to arrive at something within the present claims, with a reasonable expectation of success. For this reason alone, the rejection can be properly withdrawn.

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Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 699932000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 11, 2014

Respectfully submitted,

Electronic signature: / Bu Yin /

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Curio EX1012-p. 338
Curio v Prognosys

Electronic Patent Application Fee Transmittal

Application Number:	13080616
Filing Date:	05-Apr-2011
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Filer:	Bu Yin/Jennifer Jung
Attorney Docket Number:	699932000200

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	2251	1	100	100

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**190**

Electronic Acknowledgement Receipt

EFS ID:	19835732
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/Jennifer Jung
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	11-AUG-2014
Filing Date:	05-APR-2011
Time Stamp:	20:47:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$190
RAM confirmation Number	7067
Deposit Account	031952
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	3_Mizusawa.pdf	303782 b0d9f9014eeeaf12d8e64adf9d972c23fc503e86	no	6
Warnings:					
Information:					
2	Non Patent Literature	4_Shoemaker.pdf	1029666 57bb697ca328f0e04f0792d0b89fe9636685542f	no	7
Warnings:					
Information:					
3	Non Patent Literature	5_Worthington.pdf	1143507 6f9e8cc59af3fb596b067dc7995ad52572d59cba	no	7
Warnings:					
Information:					
4	Non Patent Literature	6_OA_13266568.pdf	339002 9b1520a1abcb1a9d1d7fded3208d1594379a06d2	no	9
Warnings:					
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5	Non Patent Literature	7_Resp_13266568.pdf	392247 59bb18d266ead279523fd457854ead4f5a3e03cd	no	11
Warnings:					
Information:					
6	Non Patent Literature	8_ExamRpt_AU2010278710.pdf	906196 0ff1215ff6187d7c229792452ff23291b650787a	no	4
Warnings:					
Information:					
7	Non Patent Literature	9_EP_ExReport_12Mar2014.pdf	332991 9483c02f96bb02668c86ae3a241a4c4b75cdef87	no	3
Warnings:					
Information:					
8	Non Patent Literature	10_EP_Resp_10Jul2014.pdf	397304 f09bbc9b893d3cc8801ecaffa0881aa61029f09a	no	1

Warnings:					
Information:					
9	Non Patent Literature	11_CA_OA_30May2014.pdf	1057389 f2b5d9bd771a8af49dd8744baf364a828d190c62	no	4
Warnings:					
Information:					
10	Non Patent Literature	12_CN_OA_3July2014.pdf	701008 0b8cb6581deaa311b14a61a4b6dfd17be55c932b	no	11
Warnings:					
Information:					
11	Non Patent Literature	13_EP117666131_Resp_11July2014.pdf	430635 cc5548b9e57406c2419639ab2183309dce4ca734	no	1
Warnings:					
Information:					
12		4178_001.pdf	203027 f297ba6a438fd752024d8c0dbd67fe88f2eabf81	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	3
	Information Disclosure Statement (IDS) Form (SB08)	4	5

Warnings:					
Information:					
13	Transmittal Letter	69993_Transmittal.pdf	24961 39b40f22645e5541f7fcaad960fa2ca34835222a	no	1
Warnings:					
Information:					
14	Extension of Time	69993_Ext_Time.pdf	22629 515998feb7e927876f57302ff59d7d72ab07a438	no	1
Warnings:					
Information:					
15		69993_Amendment.pdf	92982 1cba608727d6ed72acd3ec81b910dd1e2ec80a30	yes	22

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**

	Amendment/Req. Reconsideration-After Non-Final Reject		1		1
	Specification		2		4
	Claims		5		12
	Applicant Arguments/Remarks Made in an Amendment		13		22
Warnings:					
Information:					
16	Fee Worksheet (SB06)	fee-info.pdf	32225 10d5f1de164f80769a90d5ea270a335ee77f7840	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	7409551		

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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.

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: August 11, 2014
Electronic Signature for Jennifer Jung: /Jennifer Jung/

Patent
Docket No. 699932000200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mark S. CHEE

Application No.: 13/080,616

Filing Date: April 5, 2011

For: SPATIALLY ENCODED BIOLOGICAL ASSAYS

Examiner: J. Martinell

Group Art Unit: 1634

Confirmation No.: 2142

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98

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

Dear Madam:

Pursuant to 37 C.F.R. § 1.97 and § 1.98, Applicant submits for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. Copies of the non-patent literature are submitted herewith. The Examiner is requested to make these documents of record.

sd-646997

This Information Disclosure Statement is submitted:

☐ With the application; accordingly, no fee or separate requirements are required.

☐ With the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required.

☐ Before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☐ Within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☒ After receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance.

- ☒ The required fee is submitted herewith.
- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above; accordingly, no fee is believed to be due.

☐ After mailing of a final Office Action or Notice of Allowance, but before payment of the Issue Fee.

- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above and the required fee is submitted herewith.

Applicant would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

The information contained in this Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing Docket No. (699932000200). However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 11, 2014

Respectfully submitted,

Electronic signature: /Bu Yin/
Bu Yin
Registration No.: 68,930
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(858) 720-7912

sd-646997

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-5,002,882	03-1991	New England Biolabs	
	2.	US-5,512,439	04-1996	Dynal AS	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	3.	MIZUSAWA and WARD et al., "A bacteriophage lambda vector for cloning with BamHI and Sau3A," Gene (1982) 20(3):317-322	
	4.	SHOEMAKER et al., "Quantitative phenotypic analysis of yeast deletion mutants using a highly parallel molecular bar-coding strategy," Nat Genet (1996) 14(4):450-456	
	5.	WORTHINGTON et al., "Cloning of random oligonucleotides to create single-insert plasmid libraries," Anal Biochem (2001) 294(2):169-175	
	6.	Office Action for US 13/266,568, mailed 26 March 2014, 9 pages	
	7.	Response to Office Action for US 13/266,568, dated 26 June 2014, 11 pages	
	8.	Patent Examination Report No. 1 for AU 2010278710, issued 11 February 2014, 4 pages	
	9.	Examination Report for European Patent Application No. EP 10836568.5, dated 12 March 2014, 3 pages	
	10.	Response to Examination Report for European Patent Application No. EP 10836568.5, dated 10 July 2014, 1 page	
	11.	Office Action for Canadian Patent Application No. 2794522, issued 22 May 2014, 4 pages	
	12.	Second Examination Report for Chinese Patent Application No. CN 201180017696.3, mailed 3 July 2014, 11 pages	

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	**13/080,616**
				Filing Date	April 5, 2011
				First Named Inventor	Mark S. CHEE
				Art Unit	1634
(Use as many sheets as necessary)				Examiner Name	J. Martinell
Sheet	2	of	2	Attorney Docket Number	699932000200

	13.	Response to Search Report for European Patent Application No. EP 11766613.1, dated 11 July 2014, 1 page	

Examiner Signature		Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	29

Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply – 22 pages
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement – 3 pages
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosures:

Petition for Extension of Time in 1 page; PTO/SB/08A in 2 pages; 11 references.

Remarks

Customer No. 25225

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP		
Signature	/Bu Yin/		
Printed name	Bu Yin		
Date	August 11, 2014	Reg. No.	68,930

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: August 11, 2014 Electronic Signature for Jennifer Jung: /Jennifer Jung/

sd-647023

PTO/SB/22 (03-13)
Approved for use through 03/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 699932000200
Application Number 13/080,616	Filed April 5, 2011
For SPATIALLY ENCODED BIOLOGICAL ASSAYS	
Art Unit 1634	Examiner J. Martinell

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
[X] One month (37 CFR 1.17(a)(1))	$200	$100	$50	$ 100.00
[ ] Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
[ ] Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
[ ] Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
[ ] Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

[X] Applicant asserts small entity status. See 37 CFR 1.27.

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

[ ] A check in the amount of the fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[ ] The Director has already been authorized to charge fees in this application to a Deposit Account.

[X] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 03-1952 .

[ ] Payment made via EFS-Web.

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

I am the

[ ] applicant/inventor.

[ ] assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

[X] attorney or agent of record. Registration number 68,930 .

[ ] attorney or agent acting under 37 CFR 1.34. Registration number _____ .

/Bu Yin/	August 11, 2014
Signature	Date
Bu Yin	(858) 720-7912
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of 1 forms are submitted.

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: August 11, 2014 Electronic Signature for Jennifer Jung: /Jennifer Jung/

sd-647022

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 13/080,616	Filing Date 04/05/2011	☐ 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 $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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

AMENDMENT **08/11/2014**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 54	Minus	** 57	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***4	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ 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.

** 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 number found in the appropriate box in column 1.

LIE
/ROLITA WIMBUSH/

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

25225 7590 10/21/2014

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
MARTINELL, JAMES	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
10/21/2014	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):

PatentDocket@mofo.com
EOfficeSD@mofo.com

Office Action Summary	Application No. 13/080,616	Applicant(s) CHEE, MARK S.	
	Examiner JAMES MARTINELL	Art Unit 1634	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *8/11/14*.

☐ 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) *1-6,9,10,12,20,24-28,34,36-39 and 55-77* 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) *1-6,9,10,12,20,24-28,34, 36-39, and 55-77* 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 *4/5/11* 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 *6/30/14 and 8/11/14*.

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

4) ☐ Other: _____.

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

Regarding the Information Disclosure Statement filed (August 11, 2014), Reference No. 12 (Second Examination Report for Chinese Patent Application CN 201180017696.3, mailed 3 July 2014) has not been considered because there is no English language translation or statement of relevance in the file (see MPEP 609 and 37 CFR § 1.98(a)(3)).

Claim55 is objected to because of the following informalities: In claim 55, line 8, "comprise" should be changed to "comprises". Appropriate correction is required.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-77 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Roth et al (U.S. Patent Application Publication 2006/0046313 A1) in view of Brenner et al (U.S. Patent Application Publication 2007/0172873 A1). This is a new ground of rejection made necessary by the amendment filed August 11, 2014. It is noted that Applicant's arguments (response filed August 11, 2014, pages 14-21) are directed toward limitations that were not in the version of the claims filed on January 16, 2014. Roth et al teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (paragraphs 0032 and 0140), wherein the assay system performs the steps of providing a sample affixed to a support (paragraph 0033), delivering encoded probes for the multiple biological targets to the multiple sites in the sample is 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 (paragraph 0033), allowing the encoded probes to interact with the biological targets (paragraph 0033), separating the encoded probes that interact with the

biological targets from encoded probes that do not interact with the biological targets (paragraph 0033), determining all or a portion of a sequence of the encoded probes (paragraphs 0104 and 0122), and associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample (paragraph 0033). Roth et al also teach the use of oligonucleotide probes (*e.g.*, paragraphs 0033 and 0102-0103), washing unhybridized probes from the probes bound the targets (paragraphs 0033 and 0102-0103), delivering one or more encoding agents to locations of the multiple sites in the sample according to a known spatial pattern wherein the combination of encoding agents delivered to each site is different (paragraphs 0086 and 0097), coupling the encoding agents and the oligonucleotide probes to form encoded probes (paragraph 0086), determining all or a portion of a sequence of the encoded probes using high throughput sequencing (paragraphs 0104 and 0122) and associating the abundance or activity or both of multiple biological targets to the locations of multiple sites in the sample (paragraphs 0033, 0104, and 0122). Roth et al further teaches the biological targets are nucleic acids and the encoded probes are oligonucleotides (paragraphs 0102-0103), that there are two encoded probes for each of the multiple nucleic acid targets (paragraphs 0047 and 0091), probe regions of the encoded probes comprise antibodies, the probe regions of the encoded probes are aptamers (paragraph 0069), the probe regions of the encoded probes are small molecules (paragraph 0069), an amplification step between the separating step and the determining step (paragraph 0105), the determining step is performed by nucleic acid sequencing (paragraph 0104 and 0122), sequencing is high throughput digital nucleic acid sequencing (paragraphs 0039 and 0122-0124), the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000,000 (paragraphs 0097-0098 and 0138), the sequences of at least 1,000,000 encoding probes are determined in parallel (paragraphs 0097-0098, 0104, and 0138), the known spatial pattern is determined by histological features of the sample (paragraphs 0036 and 0038), software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step, and the associating step (paragraphs 0123-0124). Roth et al teaches the probe regions of the encoded probes are proteins (paragraph 0092) and the separating step is accomplished by encoded probes that interact

with the biological targets being captured by an affinity capture agent (paragraph 0027), Separation of interacting probes and non-interacting probes is by washing (paragraphs 0084-0085). Roth et al also teaches two oligonucleotide probes are delivered for each of the multiple nucleic acid targets (paragraph 0083) and the coupling step is performed by ligation (paragraph 0083). Brenner et al teaches the attachment of oligonucleotide tags to a variety of types of biological macromolecules for the purpose of identification by sequencing the oligonucleotide tags (*e.g.*, paragraphs 0030-0031). It would have been obvious for one of ordinary skill in the art at the time the invention was made to have prepared 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 coding tags comprise oligonucleotides, in view of Roth et al teaching the coding tags are unique and fluorescent for scanning based detection (paragraphs 0031 and 0055), and in light of Brenner et al teaching the attachment of oligonucleotide tags to a variety of types of biological macromolecules for the purpose of identification by sequencing the oligonucleotide tags (*e.g.*, paragraphs 0030-0031). All that is achieved is the known and expected result.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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. 13/080,616	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	Classification
*	A	US-2007/0172873 A1	07-2007	Brenner et al.	435/006
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	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.

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1.	Notice of Acceptance issued in Australian Patent Application No. AU 2011237729, dated 20 March 2014, 6 pages	
	2.	Examination Report issued in European Patent Application No. 10836568.5, dated 12 March 2014, 3 pages	

Examiner Signature	/James Martinell/	Date Considered	10/16/2014

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: June 30, 2014 Electronic Signature for Lauren Swan: / Lauren Swan /

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

sd-643563

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	SALLY MERKLING	1773

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

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

CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014	10/16/2014						
	1	÷	✓	✓						
	2	÷	✓	✓						
	3	÷	✓	✓						
	4	÷	✓	✓						
	5	÷	✓	✓						
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	33	÷	✓	-						
	34	÷	✓	✓						
	35	÷	✓	-						
	36	÷	✓	✓						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014	10/16/2014						
	37	÷	✓	✓						
	38	÷	✓	✓						
	39	÷	✓	✓						
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	72			✓						

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CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014	10/16/2014						
	73			✓						
	74			✓						
	75			✓						
	76			✓						
	77			✓						

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	Art Unit
	JAMES MARTINELL	1634

CPC- SEARCHED		
Symbol	Date	Examiner
C12Q1/6837, 6874; C12Q2565/501, 513, 50, 514, 518, 519, 525, 531, 537, 543, 549; G01N21/6452, 8903; 33/53	4/3/14	JM
Updated	10/16/14	JM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST text search (printout attached)	4/3/14	JM
EAST text search (printout attached)	10/16/14	JM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/JAMES MARTINELL/ Primary Examiner.Art Unit 1634

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	5533	(((high adj density) or (high adj resolution)) near5 (array$ or microarray$)) near10 (dna or (nucleic adj acid) or protein or antibod$)	US-PGPUB; USPAT	OR	ON	2014/10/16 13:33
L2	2938802	@rlad<"20110405"	US-PGPUB; USPAT	OR	ON	2014/10/16 13:34
L3	4387	l1 and l2	US-PGPUB; USPAT	OR	ON	2014/10/16 13:35
L4	65183	435/6.$[ccls]	US-PGPUB; USPAT	OR	ON	2014/10/16 13:35
L5	24141	435/7.1[ccls]	US-PGPUB; USPAT	OR	ON	2014/10/16 13:35
L6	27600	536/23.1[ccls]	US-PGPUB; USPAT	OR	ON	2014/10/16 13:35
L7	0	536/23.31[ccls]	US-PGPUB; USPAT	OR	ON	2014/10/16 13:35
L8	4046	536/24.31[ccls]	US-PGPUB; USPAT	OR	ON	2014/10/16 13:36
L9	2417	536/24.32[ccls]	US-PGPUB; USPAT	OR	ON	2014/10/16 13:36
L10	100354	l4 or l5 or l6 or l8 or l9	US-PGPUB; USPAT	OR	ON	2014/10/16 13:36
L11	2560	l3 and l10	US-PGPUB; USPAT	OR	ON	2014/10/16 13:36
L12	401539	@pd>"20140403"	US-PGPUB; USPAT	OR	ON	2014/10/16 13:36
L13	62	l11 and l12	US-PGPUB; USPAT	OR	ON	2014/10/16 13:36
L14	3653	c12q1/6837.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:37
L15	1448	c12q1/6874.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:37
L16	1234	c12q2565/501.cpc.	US-	OR	ON	2014/10/16

			PGPUB; USPAT			13:37
L17	315	c12q2565/513.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:37
L18	16	c12q2565/50.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:38
L19	171	c12q2565/514.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:38
L20	620	c12q2565/518.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:38
L21	379	c12q2565/519.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:38
L22	127	c12q2565/525.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:38
L23	64	c12q2565/531.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:38
L24	427	c12q2565/537.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:38
L25	219	c12q2565/543.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:38
L26	72	c12q2565/549.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:39
L27	2093	g01n21/6452.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:39
L28	209	g01n21/8903.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:39
L29	1149	g01n33/53.cpc.	US-PGPUB; USPAT	OR	ON	2014/10/16 13:39
L30	5451	l14 or l15 or l16 or l17 or l18	US-PGPUB; USPAT	OR	ON	2014/10/16 13:40
L31	1308	l19 or l20 or l21 or l22 or l23	US-PGPUB; USPAT	OR	ON	2014/10/16 13:40
L32	4109	l24 or l25 or l26 or l27 or l28 or l29	US-PGPUB; USPAT	OR	ON	2014/10/16 13:40
L33	9647	l30 or l31 or l32	US-PGPUB; USPAT	OR	ON	2014/10/16 13:40
L34	6461	l2 and l33	US-PGPUB; USPAT	OR	ON	2014/10/16 13:40
L35	278	l12 and l34	US-	OR	ON	2014/10/16

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ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	**13/080,616**
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-5,002,882	03-1991	~~New England Biolabs~~ Lunnen et al	
	2.	US-5,512,439	04-1996	~~Dynal AS~~ Hornes et al	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/James Martinell/	Date Considered	10/16/2014

*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	3.	MIZUSAWA and WARD et al., "A bacteriophage lambda vector for cloning with BamHI and Sau3A," Gene (1982) 20(3):317-322	
	4.	SHOEMAKER et al., "Quantitative phenotypic analysis of yeast deletion mutants using a highly parallel molecular bar-coding strategy," Nat Genet (1996) 14(4):450-456	
	5.	WORTHINGTON et al., "Cloning of random oligonucleotides to create single-insert plasmid libraries," Anal Biochem (2001) 294(2):169-175	
	6.	Office Action for US 13/266,568, mailed 26 March 2014, 9 pages	
	7.	Response to Office Action for US 13/266,568, dated 26 June 2014, 11 pages	
	8.	Patent Examination Report No. 1 for AU 2010278710, issued 11 February 2014, 4 pages	
	9.	Examination Report for European Patent Application No. EP 10836568.5, dated 12 March 2014, 3 pages	
	10.	Response to Examination Report for European Patent Application No. EP 10836568.5, dated 10 July 2014, 1 page	
	11.	Office Action for Canadian Patent Application No. 2794522, issued 22 May 2014, 4 pages	
	~~12.~~	~~Second Examination Report for Chinese Patent Application No. CN 201180017696.3, mailed 3 July 2014, 11 pages.~~	

/James Martinell/ 10/16/2014

sd-646991 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.M./

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	**13/080,616**
				Filing Date	April 5, 2011
				First Named Inventor	Mark S. CHEE
				Art Unit	1634
(Use as many sheets as necessary)				Examiner Name	J. Martinell
Sheet	2	of	2	Attorney Docket Number	699932000200

	13.	Response to Search Report for European Patent Application No. EP 11766613.1, dated 11 July 2014, 1 page	

Examiner Signature	/James Martinell/	Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

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

sd-646991

Docket No.: 699932000200
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Mark S. CHEE	Confirmation No.: 2142
Application No.: 13/080,616	Art Unit: 1634
Filed: April 5, 2011	Examiner: James Martinell
For: SPATIALLY ENCODED BIOLOGICAL ASSAYS	

AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION UNDER 37 C.F.R. 1.116

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

Dear Commissioner:

INTRODUCTORY COMMENTS

This is in response to the final Office Action dated October 21, 2014, for which a response was due on January 21, 2015. Filed herewith is a Petition and fee for a one-month extension of time, thereby extending the deadline for response to February 23, 2014, because February 21, 2015 is a Saturday, and February 22, 2015 is a Sunday. Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 10 of this paper.

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AMENDMENTS TO THE CLAIMS

1. (currently amended): A method to determine a spatial pattern of abundance or activity or both of a biological target in a sample, comprising the following steps:

delivering encoded probes for a biological target to multiple sites in a sample affixed to a support, wherein each encoded probe comprises a probe region capable of specific binding to the biological target and a coding tag comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered;

allowing the encoded probes to interact with the biological target;

separating encoded probes specifically bound to the biological target from encoded probes not specifically bound to the biological target;

determining a sequence of the encoded probes specifically bound to the biological target, wherein the sequence comprises all or a portion of the coding tag oligonucleotide sequence, thereby identifying the location of the site to which the encoded probe is delivered; and

associating the abundance or activity or both of the biological target to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the biological target in the sample.

2. (previously presented): The method of claim 1, wherein the biological target is a nucleic acid and the encoded probes are oligonucleotides.

3. (previously presented): The method of claim 2, wherein there are two encoded probes for the nucleic acid target at each of the multiple sites in the sample.

4. (previously presented): The method of claim 1, wherein the biological target is a protein, the probe regions of the encoded probes are proteins, and the coding tags comprise oligonucleotides.

5. (previously presented): The method of claim 4, wherein the biological target comprises an enzyme.

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6. (previously presented): The method of claim 1, wherein each of the probe regions of the encoded probes comprises an antibody, an aptamer, and/or a small molecule that is capable of specific binding to the biological target.

7-8. (canceled)

9. (previously presented): The method of claim 1, further comprising an amplification step between the separating step and the determining step.

10. (previously presented): The method of claim 1, wherein the determining step is performed by nucleic acid sequencing or high-throughput sequencing or high-throughput digital nucleic acid sequencing.

11. (canceled)

12. (previously presented): The method of claim 1, wherein multiple biological targets in the sample are assayed and the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 100, 1,000, 10,000, 100,000, or 1,000,000.

13-19. (canceled)

20. (previously presented): The method of claim 1, wherein the sequences of at least one hundred thousand, at least five hundred thousand, or at least one million encoded probes are determined in parallel.

21-23. (canceled)

24. (previously presented): The method of claim 1, wherein software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step and the associating step.

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25. (previously presented): The method of claim 1, wherein the probe regions of the encoded probes are proteins and the separating step is accomplished by capturing encoded probes specifically bound to the biological target using an affinity capture agent.

26. (previously presented): The method of claim 1, wherein the probe regions of the encoded probes are nucleic acids and the separating step is accomplished by washing the sample.

27. (currently amended): A method to determine a spatial pattern of abundance or activity or both of a nucleic acid target in a sample, comprising the following steps:

delivering an oligonucleotide probe capable of specific hybridization with a nucleic acid target to multiple sites in a sample affixed to a support;

allowing the oligonucleotide probe to hybridize with the nucleic acid target;

washing unhybridized oligonucleotide probe from the sample;

delivering one or more encoding agents to the multiple sites in the sample, wherein the one or more encoding agents delivered to each site comprise an oligonucleotide that identifies the location of the site in the sample;

coupling the one or more encoding agents and the oligonucleotide probe delivered to each site to form an encoded probe specifically hybridized with the nucleic acid target at the site;

determining a sequence of the encoded probes specifically bound to the nucleic acid target, wherein the sequence comprises all or a portion of the one or more encoding agent oligonucleotide sequences, thereby identifying the location of the site to which the one or more encoding agents are delivered; and

associating the abundance or activity or both of nucleic acid target to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the nucleic acid target in the sample.

28. (previously presented): The method of claim 27, wherein multiple nucleic acid targets in the sample are assayed and the product of the multiple nucleic acid targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 10,000, 100,000, or 1,000,000.

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29-33. (canceled)

34. (previously presented): The method of claim 27, wherein the sequences of at least one hundred thousand or at least one million encoded probes are determined in parallel.

35. (canceled)

36. (previously presented): The method of claim 27, wherein two oligonucleotide probes are delivered for the nucleic acid target.

37. (previously presented): The method of claim 27, wherein the coupling step is performed by ligation.

38. (previously presented): The method of claim 27, wherein the coupling step is performed by extension followed by ligation.

39. (previously presented): The method of claim 27, further comprising an amplification step between the coupling step and the determining step.

40-54. (canceled)

55. (currently amended): A method of determining a spatial pattern of abundance or activity or both of a biological target in a sample, comprising:

delivering a probe capable of specific binding to a biological target to multiple sites in a sample affixed to a support;

allowing the probe to interact with the biological target at each of the multiple sites in the sample;

delivering an encoding agent to each of the multiple sites in the sample, wherein the encoding agent delivered to each site ~~comprise~~ comprises an oligonucleotide that identifies the location of the site in the sample;

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coupling the encoding agent to the probe delivered to each of the multiple sites to form an encoded probe at each of the multiple sites;

determining a sequence of the encoded probes specifically bound to the biological target, wherein the sequence comprises all or a portion of the encoding agent oligonucleotide sequence, thereby identifying the location of the site to which the encoding agent is delivered; and

associating the abundance or activity or both of the biological target at each of the multiple sites to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the biological target in the sample.

56. (previously presented): The method of claim 55, wherein one or more biological targets in the sample are assayed in parallel.

57. (previously presented): The method of claim 56, wherein for each biological target, one or more probes capable of specific binding to the biological target are delivered to the multiple sites in the sample.

58. (previously presented): The method of claim 55, wherein at least two encoding agents are delivered to each of the multiple sites in the sample and are coupled to the probe delivered to the site to form an encoded probe comprising the at least two encoding agents.

59. (previously presented): The method of claim 55, wherein the biological target comprises a nucleic acid and the probe comprises an oligonucleotide.

60. (previously presented): The method of claim 55, wherein the biological target comprises a protein and the probe comprises a protein.

61. (previously presented): The method of claim 55, wherein the biological target comprises an enzyme, and the probe comprises a substrate or putative substrate for the enzyme.

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62. (previously presented): The method of claim 55, wherein the probe comprises an affinity capture agent, antibody, aptamer, or small molecule.

63. (previously presented): The method of claim 55, further comprising amplifying all or a portion of a sequence of the encoded probe.

64. (previously presented): The method of claim 55, wherein the determining step is performed by nucleic acid sequencing or high-throughput sequencing.

65. (previously presented): The method of claim 55, wherein multiple biological targets in the sample are assayed and the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 100, 1,000, 10,000, 100,000, or 1,000,000.

66. (previously presented): The method of claim 55, wherein the sequences of at least one hundred thousand, at least five hundred thousand, or at least one million encoded probes are determined in parallel.

67. (previously presented): The method of claim 55, wherein the probe for the biological target and/or the encoding agent are delivered to the multiple sites in the sample according to a known spatial pattern.

68. (previously presented): The method of claim 55, wherein software programmed hardware performs at least two steps of the delivering steps, the coupling step, the determining step, and the associating step.

69. (previously presented): The method of claim 55, further comprising separating probes specifically bound to the biological target from probes not specifically bound to the biological target.

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70. (previously presented): The method of claim 69, wherein the separating step is accomplished by washing the sample.

71. (previously presented): The method of claim 55, wherein the coupling step is performed by ligation, or performed by extension followed by ligation.

72. (previously presented): The method of claim 55, wherein the biological target is a nucleic acid and the probe is capable of specific hybridization with the nucleic acid target, wherein the probe sequence identifies the nucleic acid target.

73. (previously presented): The method of claim 72, wherein in the determining step, the encoded probe sequence being determined comprises all or a portion of the probe sequence and all or a portion of the encoding agent oligonucleotide sequence.

74. (previously presented): The method of claim 73, further comprising quantification of the encoded probe sequence being determined, wherein:

the determined probe sequence identifies the nucleic acid target;

the determined encoding agent oligonucleotide sequence identifies the location of the site at which the probe specific hybridizes with the nucleic acid target; and

the quantity of the encoded probe sequence indicates the amount of the probe specifically hybridized with the nucleic acid target at the site in the sample, and thereby indicates the abundance or activity of the nucleic acid target at the site in the sample.

75. (previously presented): The method of claim 55, wherein the biological target is a protein, the probe is capable of specific binding to the protein target and comprises an oligonucleotide sequence that identifies the protein target.

76. (previously presented): The method of claim 75, wherein in the determining step, the encoded probe sequence being determined comprises all or a portion of the probe oligonucleotide sequence and all or a portion of the encoding agent oligonucleotide sequence.

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77. (previously presented): The method of claim 76, further comprising quantification of the encoded probe sequence being determined, wherein:

the determined probe oligonucleotide sequence identifies the protein target;

the determined encoding agent oligonucleotide sequence identifies the location of the site at which the probe specific binds to the protein target; and

the quantity of the encoded probe sequence indicates the amount of the probe specifically binds to the protein target at the site in the sample, and thereby indicates the abundance or activity of the protein target at the site in the sample.

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REMARKS

Claim Status and Amendment

Claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-77 are pending. The typographical error kindly pointed out by the Examiner, in claim 55, has been corrected. Claims 1, 27, and 55 are amended. Support for the claim amendment is found throughout the specification as originally filed, including in the original claims, for example, at page 21, paragraph [00045] of the original specification. No new matter is added. Reconsideration and allowance of the claims as amended is respectfully requested.

The Rejections under 35 U.S.C. § 103

Claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-77 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Roth *et al.*, US2006/0046313 (hereinafter "Roth") in view of Brenner *et al.*, US2007/0172873 (hereinafter "Brenner"). Applicant respectfully traverses the rejection and requests reconsideration.

Claim 1

Instant claim 1 recites, *inter alia*:

delivering encoded probes for a biological target to multiple sites in a sample affixed to a support, wherein each encoded probe comprises a probe region capable of specific binding to the biological target and a coding tag comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered;

allowing the encoded probes to interact with the biological target;

separating encoded probes specifically bound to the biological target from encoded probes not specifically bound to the biological target;

determining a sequence of the encoded probes specifically bound to the biological target, wherein the sequence comprises all or a portion of the coding tag oligonucleotide sequence, thereby identifying the location of the site to which the encoded probe is delivered; and

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associating the abundance or activity or both of the biological target to the locations of the multiple sites in the sample to determine the spatial pattern of the abundance or activity or both of the biological target in the sample.

Roth discloses the use of probes labeled with Composite Organic-Inorganic Nanoparticles (COINs) for biological assays. COINs are typically clusters of several primary metal crystal particles with Raman-active organic compounds trapped in the junctions of the primary particles or embedded in the metal atoms, and intrinsically produce Surface Enhanced Raman Scattering (SERS) signals upon laser irradiation. *See* Roth at the abstract and at paragraph [0063]. Since most biological targets are not Raman-active, upon binding of a COIN-labeled probe to a biological target, shifts in the Raman spectrum can be used to assay the binding. *Id.*

The Office appears to acknowledge that Roth fails to teach any coding tag comprising an oligonucleotide, because Brenner is cited as allegedly teaching attachment of oligonucleotide tags to a variety of biological macromolecules for the purpose of identification by sequencing the oligonucleotide tags. Even assuming this is the case, however, the cited art still fails to teach or even suggest each and every claim element.

A. The cited art fails to teach or suggest any encoded probe that identifies the location of the site to which the encoded probe is delivered in a sample

Roth teaches lysing tissue samples in order to form "arrays of cell lysates." Roth at paragraph [0033], which is cited by the Office. These cell lysates contain the target molecules to be detected by the COIN-labeled probes. *See* Roth at paragraph [0033], and Figure 3 reproduced below. The cell lysates are "immobilized at (for example, spotted onto) individual defined locations" on an array, and the cell lysate spots are then contacted with a mixture of COIN-labeled probes. *Id.* For example, as shown in Figure 3, extracted cell proteins **330**, **331**, and **332** identify locations X_1X_1, X_1X_2, and X_2X_2, respectfully. *Id.* Since all of the cell lysate spots X_1X_1, X_1X_2, and X_2X_2 are contacted with the mixture of COIN-labeled probes, each COIN-labeled probe in the mixture does not identify the location to which it is delivered. Rather, the "defined locations" on

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the array are identified by the immobilized extracted cell proteins (*i.e.*, the targets), not by the COINs or COIN-labeled probes.

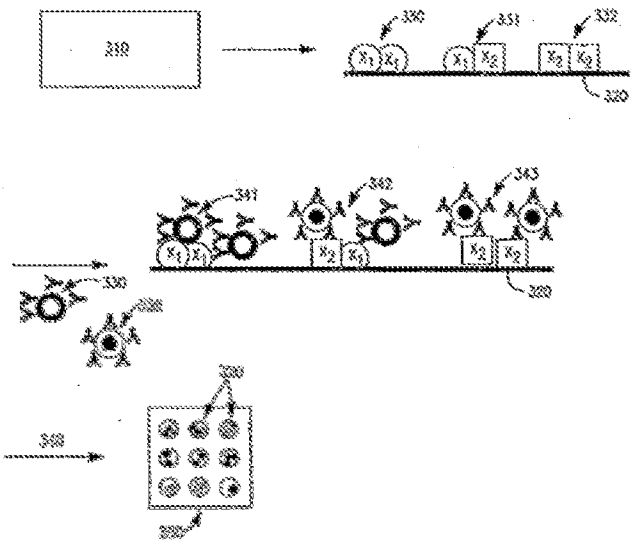


FIG. 3

COINs intrinsically produce SERS signals upon laser irradiation, and may be used to label any probe for an analyte. *See* Roth at the abstract and paragraph [0092]. The Office has not identified any teaching or suggestion that the COINs of Roth are encoded with spatial information of where the COINs or COIN-labeled probes are delivered, much less that the COINs comprise an oligonucleotide that identifies a location to which the COINs or COIN-labeled probes are delivered.

In addition, Roth requires lysing tissue samples in order to form immobilized cell lysate spots on an array. *See* Roth at paragraph [0033] and above. One of skill in the art would understand that lysing a tissue sample in order to obtain cell lysates would have disrupted the structural integrity of the tissue sample, rendering it impossible to determine the spatial pattern of abundance or activity or both of a biological target in the tissue sample. Additionally, as discussed above, since all of the cell lysate spots are contacted with a mixture of COIN-labeled probes, each COIN-labeled probe in the mixture does not identify the location to which it is delivered.

In view of the above, the Office has not identified any teaching or suggestion in Roth of any COIN that identifies the location of the site to which a COIN-labeled probe is delivered.

Brenner discloses methods and compositions for counting molecules in a sample, wherein each molecule is labeled with an oligonucleotide tag. *See* Brenner at the abstract. The tagged

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molecules are in a mixture, and the number of different tag sequences in the mixture is counted by sorting the tags into separate aliquots. *See* Brenner at Figure 1B. The Office has not identified anything in Brenner that teaches or even suggests that its oligonucleotide tags identify the location in a sample to which a tag or tagged molecule is delivered. In fact, Brenner's oligonucleotide tags or tagged molecules are not delivered to any specific location -- they simply exist in a mixture waiting to be sorted by their sequence identity.

In view of the above, the skilled artisan would have no reason to combine the teachings of Roth and Brenner, because neither reference teaches or even suggests any encoded probe that identifies the location to which it is delivered. The Office has not shown that the skilled artisan would have arrived at the present claim with any reasonable expectation of success. For this reason alone, a *prima facie* case has not been established.

B. The cited art fails to teach or suggest any encoded probe comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered in a sample

As discussed above, the Office has not identified any teaching or suggestion in Roth of any COIN that identifies the location of the site to which a COIN-labeled probe is delivered, let alone that the COIN comprises any oligonucleotide that identifies the location.

As a first matter, the COINs are composite organic-inorganic nanoparticles, which the Office has not shown to comprise any oligonucleotide. Although Roth at paragraph [0140] teaches "a COIN-labeled oligonucleotide that is complementary to the target nucleic acid sequence," such disclosure merely teaches that the probe region can be an oligonucleotide, not that the COIN (the alleged coding tag) is an oligonucleotide. Furthermore, the Office has not identified any teaching or suggestion that the oligonucleotide portion of Roth's COIN-labeled oligonucleotide probe identifies the location to which the probe is delivered.

Brenner allegedly teaches labeling a molecule with an oligonucleotide tag for the purpose of identification by sequencing the oligonucleotide tag. However, Brenner's oligonucleotide tags or tagged molecules are not delivered to any specific location. As discussed above, Brenner is concerned with counting the number of oligonucleotide tags in a mixture by sequencing, and the

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Office has not shown that Brenner's oligonucleotide tags encode any spatial information. Thus, even assuming Roth's COINs could comprise an oligonucleotide tag as disclosed in Brenner, the skilled artisan still would not arrive at the present claim with a reasonable expectation of success. This is because neither Roth's COIN nor Brenner's oligonucleotide tag identifies the location of the site to which a COIN-labeled probe or an oligonucleotide-tagged molecule is delivered. In fact, Roth specifically teaches that it is the SERS signals, not any oligonucleotide sequence of the COINs, that are collected, associated with the positions on the array, and used to characterize the target proteins. *See* Roth at paragraph [0032].

The mere fact that references can be combined or modified, or the mere statement that modifications of the cited art to meet the claimed invention would have been within the capabilities of one of ordinary skill in the art, is not sufficient to establish *prima facie* obviousness. MPEP § 2143.01, subsections III and IV. Therefore, the test of obviousness is not whether modifying Roth's COIN with Brenner's oligonucleotide tag could have been done, but whether a skilled artisan would have had a reason to do it with a reasonable expectation of success. As discussed above, the skilled artisan would have no reason to combine the teachings of Roth and Brenner, let alone arrive at the present claim with a reasonable expectation of success. A *prima facie* case has not been established, and the rejection should be withdrawn.

C. There is no reason to combine the cited references

As detailed above, Roth relies on the detection of Surface Enhanced Raman Scattering (SERS) signals upon laser irradiation of the COIN-labeled probes to assay biological samples. Upon binding to a biological target in the sample, the COIN-labeled probe exhibits a distinguishable Raman signature (the "COIN signature") that is characteristic of the binding. *See* Roth at paragraph [0012] and Figure 2. The Office acknowledges that Roth fails to teach or even suggest sequencing any oligonucleotide in the COINs, and that is why Brenner is cited.

The Office's proposed modification, however, requires that Roth's COIN comprises an oligonucleotide, and that sequencing of the COIN is performed for the purpose of identification. The skilled artisan, however, would have no reason to deviate from the specific teachings of Roth by getting rid of the detection of SERS signals and instead using sequencing as the readout. The

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Office has not shown why such a modification would have been desirable. If anything, such a modification would have contradicted the principle of operation of Roth and/or rendered the Roth method unsatisfactory for its intended purpose. The Office is respectfully reminded that if a proposed modification changes the principle of operation of a reference, or renders the reference unsatisfactory for its intended purpose, the teachings of that reference do not render the claimed invention obvious. MPEP § 2143.01.

In sum, Brenner fails to remedy the deficiencies of Roth, and a *prima facie* case has not been established. Applicant's arguments also apply to claims dependent from claim 1, because they require all the elements of the independent claim. Withdrawal of the rejections is respectfully requested.

Claim 27

Instant claim 27 recites, *inter alia*:

delivering an oligonucleotide probe capable of specific hybridization with a nucleic acid target to multiple sites in a sample affixed to a support;

allowing the oligonucleotide probe to hybridize with the nucleic acid target;

washing unhybridized oligonucleotide probe from the sample;

delivering one or more encoding agents to the multiple sites in the sample, wherein the one or more encoding agents delivered to each site comprise an oligonucleotide that identifies the location of the site in the sample;

coupling the one or more encoding agents and the oligonucleotide probe delivered to each site to form an encoded probe specifically hybridized with the nucleic acid target at the site;

determining a sequence of the encoded probes specifically bound to the nucleic acid target, wherein the sequence comprises all or a portion of the one or more encoding agent oligonucleotide sequences, thereby identifying the location of the site to which the one or more encoding agents are delivered; and

associating the abundance or activity or both of nucleic acid target to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the nucleic acid target in the sample.

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Applicant's arguments regarding claim 1 as detailed above also apply to instant claim 27. The Office has not identified any teaching or suggestion in Roth that its COIN comprises an oligonucleotide, let alone delivering any encoding agent comprising an oligonucleotide to a sample and coupling the encoding agent to any probe. Moreover, even assuming Roth's COINs may comprise an oligonucleotide, the Office still has not articulated any teaching of an oligonucleotide that identifies the location of the site to which the COIN or COIN-labeled probe is delivered, let alone determining all or a portion of the oligonucleotide sequence to identify the location. As detailed above, Brenner fails to cure the deficiencies of Roth. Therefore, a *prima facie* case has not been established. Applicant's arguments also apply to claims dependent from claim 27, because they require all the elements of the independent claim. Withdrawal of the rejections is respectfully requested.

Claim 55

Applicant's arguments regarding claims 1 and 27 as detailed above also apply to claim 55, which recites, *inter alia*, delivering an encoding agent to the multiple sites in the sample affixed to a support, wherein the encoding agent delivered to each site comprises an oligonucleotide that identifies the location of the site in the sample, and determining all or a portion of the encoding agent oligonucleotide sequence to identify the location of the site to which the encoding agent is delivered. Applicant's arguments also apply to claims dependent from claim 55, because they require all the elements of the independent claim. Withdrawal of the rejections is respectfully requested.

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Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 699932000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 23, 2015

Respectfully submitted,

Electronic signature: / Bu Yin /

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REMARKS

Claim Status and Amendment

Claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-77 are pending. The typographical error kindly pointed out by the Examiner, in claim 55, has been corrected. Claims 1, 27, and 55 are amended. Support for the claim amendment is found throughout the specification as originally filed, including in the original claims, for example, at page 21, paragraph [00045] of the original specification. No new matter is added. Reconsideration and allowance of the claims as amended is respectfully requested.

The Rejections under 35 U.S.C. § 103

Claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-77 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Roth *et al.*, US2006/0046313 (hereinafter "Roth") in view of Brenner *et al.*, US2007/0172873 (hereinafter "Brenner"). Applicant respectfully traverses the rejection and requests reconsideration.

Claim 1

Instant claim 1 recites, *inter alia*:

delivering encoded probes for a biological target to multiple sites in a sample affixed to a support, wherein each encoded probe comprises a probe region capable of specific binding to the biological target and a coding tag comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered;

allowing the encoded probes to interact with the biological target;

separating encoded probes specifically bound to the biological target from encoded probes not specifically bound to the biological target;

determining a sequence of the encoded probes specifically bound to the biological target, wherein the sequence comprises all or a portion of the coding tag oligonucleotide sequence, thereby identifying the location of the site to which the encoded probe is delivered; and

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associating the abundance or activity or both of the biological target to the locations of the multiple sites in the sample to determine the spatial pattern of the abundance or activity or both of the biological target in the sample.

Roth discloses the use of probes labeled with Composite Organic-Inorganic Nanoparticles (COINs) for biological assays. COINs are typically clusters of several primary metal crystal particles with Raman-active organic compounds trapped in the junctions of the primary particles or embedded in the metal atoms, and intrinsically produce Surface Enhanced Raman Scattering (SERS) signals upon laser irradiation. *See* Roth at the abstract and at paragraph [0063]. Since most biological targets are not Raman-active, upon binding of a COIN-labeled probe to a biological target, shifts in the Raman spectrum can be used to assay the binding. *Id.*

The Office appears to acknowledge that Roth fails to teach any coding tag comprising an oligonucleotide, because Brenner is cited as allegedly teaching attachment of oligonucleotide tags to a variety of biological macromolecules for the purpose of identification by sequencing the oligonucleotide tags. Even assuming this is the case, however, the cited art still fails to teach or even suggest each and every claim element.

A. The cited art fails to teach or suggest any encoded probe that identifies the location of the site to which the encoded probe is delivered in a sample

Roth teaches lysing tissue samples in order to form "arrays of cell lysates." Roth at paragraph [0033], which is cited by the Office. These cell lysates contain the target molecules to be detected by the COIN-labeled probes. *See* Roth at paragraph [0033], and Figure 3 reproduced below. The cell lysates are "immobilized at (for example, spotted onto) individual defined locations" on an array, and the cell lysate spots are then contacted with a mixture of COIN-labeled probes. *Id.* For example, as shown in Figure 3, extracted cell proteins **330**, **331**, and **332** identify locations X_1X_1, X_1X_2, and X_2X_2, respectfully. *Id.* Since all of the cell lysate spots X_1X_1, X_1X_2, and X_2X_2 are contacted with the mixture of COIN-labeled probes, each COIN-labeled probe in the mixture does not identify the location to which it is delivered. Rather, the "defined locations" on

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the array are identified by the immobilized extracted cell proteins (*i.e.*, the targets), not by the COINs or COIN-labeled probes.

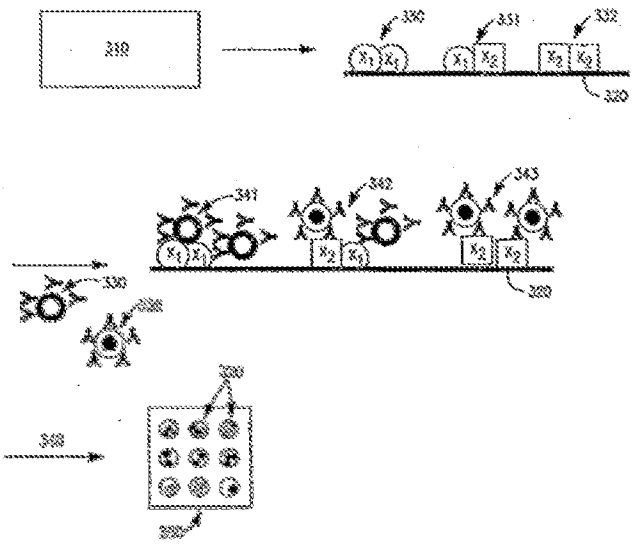


FIG. 3

COINs intrinsically produce SERS signals upon laser irradiation, and may be used to label any probe for an analyte. *See* Roth at the abstract and paragraph [0092]. The Office has not identified any teaching or suggestion that the COINs of Roth are encoded with spatial information of where the COINs or COIN-labeled probes are delivered, much less that the COINs comprise an oligonucleotide that identifies a location to which the COINs or COIN-labeled probes are delivered.

In addition, Roth requires lysing tissue samples in order to form immobilized cell lysate spots on an array. *See* Roth at paragraph [0033] and above. One of skill in the art would understand that lysing a tissue sample in order to obtain cell lysates would have disrupted the structural integrity of the tissue sample, rendering it impossible to determine the spatial pattern of abundance or activity or both of a biological target in the tissue sample. Additionally, as discussed above, since all of the cell lysate spots are contacted with a mixture of COIN-labeled probes, each COIN-labeled probe in the mixture does not identify the location to which it is delivered.

In view of the above, the Office has not identified any teaching or suggestion in Roth of any COIN that identifies the location of the site to which a COIN-labeled probe is delivered.

Brenner discloses methods and compositions for counting molecules in a sample, wherein each molecule is labeled with an oligonucleotide tag. *See* Brenner at the abstract. The tagged

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molecules are in a mixture, and the number of different tag sequences in the mixture is counted by sorting the tags into separate aliquots. *See* Brenner at Figure 1B. The Office has not identified anything in Brenner that teaches or even suggests that its oligonucleotide tags identify the location in a sample to which a tag or tagged molecule is delivered. In fact, Brenner's oligonucleotide tags or tagged molecules are not delivered to any specific location -- they simply exist in a mixture waiting to be sorted by their sequence identity.

In view of the above, the skilled artisan would have no reason to combine the teachings of Roth and Brenner, because neither reference teaches or even suggests any encoded probe that identifies the location to which it is delivered. The Office has not shown that the skilled artisan would have arrived at the present claim with any reasonable expectation of success. For this reason alone, a *prima facie* case has not been established.

B. The cited art fails to teach or suggest any encoded probe comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered in a sample

As discussed above, the Office has not identified any teaching or suggestion in Roth of any COIN that identifies the location of the site to which a COIN-labeled probe is delivered, let alone that the COIN comprises any oligonucleotide that identifies the location.

As a first matter, the COINs are composite organic-inorganic nanoparticles, which the Office has not shown to comprise any oligonucleotide. Although Roth at paragraph [0140] teaches "a COIN-labeled oligonucleotide that is complementary to the target nucleic acid sequence," such disclosure merely teaches that the probe region can be an oligonucleotide, not that the COIN (the alleged coding tag) is an oligonucleotide. Furthermore, the Office has not identified any teaching or suggestion that the oligonucleotide portion of Roth's COIN-labeled oligonucleotide probe identifies the location to which the probe is delivered.

Brenner allegedly teaches labeling a molecule with an oligonucleotide tag for the purpose of identification by sequencing the oligonucleotide tag. However, Brenner's oligonucleotide tags or tagged molecules are not delivered to any specific location. As discussed above, Brenner is concerned with counting the number of oligonucleotide tags in a mixture by sequencing, and the

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Office has not shown that Brenner's oligonucleotide tags encode any spatial information. Thus, even assuming Roth's COINs could comprise an oligonucleotide tag as disclosed in Brenner, the skilled artisan still would not arrive at the present claim with a reasonable expectation of success. This is because neither Roth's COIN nor Brenner's oligonucleotide tag identifies the location of the site to which a COIN-labeled probe or an oligonucleotide-tagged molecule is delivered. In fact, Roth specifically teaches that it is the SERS signals, not any oligonucleotide sequence of the COINs, that are collected, associated with the positions on the array, and used to characterize the target proteins. *See* Roth at paragraph [0032].

The mere fact that references can be combined or modified, or the mere statement that modifications of the cited art to meet the claimed invention would have been within the capabilities of one of ordinary skill in the art, is not sufficient to establish *prima facie* obviousness. MPEP § 2143.01, subsections III and IV. Therefore, the test of obviousness is not whether modifying Roth's COIN with Brenner's oligonucleotide tag could have been done, but whether a skilled artisan would have had a reason to do it with a reasonable expectation of success. As discussed above, the skilled artisan would have no reason to combine the teachings of Roth and Brenner, let alone arrive at the present claim with a reasonable expectation of success. A *prima facie* case has not been established, and the rejection should be withdrawn.

C. There is no reason to combine the cited references

As detailed above, Roth relies on the detection of Surface Enhanced Raman Scattering (SERS) signals upon laser irradiation of the COIN-labeled probes to assay biological samples. Upon binding to a biological target in the sample, the COIN-labeled probe exhibits a distinguishable Raman signature (the "COIN signature") that is characteristic of the binding. *See* Roth at paragraph [0012] and Figure 2. The Office acknowledges that Roth fails to teach or even suggest sequencing any oligonucleotide in the COINs, and that is why Brenner is cited.

The Office's proposed modification, however, requires that Roth's COIN comprises an oligonucleotide, and that sequencing of the COIN is performed for the purpose of identification. The skilled artisan, however, would have no reason to deviate from the specific teachings of Roth by getting rid of the detection of SERS signals and instead using sequencing as the readout. The

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Office has not shown why such a modification would have been desirable. If anything, such a modification would have contradicted the principle of operation of Roth and/or rendered the Roth method unsatisfactory for its intended purpose. The Office is respectfully reminded that if a proposed modification changes the principle of operation of a reference, or renders the reference unsatisfactory for its intended purpose, the teachings of that reference do not render the claimed invention obvious. MPEP § 2143.01.

In sum, Brenner fails to remedy the deficiencies of Roth, and a *prima facie* case has not been established. Applicant's arguments also apply to claims dependent from claim 1, because they require all the elements of the independent claim. Withdrawal of the rejections is respectfully requested.

Claim 27

Instant claim 27 recites, *inter alia*:

delivering an oligonucleotide probe capable of specific hybridization with a nucleic acid target to multiple sites in a sample affixed to a support;

allowing the oligonucleotide probe to hybridize with the nucleic acid target;

washing unhybridized oligonucleotide probe from the sample;

delivering one or more encoding agents to the multiple sites in the sample, wherein the one or more encoding agents delivered to each site comprise an oligonucleotide that identifies the location of the site in the sample;

coupling the one or more encoding agents and the oligonucleotide probe delivered to each site to form an encoded probe specifically hybridized with the nucleic acid target at the site;

determining a sequence of the encoded probes specifically bound to the nucleic acid target, wherein the sequence comprises all or a portion of the one or more encoding agent oligonucleotide sequences, thereby identifying the location of the site to which the one or more encoding agents are delivered; and

associating the abundance or activity or both of nucleic acid target to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the nucleic acid target in the sample.

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Applicant's arguments regarding claim 1 as detailed above also apply to instant claim 27. The Office has not identified any teaching or suggestion in Roth that its COIN comprises an oligonucleotide, let alone delivering any encoding agent comprising an oligonucleotide to a sample and coupling the encoding agent to any probe. Moreover, even assuming Roth's COINs may comprise an oligonucleotide, the Office still has not articulated any teaching of an oligonucleotide that identifies the location of the site to which the COIN or COIN-labeled probe is delivered, let alone determining all or a portion of the oligonucleotide sequence to identify the location. As detailed above, Brenner fails to cure the deficiencies of Roth. Therefore, a *prima facie* case has not been established. Applicant's arguments also apply to claims dependent from claim 27, because they require all the elements of the independent claim. Withdrawal of the rejections is respectfully requested.

Claim 55

Applicant's arguments regarding claims 1 and 27 as detailed above also apply to claim 55, which recites, *inter alia*, delivering an encoding agent to the multiple sites in the sample affixed to a support, wherein the encoding agent delivered to each site comprises an oligonucleotide that identifies the location of the site in the sample, and determining all or a portion of the encoding agent oligonucleotide sequence to identify the location of the site to which the encoding agent is delivered. Applicant's arguments also apply to claims dependent from claim 55, because they require all the elements of the independent claim. Withdrawal of the rejections is respectfully requested.

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Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 699932000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 23, 2015

Respectfully submitted,

Electronic signature: / Bu Yin /

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Electronic Patent Application Fee Transmittal

Application Number:	13080616
Filing Date:	05-Apr-2011
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Filer:	Bu Yin/Jennifer Jung
Attorney Docket Number:	699932000200

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	2251	1	100	100
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	21575896
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/Jennifer Jung
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	23-FEB-2015
Filing Date:	05-APR-2011
Time Stamp:	18:19:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$100
RAM confirmation Number	5577
Deposit Account	031952
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		02_00_Amendment.pdf	145730 d425f4505231041c82d59aaeea19f988da887688	yes	17

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	17

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30654 ae267215bd193840d2dcfc3c23a3c9bdfbf2f35c	no	2

Warnings:

Information:

Total Files Size (in bytes):	176384

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/080,616	Filing Date 04/05/2011	☐ 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 $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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

AMENDMENT **02/23/2015**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 43	Minus	** 57	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***4	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ 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.

** 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 number found in the appropriate box in column 1.

LIE
/CAROLYN THOMAS/

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

25225 7590 03/17/2015

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EXAMINER	
MARTINELL, JAMES	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
03/17/2015	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):

PatentDocket@mofo.com
EOfficeSD@mofo.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 13/080,616	**Applicant(s)** CHEE, MARK S.	
	Examiner JAMES MARTINELL	**Art Unit** 1634	**AIA (First Inventor to File) Status** No

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

THE REPLY FILED 23 February 2015 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☐ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.

   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): none.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☐ will not be entered, or (b) ☒ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Applicant's arguments (response filed 3/11/15, pages 8-16) are not persuasive because the claims are not so limited as applicant argues. For example, the claims embrace localization of tagged probes to targets immobilized on arrays.
13. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed: none.
    Claim(s) objected to: none.
    Claim(s) rejected: 1-6,9,10,12,20,24-28,34,36-39 and 55-77.
    Claim(s) withdrawn from consideration: none.

/JAMES MARTINELL/
Primary Examiner, Art Unit 1634

OK TO ENTER: /J.M./

03/11/2015

Docket No.: 699932000200
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Mark S. CHEE	Confirmation No.: 2142
Application No.: 13/080,616	Art Unit: 1634
Filed: April 5, 2011	Examiner: James Martinell
For: SPATIALLY ENCODED BIOLOGICAL ASSAYS	

AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION UNDER 37 C.F.R. 1.116

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

Dear Commissioner:

INTRODUCTORY COMMENTS

This is in response to the final Office Action dated October 21, 2014, for which a response was due on January 21, 2015. Filed herewith is a Petition and fee for a one-month extension of time, thereby extending the deadline for response to February 23, 2014, because February 21, 2015 is a Saturday, and February 22, 2015 is a Sunday. Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 10 of this paper.

Curio EX1012-p. 402
Curio v Prognosys

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.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

25225 7590 03/31/2015

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
MARTINELL, JAMES	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
03/31/2015	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):

PatentDocket@mofo.com
EOfficeSD@mofo.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/080,616	CHEE, MARK S.	
	Examiner	Art Unit	
	JAMES MARTINELL	1634	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JAMES MARTINELL*. (3) *Dr. Chen*.

(2) *Mr. Yin*. (4)_____.

Date of Interview: *24 March 2015*.

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

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

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 27*.

Identification of prior art discussed: *Roth et al US 2006/0046313 A1) and Brenner et al (US 2007/0172873 A1)*.

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...)

The nature of the invention in reference to claim 1 and figure 5 was discussed. The steps include: (1) Fix a tissue sample onto a surface. (2) Probe the surface at with combinations of probes a1-a4, b1-b4, TS01, and TS02.(3) Wash unbound probes (4) read sequences by sequencing reactions in the pool of probes to determine which probes bound to the sample. Applicant explained that the probes are sequenced. Examiner indicated that sequence can be "determined" by merely identifying which of certain labelled probes bind and referred to the 103(a) rejection. Examiner favorably impressed pending amendment of independent claims (1 and 27) limiting them to include a sequencing reaction step and further indicated that such an amendment would be entered after a final rejection.. Applicant intends to respond.. .

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 examiner's 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 applicant's 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 applicant's 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 examiner's 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 examiner's initials.

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	13080616	Filing Date	2011-04-05	Docket Number (if applicable)	699932000200	Art Unit	1634
First Named Inventor	Mark S. CHEE			Examiner Name	J. Martinell		

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

SUBMISSION REQUIRED UNDER 37 CFR 1.114

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

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

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

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

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

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 03-1952

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Bu Yin/	Date (YYYY-MM-DD)	2015-04-20
Name	Bu Yin	Registration Number	68930

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

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

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 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 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.

Electronic Patent Application Fee Transmittal

Application Number:	13080616
Filing Date:	05-Apr-2011
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Filer:	Bu Yin/Jennifer Jung
Attorney Docket Number:	699932000200

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $100 paid	2253	1	600	600
Miscellaneous:				
Request for Continued Examination	2801	1	600	600
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt

EFS ID:	22114809
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/Jennifer Jung
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	20-APR-2015
Filing Date:	05-APR-2011
Time Stamp:	19:53:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1200
RAM confirmation Number	6821
Deposit Account	031952
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	69993_IDS_Transmittal.pdf	25559 2fea69a760923eefc783ae6d275b78c663f85057	no	3
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	69993_IDS_SB08.pdf	33305 2582f2c8c5f436d7fd7eef5ac88b60c7630814db	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	12_WO2014210223.pdf	6872768 eec3660b58edae604e4c3078aeb97230b7c5e4ce	no	133
Warnings:					
Information:					
4	Foreign Reference	13_WO2014210225.pdf	5904036 07abeca3f1e17cbc0834bca2998a73beb574ae26	no	113
Warnings:					
Information:					
5	Non Patent Literature	14_RspCAOA09172014.pdf	6113458 99511220e7d0f0ed81db0b0db877a4528075d93a	no	28
Warnings:					
Information:					
6	Non Patent Literature	15_RspCNOA09172014.pdf	8390500 4ca969cdd40fffcc4ef77ec86daf6129ce90e282	no	16
Warnings:					
Information:					
7	Non Patent Literature	17_RspCNOA04132015.pdf	5530530 5b067388182538fa2b93f35d10decaeddd45f36b	no	11
Warnings:					
Information:					

8	Non Patent Literature	18_EPOA08222014.pdf	95330 bf7691e9b634ee97f2b15c3d41c5d43ec2451afd	no	4
Warnings:					
Information:					
9	Non Patent Literature	19_RspEPOA01082015.pdf	6582527 a4d81c1ba6999a4f13aa1b0f06d059d4c41c7f4b	no	28
Warnings:					
Information:					
10	Non Patent Literature	20_US13442637OA01222015.pdf	625140 f8ab77a756798bcc7480abe8b84f31b2a71a1dcb	no	15
Warnings:					
Information:					
11	Non Patent Literature	22_ISR08192014.pdf	2556287 febfd32145c8ca4ed3c684c1d3c30cd5c8e49cc6	no	11
Warnings:					
Information:					
12	Non Patent Literature	23_ISR11072014.pdf	3445804 d04c4107cca7f48aa6654269b67d699d91cd8705	no	11
Warnings:					
Information:					
13	Non Patent Literature	24_ISR_PCTUS2014044196_11072014.pdf	5353891 6124381c6e2be566d24e78f116e6550fb23ea4a2	no	16
Warnings:					
Information:					
14	Non Patent Literature	25_ISR03112015.pdf	1782769 a883613f1d3b643eea08893092fee0d4ff82b758	no	23
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15	Non Patent Literature	26_Valencia.pdf	1326521 b1ff731b8fc8fe32587f1d0353e7f07a8740d41e	no	9
Warnings:					
Information:					
16	Non Patent Literature	27_Osada.pdf	657102 4490a4e2fa3aa991720a265827557e7479d23fcd	no	8
Warnings:					
Information:					

17	Non Patent Literature	28_Routenberg.pdf	1975611 ed840f165ad60f532b87fef6f9d4965d2ba364a2	no	5
Warnings:					
Information:					
18	Non Patent Literature	29_Weichhart.pdf	1558858 5c4e1e1437d1b4543d23dc22f7486cae7fa32abe	no	9
Warnings:					
Information:					
19	Non Patent Literature	16_CNOA01272015.pdf	878347 c0e5caeff2da1abbb72cc34959c0d60b15a0f13e	no	4
Warnings:					
Information:					
20	Non Patent Literature	21_ESR11182014.pdf	200413 0a62206579f68e33997b506373d3821d8ee73137	no	6
Warnings:					
Information:					
21		69993_Amend.pdf	39069 24fe515cbb38f9a88a2568c97e319a2a15fd6834	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment Submitted/Entered with Filing of CPA/RCE	1	2
Claims	3	10
Applicant Arguments/Remarks Made in an Amendment	11	12

Warnings:					
Information:					
22	Request for Continued Examination (RCE)	69993_RCE.pdf	697653 f0d5f99dae44d6efb8876967be1bb12cf8bfb01b	no	3
Warnings:					
Information:					
23	Fee Worksheet (SB06)	fee-info.pdf	32474 311376ac889107940999204207496f63d8627a87	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	60677952	

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.

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: April 20, 2015
Electronic Signature for Jennifer Jung: /Jennifer Jung/

Patent
Docket No. 699932000200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mark S. CHEE

Application No.: 13/080,616 | Confirmation No.: 2142

Filed: April 5, 2011 | Art Unit: 1634

For: SPATIALLY ENCODED BIOLOGICAL ASSAYS | Examiner: J. Martinell

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98

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

Dear Madam:

Pursuant to 37 C.F.R. § 1.97 and § 1.98, Applicant submits for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. Copies of the foreign documents and non-patent literature are submitted herewith. The Examiner is requested to make these documents of record.

sd-660392

This Information Disclosure Statement is submitted:

☐ With the application; accordingly, no fee or separate requirements are required.

☒ With the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required.

☐ Before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☐ Within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) has been provided.

☐ After receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance.

- ☐ The required fee is submitted herewith.
- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above; accordingly, no fee is believed to be due.

☐ After mailing of a final Office Action or Notice of Allowance, but before payment of the Issue Fee.

- ☐ A Certification under 37 C.F.R. § 1.97(e) is provided above and the required fee is submitted herewith.

Applicant would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

The information contained in this Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

sd-660392

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing (699932000200). However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 20, 2015

Respectfully submitted,

Electronic signature: /Bu Yin/
Bu Yin
Registration No.: 68,930
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego, California 92130-2040
(858) 720-7912

sd-660392

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-7,393,665	07-01-2008	Brenner	
	2.	US-7,407,757	08-2008	Brenner	
	3.	US-7,537,897	05-26-2009	Brenner et al.	
	4.	US-7,579,153	08-25-2009	Brenner et al.	
	5.	US-7,635,566	12-22-2009	Brenner	
	6.	US-8,337,851	12-25-2012	Aukerman et al.	
	7.	US-8,343,500	01-01-2013	Wraith et al.	
	8.	US-2003/0162216	08-28-2003	Gold et al.	
	9.	US-2012/0195810	08-02-2012	Cohen et al.	
	10.	US-2013/0109595	05-02-2013	Routenberg	
	11.	US-2013/0096033	04-18-2013	Routenberg	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	12.	WO-2014/210223	12-2014	Chee et al.		
	13.	WO-2014/210225	12-2014	Chee et al.		

Examiner Signature		Date Considered	

*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	14.	Response to Office Action for CA 2794522, dated 17 September 2014	
	15.	Response to Second Examination Report for CN 201180017696.3, filed 17 September 2014	
	16.	Third Examination Report for CN 201180017696.3, mailed 27 January 2015	
	17.	Response to Third Examination Report for CN 201180017696.3, filed 13 April 2015	
	18.	European Examination Report for EP 11766613.1, dated 22 August 2014	
	19.	Response to European Examination Report for EP 11766613.1, filed 8 January 2015	
	20.	Office Action for US 13/442,637, mailed 22 January 2015	
	21.	Extended European Search Report for EP 12767937.1-1403, mailed 18 November 2014	
	22.	International Search Report and Written Opinion of PCT/US14/29691, mailed 19 August 2014	

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/080,616
				Filing Date	April 5, 2011
				First Named Inventor	Mark S. CHEE
				Art Unit	1634
				Examiner Name	J. Martinell
Sheet	2	of	2	Attorney Docket Number	699932000200

	23.	International Search Report and Written Opinion of PCT/US14/44191, mailed 7 November 2014	
	24.	International Search Report and Written Opinion of PCT/US14/44196, mailed 7 November 2014	
	25.	International Search Report and Written Opinion of PCT/US14/64588, mailed 11 March 2015	
	26.	ALEXANDER VALENCIA et al., "mRNA-display-based selections for proteins with desired functions: A protease-substrate case study," Biotechnology Progress, 2008, 24(3): 561-569	
	27.	OSADA et al., "Epitope mapping using ribosome display in a resconstituted cell-free protein synthesis system," Journal of Biochemistry, 2009, 145(5):693-700	
	28.	ROUNTENBERG et al., "Microfluidic probe: a new tool for integrating microfluidic environments and electronic wafer-probing," Lab Chip, 29 October 2009, 10: 123-127	
	29.	WEICHHART et al., "Functional selection of vaccine candidate peptides from Staphylococcus aureus whole-genome expression libraries in vitro," Infection and Immunity, 2003, 71(8):4333-4641	

Examiner Signature		Date Considered	

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

MORRISON | FOERSTER
PROCESSED
August 26, 2014

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: Bu Yin
Morrison & Foerster LLP
12531 High Bluff Drive, Suite 100
San Diego, CA 92130-2040
United States of America

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing (day/month/year) 19 AUG 2014
Applicant's or agent's file reference: 699932000140	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No.: PCT/US14/29691	International filing date (day/month/year) 14 March 2014 (14.03.2014)
Applicant: Prognosys Biosciences, Inc. /cts	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 Telephone No. PCT Office: 571-272-7774

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 690032000140	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US14/29691	International filing date *(day/month/year)* 14 March 2014 (14.03.2014)	(Earliest) Priority Date *(day/month/year)* 15 March 2013 (15.03.2013)
Applicant *Prognosys Biosciences, Inc.*		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. 8A

   ☒ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/28691

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)
   - ☐ on paper
   - ☒ in electronic form

   b. (time)
   - ☐ in the international application as filed
   - ☐ together with the international application in electronic form
   - ☒ subsequently to this Authority for the purposes of search

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/29691

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 15-21
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/28681

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/567, 33/53; C12Q 1/00 (2014.01)
USPC - 435/7.21, 7.2, 7.1, 4
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): G01N 33/567, 33/53, 33/574; C12Q 1/00, 1/68; C07H 21/04; C12N 15/11, 15/62, 15/09; A61K 39/02, 38/17, 09/396 (2014.01)
USPC: 435/7.21, 7.2, 7.1, 4, 6, 69.1, 7.23; 424/185.1, 192.1, 144.1, 93.21, 88, 243.1; 514/44, 12; 530/403, 402

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; ProQuest; peptide, 'MHC,' conjugated

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 8343500 B2 (WRAITH, DC et al.) 01 January 2013; abstract; column 31, line 47; column 8, line 48; column 4, line 18; column 31, line 31; column 1, line 19; column 17, line 64; column 29, lines 9-10; column 8, lines 8-10; column 4, line 41; column 8, line 26; column 6, line 52; column 2, line 51; column 1, line 43; column 8, line 47; column 11, line 13; column 31, line 65; column 4, line 24; column 33, line 8; column 14, line 23; column 28, lines 15-16; column 28, line 9; column 6, lines 36-38; column 5, line 48; column 1, lines 32-38; column 1, line 37; column 1, lines 36-37; column 7, lines 44-45	1-6, 7-9, 10/8, 10/9, 11-13, 14/11-14/13 ----- 6
Y	US 8337851 B2 (AUKERMAN, SL et al.) 25 December 2012; column 24, lines 27-31	6

☐ Further documents are listed in the continuation of Box C. ☐

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent but published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2014 (25.07.2014)	19 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shawn Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Bu Yin
Morrison & Foerster LLP
12531 High Bluff Drive, Suite 100
San Diego, CA 92130-2040
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	19 AUG 2014
Applicant's or agent's file reference 699932000140	FOR FURTHER ACTION See paragraph 2 below

International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US14/29691	14 March 2014 (14.03.2014)	15 March 2013 (15.03.2013)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G01N 33/567, 33/53; C12Q 1/00 (2014.01)
USPC - 435/7.21, 7.2, 7.1, 4

Applicant Prognosys Biosciences, Inc.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	25 July 2014 (25.07.2014)	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/28081

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☒ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☒ subsequently to this Authority for the purposes of search

4. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/28691

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 15-21

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 15-21 are so unclear that no meaningful opinion could be formed *(specify)*:

Claim Nos. 15-21 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 15-21

☐ a meaningful opinion could not be formed without the sequence listing: the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/28891

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	8	YES
	Claims	1-5, 7-14	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-14	NO
Industrial applicability (IA)	Claims	1-14	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-6, 7-9, 10/8, 10/9, 11-13 and 14/11-14/13 lack novelty under PCT Article 33(2) as being anticipated by US 8,343,500 B2 to Wraith, et al. (hereinafter 'Wraith').

Regarding claim 1, Wraith discloses an MHC-binding peptide (MHC binding peptide; abstract) conjugated to (binding to (conjugated to); abstract) a polynucleotide (DNA (polynucleotide); column 31, line 47).

Regarding claim 2, Wraith discloses a library of at least two MHC-binding peptides (library of peptides (library of at least two MHC-binding peptides), column 9, line 48; MHC-binding peptide (MHC-binding peptides), abstract) each (each; column 4, line 15) conjugated to (binding to (conjugated to); abstract) a polynucleotide (DNA (polynucleotide); column 31, line 47), wherein each said polynucleotide (DNA (each said polynucleotide); column 31, line 47) is identified by (identified by; column 1, line 19) a probe (probe; column 31, line 31) that specifically (specific (specifically); column 17, line 64) binds to (binds to; column 29, lines 9-10) said polynucleotide (DNA (said polynucleotide); column 31, line 47).

Regarding claim 3, Wraith discloses a composition (composition; abstract) comprising at least two MHC-binding peptides (library of peptides (at least two MHC-binding peptides), column 9, line 48; MHC-binding peptide (MHC-binding peptides), abstract) each (each; column 4, line 15) conjugated to (binding to (conjugated to); abstract) a polynucleotide (DNA (polynucleotide); column 31, line 47), wherein the at least two MHC-binding peptides (library of peptides (at least two MHC-binding peptides), column 9, line 48; MHC-binding peptide (MHC-binding peptides), abstract) are oligomerized (peptides 15-mer, 10-mer and 17-mer in length (oligomerized); column 6, lines 8-10).

Regarding claim 4, Wraith discloses the composition of claim 3, and Wraith further discloses wherein the at least two MHC-binding peptides (library of peptides (at least two MHC-binding peptides), column 9, line 48; MHC-binding peptide (MHC-binding peptides), abstract) are conjugated to (binding to (conjugated to), abstract) the same (same; column 4, line 41) polynucleotide (DNA (polynucleotide); column 31, line 47) and are thus oligomerized (peptides 15-mer, 10-mer and 17-mer in length (oligomerized); column 6, lines 8-10).

Regarding claim 5, Wraith discloses the composition of claim 3, and Wraith further discloses wherein the at least two MHC-binding peptides (library of peptides (at least two MHC-binding peptides), column 9, line 48; MHC-binding peptide (MHC-binding peptides), abstract) are each (each; column 4, line 15) conjugated to (binding to (conjugated to), abstract) a separate (separate; column 5, line 36; column 5, line 52) polynucleotide (DNA (polynucleotide); column 31, line 47), wherein the polynucleotides (DNA (polynucleotides); column 31, line 47) mediate (mediate (mediate); column 2, line 61) the oligomerization (peptides 15-mer, 10-mer and 17-mer in length (oligomerization); column 6, lines 8-10) of the at least two MHC-binding peptides (library of peptides (at least two MHC-binding peptides), column 9, line 48; MHC-binding peptide (MHC-binding peptides), abstract).

Regarding claim 7, Wraith discloses a method (method, abstract) for detecting (identifying (detecting); column 9, line 47) binding of a peptide to an MHC molecule (peptide binding to an MHC molecule (binding of a peptide to an MHC molecule), abstract), comprising: contacting (contacts (contacting),; claim 11, line 13) said MHC molecule (said MHC molecule, abstract) with a polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate column 31, line 55), said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 55) comprising said peptide (peptide (said peptide); abstract) and a polynucleotide (DNA (polynucleotide); column 31, line 47); contacting (contacts (contacting); column 11, line 13) said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 55) with a probe (probe; column 31, line 31) that specifically (specific (specifically); column 17, line 64) binds to (binds to; column 29, lines 9-10) said polynucleotide (DNA (said polynucleotide), column 31, line 47; detecting (identifying (detecting); column 9, line 47) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to said polynucleotide (DNA (said polynucleotide); column 31, line 47); and correlating (correlating; column 33, line 8) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to said polynucleotide (DNA (said polynucleotide); column 31, line 47) with binding of said peptide to said MHC molecule (peptide binding to an MHC molecule (binding of said peptide to said MHC molecule); abstract).

-***-Continued Within the Next Supplemental Box-***-

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Box No. V:
-Continued from Citations and Explanations:

Regarding claim 8, Wraith discloses a method (method; abstract) for simultaneously (simultaneously; column 14 , line 23) detecting (identifying (detecting)); column 9, line 47) binding of (binding of; column 4, line 24) a library of peptides (library of peptides; column 8, line 48) to an MHC molecule (abstract), comprising: providing (provided (providing); abstract) a polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) for each said peptide (peptide; abstract), said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) comprising said peptide (peptide (said peptide), abstract) and a polynucleotide (DNA (a polynucleotide); column 31, line 47); contacting (contacts (contacting); column 11, line 13) said MHC molecule (MHC molecule (said MHC molecule), abstract) with a pool (pool; column 9, line 39) of said polynucleotide-peptide conjugates (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugates, column 31, line 65); contacting (contacts (contacting); column 11, line 13) each of (each of; column 13, line 56) said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) with a probe (probe; column 31, line 31) that specifically (specific (specifically); column 17, line 64) binds to (binds to; column 29, lines 9-10) each said polynucleotide (DNA (each said polynucleotide), column 31, line 47); detecting (identifying (detecting)); column 9, line 47) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to each (each; column 4, line 16) corresponding (corresponding; column 28, lines 15-16) polynucleotide (DNA (polynucleotide); column 31, line 47) that each said probe (probe (each said probe); column 31, line 31) specifically (specific (specifically); column 17, line 64) binds (binds; column 29, line 9); and correlating (correlating; column 33, line 8) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to each (each; column 4, line 15) corresponding (corresponding; column 28, lines 15-16) polynucleotide (DNA (polynucleotide); column 31, line 47) with binding of each corresponding peptide to said MHC molecule (peptide binding to an MHC molecule (binding of each corresponding peptide to said MHC molecule); abstract).

Regarding claim 9, Wraith discloses a method (method, abstract) for detecting (identifying (detecting)); column 9, line 47) in a library of peptides (library of peptides; column 8, line 48) competitive binding of each said peptide to an MHC molecule (dominance of a particular peptide depends on relative affinity for binding the MHC molecule (competitive binding of each said peptide to an MHC molecule); column 8, lines 36-38) comprising: providing (provided (providing), abstract) a polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) for each said peptide (peptide (each said peptide); abstract), said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) comprising said peptide (peptide (said peptide); abstract) and a polynucleotide (DNA (a polynucleotide); column 31, line 47); contacting (contacts (contacting)); column 11, line 13) said MHC molecule (MHC molecule (said MHC molecule); abstract) with a pool (pool; column 9, line 39) of said polynucleotide-peptide conjugates (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugates (conjugate; column 31, line 65); contacting (contacts (contacting); column 11, line 13) each of (each of; column 13, line 56) said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) with a probe (probe; column 31, line 31) that specifically (specific (specifically); column 17, line 64) binds to (binds to; column 29, lines 9-10) each said polynucleotide (DNA (each said polynucleotide); column 31, line 47); detecting (identifying (detecting)); column 9, line 47) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to each (each; column 4, line 16) corresponding (corresponding; column 28, lines 15-16) polynucleotide (DNA (polynucleotide); column 31, line 47) that each said probe (probe (each said probe); column 31, line 31) specifically (specific (specifically); column 17, line 64) binds (binds; column 29, line 9); and correlating (correlating; column 33, line 8) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to each (each; column 4, line 15) corresponding (corresponding; column 28, lines 15-16) polynucleotide (DNA (polynucleotide); column 31, line 47) with binding of each corresponding peptide to said MHC molecule (peptide binding to an MHC molecule (binding of each corresponding peptide to said MHC molecule); abstract), wherein said peptides compete for binding of said MHC molecule (dominance of a particular peptide depends on relative affinity for binding the MHC molecule (said peptides compete for binding of said MHC molecule); column 8, lines 36-38).

Regarding claims 10/8 and 10/9, Wraith discloses a method of claims 8 and 9, and Wraith discloses further comprising comparing (compared (comparing)); column 8, line 48) binding of each said peptide to said MHC molecule (peptide binding to an MHC molecule (binding of each said peptide to said MHC molecule); abstract), among the peptides in said library (library of peptides (peptides in said library)); column 9, line 48).

Regarding claim 11, Wraith discloses a method (method, abstract) of detecting (identifying (detecting)); column 9, line 47) binding of a peptide to a TCR (peptide-MHC complex carried to cell surface and peptide is recognized by a T cell via the TCR (binding of a peptide to a TCR); column 1, lines 32-38), comprising: contacting (contacts (contacting)); column 11, line 13) said TCR (TCR (said TCR); column 1, line 37) with an MHC molecule (MHC molecule; abstract) and a polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65), said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65); comprising said peptide (peptide, abstract) and a polynucleotide (DNA (polynucleotide), column 31, line 47); contacting (contacts (contacting), column 11, line 13) said polynucleotide-peptide conjugate (DNA (polynucleotide); column 31, line 47; peptide, abstract; conjugate, column 31, line 65) with a probe (probe; column 31, line 31) that specifically (specific (specifically); column 17, line 64) binds to (binds to; column 29, lines 9-10) said polynucleotide (DNA (said polynucleotide); column 31, line 47); detecting (identifying (detecting)); column 9, line 47) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to said polynucleotide (DNA (said polynucleotide); column 31, line 47); and correlating (correlating, column 33, line 8) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to said polynucleotide (DNA (said polynucleotide); column 31, line 47) with binding of said peptide to said TCR (peptide-MHC complex carried to cell surface and peptide is recognized by a T cell via the TCR (binding of said peptide to said TCR); column 1, lines 32-38).

-***-Continued Within the Next Supplemental Box-***-

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/29881

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Box No. V:
-Continued from Citations and Explanations:

Regarding claim 12, Wraith discloses a method (method; abstract) for simultaneously (simultaneously; column 14 , line 23) detecting (identifying (detecting); column 8, line 47) binding of (binding of; column 4, line 24) a library of peptides (library of peptides; column 8, line 48) to a TCR (TCR; column 1, line 37), comprising: providing (provided (providing)), abstract) a polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, Aabstract; conjugate, column 31, line 65) for each said peptide (peptide (each said peptide); abstract), said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) comprising said peptide (peptide (said peptide); abstract) and a polynucleotide (DNA (polynucleotide), column 31, line 47); contacting (contacts (contacting); column 11, line 13) said TCR (TCR (said TCR)); column 1, line 37) with a pool (pool; column 9, line 39) of said polynucleotide-peptide conjugates (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugates (conjugate (conjugates), column 31, line 65) and an MHC molecule (MHC molecule, abstract); contacting (contacts (contacting)), column 11, line 13) each of (each of; column 13, line 56) said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) with a probe (probe; column 31, line 31) that specifically (specific (specifically); column 17, line 64) binds to (binds to; column 29, lines 9-10) each said polynucleotide (DNA (each said polynucleotide); column 31, line 47); detecting (identifying (detecting)); column 8, line 47) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to each (each; column 4, line 15) corresponding (corresponding; column 28, lines 15-16) polynucleotide (DNA (polynucleotide); column 31, line 47) that each said probe (probe (each said probe); column 31, line 31) specifically (specific (specifically); column 17, line 64) binds (binds; column 29, line 9); and correlating (correlating; column 33, line 8) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to each (each; column 4, line 15) corresponding (corresponding; column 28, lines 15-16) polynucleotide (DNA (polynucleotide); column 31, line 47) with binding of each corresponding peptide to said TCR (peptide-MHC complex carried to cell surface and peptide is recognized by a T cell via the TCR (binding of each corresponding peptide to said TCR)); column 1, lines 32-38).

Regarding claim 13, Wraith discloses a method (method; abstract) for detecting (identifying (detecting); column 8, line 47) in a library of peptides (library of peptides; column 8, line 48) competitive binding of each said peptide (dominance of a particular peptide depends on relative affinity for binding (competitive binding of each said peptide); column 8, lines 36-38) to a TCR (TCR; column 1, line 37), comprising: providing (provided (providing)); abstract) a polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) for each said peptide (peptide (each said peptide), abstract), said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugate, column 31, line 65) comprising said peptide (peptide (said peptide), abstract) and a polynucleotide (DNA (polynucleotide); column 31, line 47); contacting (contacts (contacting); column 11, line 13) said TCR (TCR (said TCR)); column 1, line 37) with a pool (pool; column 9, line 39) of said polynucleotide-peptide conjugates (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugates, column 31, line 65) and an MHC molecule (MHC molecule; abstract); contacting (contacts (contacting)); column 11, line 13) each of (each of; column 13, line 56) said polynucleotide-peptide conjugate (DNA (polynucleotide), column 31, line 47; peptide, abstract; conjugates (conjugate (conjugates)); column 31, line 65) with a probe (probe; column 31, line 31) that specifically (specific (specifically); column 17, line 64) binds to (binds to; column 29, lines 9-10) each said polynucleotide (DNA (each said polynucleotide); column 31, line 47); detecting (identifying (detecting)); column 8, line 47) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to each (each; column 4, line 15) corresponding (corresponding; column 28, lines 15-16) polynucleotide (DNA (polynucleotide); column 31, line 47) that each said probe (probe (each said probe); column 31, line 31) specifically (specific (specifically); column 17, line 64) binds (binds; column 29, line 9); and correlating (correlating; column 33, line 8) binding of (binding of; column 4, line 24) said probe (probe (said probe); column 31, line 31) to each (each; column 4, line 15) corresponding (corresponding; column 28, lines 15-16) polynucleotide (DNA (polynucleotide); column 31, line 47) with binding of (binding of; column 4, line 24) each (each; column 4, line 15) corresponding (corresponding; column 28, lines 15-16) peptide (peptide, abstract) to said TCR (TCR (said TCR)); column 1, line 37), wherein said peptides compete for binding of said MHC molecule (dominance of a particular peptide depends on relative affinity for binding the MHC molecule (wherein said peptides compete for binding of said MHC molecule)); column 8, lines 36-38) and said TCR (TCR (said TCR); column 1, line 37).

Regarding claims 14/11-14/13, Wraith discloses the method of claims 11-13, and Wraith further discloses wherein said TCR (TCR (said TCR)); column 1, line 37) is a TCR on a T cell (TCR on a T cell; column 1, lines 36-37; column 7, lines 44-45).

Claim 6 lacks an inventive step under PCT Article 33(3) as being obvious over Wraith in view of US 8,337,861 B2 to Ackerman, et al. (hereinafter 'Ackerman').

Regarding claim 6, Wraith discloses the composition of claim 5, and Wraith further discloses wherein the mediation (mediated (mediation); column 2, line 61) is through (through; column 1, line 43). Wraith does not disclose wherein the mediation is through nucleotide sequence complementarity. Ackerman discloses nucleotide sequence complementarity (complement of DNA (nucleotide sequence complementarity), column 24, lines 27-31), in methods of monitoring the efficacy of anti-CD40 antibodies in treating a subject for a CD40-expressing cancer (abstract). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified a composition comprising at least two MHC-binding peptides, each conjugated to a polynucleotide, as previously disclosed by Wraith, for integrating nucleotide sequence complementarity, since the combination would have produced a therapeutic composition containing multiple peptide-DNA conjugates hybridized to one another, in order to form a multivalent conjugate.

Claims 1-14 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

MORRISON | FOERSTER
PROCESSED
November 11, 2014

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: BU YIN
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE, SUITE 100
SAN DIEGO, CA 92130-2040

-REF CHECK
12/7/2014
2/7/2015
-RESP TO SR
12/7/2014
1/7/2015 - F

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 699932000340 -RESP TO WO 3/25/2015 4/25/2015 - F	Date of mailing *(day/month/year)* 07 NOV 2014
International application No. PCT/US2014/044191	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant PROGNOSYS BIOSCIENCES, INC. /fxm	International filing date *(day/month/year)* 25 June 2014

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 699932000340	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2014/044191	International filing date *(day/month/year)* 25 June 2014	(Earliest) Priority Date *(day/month/year)* 25 June 2013
Applicant PROGNOSYS BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. FIG.8

   ☒ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

Curio EX1012-p. 433
Curio v Prognosys

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/044191

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-41, 45-53
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/044191

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2014.01)
CPC - C12Q 1/6809 (2014.09)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C12N 15/11, 15/115; C12Q 1/68; C40B 30/04, 60/04; G01N 33/50, 33/53, 33/543, 37/00 (2014.01)
USPC - 506/8, 9, 15, 24, 32

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C12Q 1/6809, 1/6834, 1/6837, 1/6841, 1/6869; C40B 60/04, 30/04; G01N 33/6845, 2458/10 (2014.09)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar, Google, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/0245111 A1 (CHEE) 06 October 2011 (06.10.2011) entire document	1-4, 42-43
Y	ROUTENBERG et al. "Microfluidic probe: a new tool for integrating microfluidic environments and electronic wafer-probing," Lab Chip, 29 October 2009 (29.10.2009), Vol. 10, Pgs. 123-127. entire document	1-4, 42-43
A	US 2012/0270748 A1 (CHEE) 25 October 2012 (25.10.2012) entire document	1-4, 42-43
A	US 2012/0195810 A1 (COHEN et al) 02 August 2012 902.08.2012) entire document	1-4, 42-43
A	US 2003/0162216 A1 (GOLD et al) 28 August 2003 (28.08.2003) entire document	1-4, 42-43

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2014	07 NOV 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: BU YIN
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE, SUITE 100
SAN DIEGO, CA 92130-2040

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 NOV 2014
Applicant's or agent's file reference 699932000340	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2014/044191	25 June 2014	25 June 2013

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/86 (2014.01)
CPC - C12Q 1/8609 (2014.09)

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	10 October 2014	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/044191

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/044191

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5-41, 45-53

because:

☐ the said international application, or the said claims Nos. ..... relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5-41, 45-53 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 5-41 and 45-53 are multiple dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. ..... are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 5-41, 45-53

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and mannacceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and mannacceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-4, 42-44	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-4, 42-44	NO
Industrial applicability (IA)	Claims	1-4, 42-44	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-4, and 42-44 lack an inventive step under PCT Article 33(3) as being obvious over Chee in view of Routenberg et al. (hereafter Routenberg).

Regarding claim 1, Chee discloses a method of determining a spatial pattern of abundance, expression and/or activity of a biological target in a sample (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, Para. [0008]), comprising: (a) delivering a probe for a biological target to a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]), the probe comprising a binding moiety capable of binding to the biological target, wherein the probe comprises an identity tag that identifies the biological target or target-binding moiety (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); (b) affixing the sample from step (a) to a first microfluidic device having multiple first addressing channels, wherein each first addressing channel identifies a first area in the sample (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, Para. [0076]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; biological sample in ten discrete areas, Para. [0063]); (c) delivering a first address tag through each of the first addressing channels to each first area in the sample, wherein each first address tag is to be coupled to the probe and/or the adaptor (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; Biological targets can include…proteins, Para. [0042]); (d) affixing the sample from step (c) to a second microfluidic device having multiple second addressing channels, wherein each second addressing channel identifies in the sample a second area that intersects with a first area identified by the first (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, Para. [0076]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; biological sample in ten discrete areas, Para. [0063]); (e) delivering a second address tag through each of the second addressing channels to each second area in the sample (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, Para. [0042]; 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, Para. [0076]), wherein each second address tag is to be coupled to the probe and/or the adaptor, whereby the first address tag and the second address tag at an intersection between a first area and a second area determine the intersection's address (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, Para. [0061]; a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a); (f) analyzing the probe and/or the adaptor bound to the biological target (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), the analysis comprising: (1) determining the abundance, expression and/or activity of the biological target by assessing the amount of the probe and/or the adaptor bound to the biological target (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); and (2) determining the identities of the identity tag and the first and second address tags at each address (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); and (g) determining a spatial pattern of the biological target abundance, expression and/or activity in the sample based on the analysis of step (f) (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), but fails to explicitly disclose addressing channels at an angle greater than 0 degree.
However, Routenberg is in the field of integrated microfluidic addressing systems (Abstract) and teaches addressing channels at an angle greater than 0 degree (Schematic cross-section of patterning probe; (b) patterned channels and through holes; (c) fan-out connects to patterning channels and (d) resulting pattern on substrate after selective area functionalization, Pg. 126, right-hand column, top of page; See FIG. 5, esp. 5c).
It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method of Chee to include the addressing channels at an angle greater than 0 degree as taught by Routenberg. The motivation would have been to allow measurements to be taken in spatial patterns (Routenberg, left-hand column, first paragraph).

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Regarding claim 2 Chee discloses a method of determining a spatial pattern of abundance, expression and/or activity of a biological target in a sample (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, Para. [0008]), comprising: (a) affixing a sample to a first microfluidic device having multiple first addressing Channels (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; provide a biological sample affixed to a support, See FIG. 1), wherein each first addressing channel identifies a first area in the Sample (coding tags, which identify the positions in the sample of the biological targets being assayed, Para. [0042]; delivered to the sample according to a known spatial pattern, allowing the probes to interact or react with biological targets, Para. [0051]);
(b) delivering a first probe for a biological target through each of the first addressing channels to each first area in the sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; Biological targets can include… proteins, Para. [0042]; invention can include instru mentation 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, Para. [0074]), the probe comprising: (1) a first binding moiety capable of binding to the biological target (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); (2) a first address tag that identifies an area in the sample to which the first probe is delivered (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, Para. [0042]); and (3) a first identity tag that identifies the biological target or the first binding moiety (a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); (c) affixing the sample from step (b) to a second microfluidic device having multiple second addressing channels, wherein each second addressing channel identifies in the sample a second area that intersects with a first area identified by the first (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; provide a biological sample affixed to a support, See FIG. 1; 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, Para. [0076]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; biological sample in ten discrete areas, Para. [0063]); (d) delivering a second probe for the biological target through each of the second addressing channels to each second area in the sample (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, Para. [0051]; a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a, the probe comprising: (1) a second binding moiety capable of binding to the biological target (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; Biological targets can include…proteins, Para. [0042]); (2) a second address tag that identifies an area in the sample to which the first probe is delivered; and (3) a second identity tag that identifies the biological target or the second binding moiety, whereby the first address tag and the second address tag at an intersection between a first area and a second area determine the intersection's address (a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); (e) analyzing the probes bound to the biological target target (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), the analysis comprising: (1) determining the abundance, expression and/or activity of the biological target by assessing the amount of the probes bound to the biological target; and (2) determining the identities of the first and second identity tags and the first and second address tags at each address (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); and
(f) determining a spatial pattern of the biological target abundance, expression and/or activity in the sample based on the analysis of step (e) (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), but fails to explicitly disclose addressing channels at an angle greater than 0 degree.
However, Routenberg is in the field of integrated microfluidic addressing systems (Abstract) and teaches addressing channels at an angle greater than 0 degree (Schematic cross-section of patterning probe; (b) patterned channels and through holes; (c) fan-out connects to patterning channels and (d) resulting pattern on substrate after selective area functionalization, Pg. 126, right-hand column, top of page; See FIG. 5, esp. 5c).
It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method of Chee to include the addressing channels at an angle greater than 0 degree as taught by Routenberg. The motivation would have been to allow measurements to be taken in spatial patterns (Routenberg, left-hand column, first paragraph).

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/044191

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding claim 3, Chee discloses a method of determining a spatial pattern of abundance, expression and/or activity of a biological target in a sample (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, Para. [0008]), comprising: (a) affixing a sample to a first microfluidic device having multiple first addressing Channels (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; provide a biological sample affixed to a support, See FIG. 1), wherein each first addressing channel identifies a first area in the sample (coding tags, which identify the positions in the sample of the biological targets being assayed, Para. [0042]; delivered to the sample according to a known spatial pattern, allowing the probes to interact or react with biological targets, Para. [0051]); (b) delivering a probe for a biological target through each of the first addressing channels to each first area in the sample, the probe comprising a binding moiety capable of binding to the biological target (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; Biological tar gets can include…proteins, Para. [0042]; invention can include instru mentation 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, Para. [0074]), wherein the probe and/or the adaptor comprises: (1) a first address tag that identifies an area in the sample to which the probe is delivered (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); and (2) an identity tag that identifies the biological target or the binding moiety (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, Para. [0042]); (c) affixing the sample from step (b) to a second microfluidic device having multiple second addressing channels, wherein each second addressing channel identifies in the sample a second area that intersects with a first area identified by the first (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; provide a biological sample affixed to a support, See FIG. 1; 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, Para. [0076]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; biological sample in ten discrete areas, Para. [0063]); (d) delivering a second address tag through each of the second addressing channels to each second area in the sample, wherein each second address tag is to be coupled to the probe and/or the adaptor, whereby the first address tag and the second address tag at an intersection between a first area and a second area determine the intersection's address (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); (e) analyzing the probe and/or the adaptor bound to the biological target, the analysis comprising: (1) determining the abundance, expression and/or activity of the biological target by assessing the amount of the probe and/or the adaptor bound to the biological target; and (2) determining the identities of the identity tag and the first and second address tags at each address (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and (f) determining a spatial pattern of the biological target abundance, expression and/or activity in the sample based on the analysis of step (e) (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), but fails to explicitly disclose addressing channels at an angle greater than 0 degree.
However, Routenberg is in the field of integrated microfluidic addressing systems (Abstract) and teaches addressing channels at an angle greater than 0 degree (Schematic cross-section of patterning probe; (b) patterned channels and through holes; (c) fan-out connects to patterning channels and (d) resulting pattern on substrate after selective area functionalization, Pg. 126, right-hand column, top of page; See FIG. 5, esp. 5c).
It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method of Chee to include the addressing channels at an angle greater than 0 degree as taught by Routenberg. The motivation would have been to allow measurements to be taken in spatial patterns (Routenberg, left-hand column, first paragraph).

Regarding claim 4, modified Chee discloses the method of claim 3. Chee fails to explicitly disclose wherein the angle is about 90 degrees, about 80 degrees, about 70 degrees, about 60 degrees, about 50 degrees, about 40 degrees, about 30 degrees, about 20 degrees, or about 10 degrees.
However, Routenberg teaches the angle is about 90 degrees (Schematic cross-section of patterning probe; (b) patterned channels and through holes; (c) fan-out connects to patterning channels and (d) resulting pattern on substrate after selective area functionalization, Pg. 126, right-hand column, top of page; See FIG. 5, esp. 5b, Patterning channels are perpendicular to the through-hold channels).
It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method of Chee to include the angle is about 90 degrees as taught by Routenberg. The motivation would have been to allow measurements to be taken in spatial patterns (Routenberg, left-hand column, first paragraph).

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Regarding claim 42, Chee discloses a method of address coding multiple sites in a sample (delivering encoded probes for the multiple protein targets to the multiple sites in the sample in a known spatial pattern, Para. [0015]; 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, Para. [0008]), comprising: (a) providing a sample affixed to a first microfluidic device having multiple first addressing channels (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; provide a biological sample affixed to a support, See FIG. 1), wherein each first addressing channel identifies a first area in the sample (coding tags, which identify the positions in the sample of the biological targets being assayed, Para. [0042]; delivered to the sample according to a known spatial pattern, allowing the probes to interact or react with biological targets, Para. [0051]); (b) delivering a first probe capable of binding to a target in the sample through each of the first addressing channels to each first area in the sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; (coding tags, which identify the positions in the sample of the biological targets being assayed, Para. [0042]; delivered to the sample according to a known spatial pattern, allowing the probes to interact or react with biological targets, Para. [0051]); (c) affixing the sample from step (b) to a second microfluidic device having multiple second addressing channels (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; provide a biological sample affixed to a support, See FIG. 1, wherein each second addressing channel identifies in the sample a second area that intersects with a first area identified by the first (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; provide a biological sample affixed to a support, See FIG. 1; 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, Para. [0076]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; biological sample in ten discrete areas, Para. [0063]); (d) delivering a second probe capable of binding to the target in the sample through each of the second addressing channels to each second area in the sample (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); and (e) determining an address of an intersection between a first area and a second area in the sample based on the first probe and the second probe bound to the target at the intersection (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), but fails to explicitly disclose addressing channels at an angle greater than 0 degree. However, Routenberg is in the field of integrated microfluidic addressing systems (Abstract) and teaches addressing channels at an angle greater than 0 degree (Schematic cross-section of patterning probe; (b) patterned channels and through holes; (c) fan-out connects to patterning channels and (d) resulting pattern on substrate after selective area functionalization, Pg. 126, right-hand column, top of page; See FIG. 5, esp. 5c).
It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method of Chee to include the addressing channels at an angle greater than 0 degree as taught by Routenberg. The motivation would have been to allow measurements to be taken in spatial patterns (Routenberg, left-hand column, first paragraph).

Regarding claim 43, modified Chee discloses the method of claim 42. Chee fails to explicitly disclose wherein the angle is about 90 degrees, about 80 degrees, about 70 degrees, about 60 degrees, about 50 degrees, about 40 degrees, about 30 degrees, about 20 degrees, or about 10 degrees.
However, Routenberg teaches the angle is about 90 degrees (Schematic cross-section of patterning probe; (b) patterned channels and through holes; (c) fan-out connects to patterning channels and (d) resulting pattern on substrate after selective area functionalization, Pg. 126, right-hand column, top of page; See FIG. 5, esp. 5b, Patterning channels are perpendicular to the through-hold channels).
It would have been obvious to one of ordinary skill in the art at the time of invention to modify the method of Chee to include the angle is about 90 degrees as taught by Routenberg. The motivation would have been to allow measurements to be taken in spatial patterns (Routenberg, left-hand column, first paragraph).

Regarding claim 44, modified Chee discloses the method of claim 42. Chee further discloses wherein the first addressing channels substantially parallel each other and the second addressing channels substantially parallel each other (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, Para. [0075]; 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, Para. [0063]; See FIG. 4).

Claims 1-4 and 42-44 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

MORRISON | FOERSTER
PROCESSED
November 11, 2014

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: BU YIN
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE, SUITE 100
SAN DIEGO, CA 92130-2040

-REF CHECK
12/7/2014
2/7/2015
-RESP TO SR
12/7/2014
1/7/2015 - F

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 699932000440 -RESP TO WO 3/25/2015 4/25/2015 - F	Date of mailing *(day/month/year)* 07 NOV 2014
International application No. PCT/US2014/044196	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant PROGNOSYS BIOSCIENCES, INC. /fxm	International filing date *(day/month/year)* 25 June 2014

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450	Authorized officer Blaine R. Copenheaver
Facsimile No. 571-273-3201	Telephone No. PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 699932000440	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2014/044196	International filing date *(day/month/year)* 25 June 2014	(Earliest) Priority Date *(day/month/year)* 25 June 2013
Applicant PROGNOSYS BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 6A

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

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Curio v Prognosys

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/044196

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-11, 18-51, 64
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/044196

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2014.01)
CPC - C12Q 1/6809 (2014.09)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C12N 15/11, 15/115; C12Q 1/68; C40B 30/04, 60/04; G01N 33/50, 33/53, 33/543, 37/00 (2014.01)
USPC - 506/8, 9, 15, 24, 32

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C12Q 1/6809, 1/6834, 1/6837, 1/6841, 1/6869; C40B 60/04, 30/04; G01N 33/6845, 2458/10 (2014.09)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit, Google Patents, Google Scholar, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0245111 A1 (CHEE) 06 October 2011 (06.10.2011) entire document	1-5, 12-17, 52-63
A	ROUTENBERG et al. "Microfluidic probe: a new tool for integrating microfluidic environments and electronic wafer-probing," Lab Chip, 29 October 2009 (29.10.2009), Vol. 10, Pgs. 123-127, entire document	1-5, 12-17, 52-63
A	US 2012/0270748 A1 (CHEE) 25 October 2012 (25.10.2012) entire document	1-5, 12-17, 52-63
A	US 2012/0196810 A1 (COHEN et al) 02 August 2012 (02.08.2012) entire document	1-5, 12-17, 52-63
A	US 2003/0162216 A1 (GOLD et al) 28 August 2003 (28.08.2003) entire document	1-5, 12-17, 52-63

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2014	07 NOV 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: BU YIN
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE, SUITE 100
SAN DIEGO, CA 92130-2040

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 NOV 2014
Applicant's or agent's file reference 699932000440	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2014/044196	25 June 2014	25 June 2013

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68 (2014.01)
CPC - C12Q 1/6809 (2014.09)

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	10 October 2014	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/044196

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No PCT/US2014/044196

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6-11, 18-51, 64

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 6-11, 18-51, 64 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 6-11, 18-51, 64 are multiple dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 6-11, 18-51, 64

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and mannacceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and mannacceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/044196

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	None	YES
	Claims	1-5, 12-17, 52-63	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-5, 12-17, 52-63	NO
Industrial applicability (IA)	Claims	1-5, 12-17, 52-63	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-5, 12-17, and 52-63 lack novelty under PCT Article 33(2) as being anticipated by Chee.

Regarding claim 1, Chee discloses a method of determining a spatial pattern of abundance, expression, and/or activity of one or more biological targets across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for each of one or more biological targets to multiple sites in a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]), wherein each probe comprises: (1) a target-binding moiety capable of binding to the probe's corresponding biological target (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); (2) an address tag that identifies each of the multiple sites to which the probe is delivered (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, Para. [0042]); and (3) an identity tag that identifies the probe's corresponding biological target or target-binding moiety (a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); allowing each probe to bind to its corresponding biological target in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); analyzing the probe bound to the one or more biological targets, the analysis comprising: (1) determining abundance, expression, and/or activity of each of the one or more biological targets by assessing the amount of the probe bound to the biological target (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and (2) determining the identities of the identity tag and the address tag of the probe (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]); and determining a spatial pattern of abundance and/or activity of the one or more biological targets across the multiple sites in the sample based on the analysis (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), wherein the method does not depend on an imaging technique for determining spatial information of the one or more biological targets in the sample (In an optional embodiment, the assay system comprises imaging means to determine features and organization of the biological sample of interest, Para. [0080]; US 2011/024511 Claims: 1-57, do not explicitly cite an imagining technique, and because alternative elements are positively recited in the specification, they may be explicitly excluded in the claims, therefore the US 2011/024511 patent possessed the invention disclosed in the instant application's claims which include the negative limitation "the method does not depend on an imaging technique").

Curio EX1012-p. 450
Curio v Prognosys

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Regarding claim 2, Chee discloses a method of determining a spatial pattern of abundance, expression, and/or activity of one or more biological targets across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for each of one or more biological targets to multiple sites in a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]), wherein each probe comprises: (1) a target-binding moiety capable of binding to the probe's corresponding biological target (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); (2) an address tag having a sequence that identifies each of the multiple sites to which the probe is delivered (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, Para. [0042]); and (3) an identity tag having a sequence that identifies the probe's corresponding biological target or target-binding moiety (a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); allowing each probe to bind to its corresponding biological target in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); analyzing the probe bound to the one or more biological targets by sequencing (determining all or a portion of a sequence of the encoded probes, Para. [0008]), wherein the amount of a sequencing product indicates abundance, expression, and/or activity of each of the one or more 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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), the sequencing product comprising all or a portion of the address tag sequence and all or a portion of the identity tag sequence (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, Para. [0049]); and determining a spatial pattern of abundance, expression, and/or activity of the one or more biological targets across the multiple sites in the sample based on the analysis (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]).

Regarding claim 3, Chee discloses a method of determining a spatial pattern of abundance, expression, and/or activity of one or more biological targets across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for each of one or more biological targets to multiple sites in a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]), wherein each probe comprises: (1) a target-binding moiety capable of binding to the probe's corresponding biological target (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); and (2) an identity tag that identifies the probe's corresponding biological target or target-binding moiety (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, Para. [0042]); allowing each probe to bind to its corresponding biological target in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); delivering an address tag to each of the multiple sites in the sample, wherein the address tag is to be coupled to the probe bound to the biological target and identifies the site to which the address tag is delivered (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, Para. [0051]; a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); analyzing the probe/address tag conjugate bound to the one or more biological targets (determining all or a portion of a sequence of the encoded probes, Para. [0008]), the analysis comprising: (1) determining abundance, expression, and/or activity of each of the one or more biological targets by assessing the amount of the probe/address tag conjugate bound to the biological target (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); and (2) determining the identities of the identity tag and the address tag of the probe/address tag conjugate (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); and determining a spatial pattern of abundance, expression, and/or activity of the one or more biological targets across the multiple sites in the sample based on the analysis (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), wherein the method does not depend on an imaging technique for determining spatial information of the one or more biological targets in the sample (In an optional embodiment, the assay system comprises imaging means to determine features and organization of the biological sample of interest, Para. [0080]; US 2011/024511 Claims: 1-57, do not explicitly cite an imagining technique, and because alternative elements are positively recited in the specification, they may be explicitly excluded in the claims, therefore the US 2011/024511 patent possessed the invention disclosed in the instant application's claims which include the negative limitation "the method does not depend on an imaging technique").

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Regarding claim 4, Chee discloses a method of determining a spatial pattern of abundance, expression, and/or activity of one or more biological targets across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for each of one or more biological targets to multiple sites in a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]), wherein each probe comprises: (1) a target-binding moiety capable of binding to the probe's corresponding biological target (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); and (2) an identity tag having a sequence that identifies the probe's corresponding biological target or target-binding moiety (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, Para. [0042]); allowing each probe to bind to its corresponding biological target in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); delivering an address tag to each of the multiple sites in the sample, wherein the address tag is to be coupled to the probe bound to the biological target and identifies the site to which the address tag is delivered (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, Para. [0051]; a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); analyzing the probe/address tag conjugate bound to the one or more biological targets by sequencing (determining all or a portion of a sequence of the encoded probes, Para. [0008]), wherein the amount of a sequencing product indicates abundance, expression, and/or activity of each of the one or more biological targets, the sequencing product comprising all or a portion of the address tag sequence and all or a portion of the identity tag sequence (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and determining a spatial pattern of abundance, expression, and/or activity of the one or more biological targets across the multiple sites in the sample based on the analysis (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]).

Regarding claim 5, Chee discloses the method of claim 1, wherein the one or more biological targets are non-nucleic acid molecules (Biological targets can include any molecule of interest, such as...proteins, enzymes and the like, Para. [0042]).

Regarding claim 12, Chee discloses a method of determining a spatial pattern of abundance, expression, and/or activity of a target protein across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for a target protein to multiple sites in a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; Biological tar gets can include...proteins, Para. [0042]), wherein the probe comprises: (1) a target-binding moiety capable of binding to the target protein (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); (2) a first address tag that identifies each of the multiple sites to which the probe is delivered (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, Para. [0042]); and (3) an identity tag that identifies the target protein or the target-binding moiety (a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); allowing the probe to bind to the target protein in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]);
analyzing the probe bound to the target protein, the analysis comprising: (1) determining abundance, expression, and/or activity of the target protein by assessing the amount of the probe bound to the target protein (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and (2) determining the identities of the identity tag and the first address tag of the probe for the target protein (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]); and determining a spatial pattern of abundance, expression, and/or activity of the target protein across the multiple sites in the sample based on the analysis (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]).

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Regarding claim 13, Chee discloses the method of claim 12, further comprising: delivering a probe for a target polynucleotide to each of the multiple sites in the sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; oligonucleotides to hybridize to nucleic acid targets, Para. [0044]), wherein the probe for the target polynucleotide comprises: (1) a sequence that hybridizes to and identifies the target polynucleotide; (2) a second address tag that identifies each of the multiple sites to which the probe for the target polynucleotide is delivered (the oligonucleotide probes are allowed to interact with (hybridize to) the nucleic acid targets, Para. [0047]; coding tags, which identify the positions in the sample of the biological targets being assayed, Para. [0042]); allowing the probe for the target polynucleotide to bind to the target polynucleotide in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); analyzing the probe bound to the target polynucleotide, the analysis comprising: (1) determining abundance, expression, and/or activity of the target polynucleotide by assessing the amount of the probe bound to the target polynucleotide (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and (2) determining the identities of the sequence that hybridizes to and identifies the target polynucleotide and the second address tag of the probe for the target polynucleotide (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); and determining a spatial pattern of abundance, expression, and/or activity of the target polynucleotide across the multiple sites in the sample based on the analysis of the probe bound to the target polynucleotide at each of the multiple sites in the sample (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]).

Regarding claim 14, Chee discloses method of determining a spatial pattern of abundance, expression, and/or activity of a target protein across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for a target protein to multiple sites in the sample, wherein the probe comprises: (1) a target-binding moiety capable of binding to the target protein (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; Biological tar gets can include…proteins, Para. [0042]); and (2) an identity tag that identifies the target protein or the protein-binding moiety (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, Para. [0042]) allowing the probe to bind to the target protein in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); delivering a first address tag to each of the multiple sites in the sample, wherein the first address tag is to be coupled to the probe bound to the target protein and identifies the site to which it is delivered (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; Biological tar gets can include…proteins, Para. [0042]); analyzing the probe/first address tag conjugate bound to the target protein, the analysis comprising: (1) determining abundance, expression, and/or activity of the target protein by assessing the amount of the probe/first address tag conjugate bound to the target protein (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and (2) determining the identities of the identity tag and the first address tag of the probe/first address tag conjugate; and determining a spatial pattern of abundance, expression, and/or activity of the target protein across the multiple sites in the sample based on the analysis (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application).

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Regarding claim 15, Chee discloses the method of claim 14, further comprising: delivering a probe for a target polynucleotide to each of the multiple sites in the sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; oligonucleotides to hybridize to nucleic acid targets, Para. [0044]), wherein the probe for the target polynucleotide comprises a sequence that hybridizes to and identifies the target polynucleotide (the oligonucleotide probes are allowed to interact with (hybridize to) the nucleic acid targets, Para. [0047]; coding tags, which identify the positions in the sample of the biological targets being assayed, Para. [0042]); allowing the probe for the target polynucleotide to bind to the target polynucleotide in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); delivering a second address tag to each of the multiple sites in the sample, wherein the second address tag is to be coupled to the probe bound to the target polynucleotide and identifies the site to which it is delivered a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); analyzing the probe/second address tag conjugate bound to the target polynucleotide (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), the analysis comprising: (1) determining abundance, expression, and/or activity of the target polynucleotide by assessing the amount of the probe/second address tag conjugate bound to the target polynucleotide (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); and (2) determining the identities of the sequence that hybridizes to and identifies the target polynucleotide and the second address tag of the probe/second address tag conjugate (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); and determining a spatial pattern of abundance, expression, and/or activity of the target polynucleotide across the multiple sites in the sample based on the analysis of the probe/second address tag conjugate bound to the target polynucleotide at each of the multiple sites in the sample (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]).

Regarding claim 16, Chee discloses the method of claim 15, wherein the target polynucleotide or the complement thereof encodes all or a portion of the target protein (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, Para. [0059]).

Regarding claim 17, Chee discloses the method of claim 15, wherein the step of analyzing the probe or probe/first address tag conjugate bound to the target protein and the step of analyzing the probe or probe/second address tag conjugate bound to the target polynucleotide are performed in parallel in the same reaction run (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application; In other aspects, the sequence of at least fifty thousand encoding probes are determined in parallel, Para. [0011]).

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Regarding claim 52, Chee discloses a system for determining a spatial pattern of abundance, expression, and/or activity of one or more biological targets across multiple sites in a sample (The invention encompasses assay systems that provide high-resolution spatial maps of biological activity in tissues, Para. [0007]; 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, Para. [0008]), comprising: a first module for delivering a probe for each of one or more biological targets to multiple sites in a sample target (delivering encoded probes for the multiple biological targets to the multiple sites in the sample..Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]), wherein each probe comprises: (1) a target-binding moiety capable of binding to the probe's corresponding biological target (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); and (2) an identity tag that identifies the probe's corresponding biological target or target-binding moiety (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, Para. [0042]); a second module for delivering an address tag to each of the multiple sites in the sample, wherein the address tag is to be coupled to the probe bound to the biological target and identifies the site to which the address tag is delivered (a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); a third module for analyzing the probe/address tag conjugate bound to the one or more biological targets (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, Para. [0015]), the analysis comprising: (1) determining abundance, expression, and/or activity of the one or more biological targets by assessing the amount of the probe/address tag conjugate bound to the biological target (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and (2) determining the identities of the identity tag and the address tag of the probe/address tag conjugate (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]); and a fourth module for determining a spatial pattern of abundance, expression (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), and/or activity of the one or more biological targets across the multiple sites in the sample based on the analysis, wherein the system does not depend on an imaging technique for determining spatial information of the one or more biological targets in the sample (In an optional embodiment, the assay system comprises imaging means to determine features and organization of the biological sample of interest, Para. [0080]; US 2011/024511 Claims: 1-57, do not explicitly cite an imagining technique, and because alternative elements are positively recited in the specification, they may be explicitly excluded in the claims, therefore the US 2011/024511 patent possessed the invention disclosed in the instant application's claims which include the negative limitation "the method does not depend on an imaging technique").

Regarding claim 53, Chee discloses the system of claim 52, wherein the second module comprises one or more microfluidic devices for delivering the address tags (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, Para. [0076]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008])

Regarding claim 54, Chee discloses the system of claim 53, wherein the one or more microfluidic devices comprise a first set of multiple addressing channels, each delivering a different first address tag to the sample (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, Para. [0076]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; 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, Para. [0014]).

Regarding claim 55, Chee discloses the system of claim 54, wherein the one or more microfluidic devices further comprise a second set of multiple addressing channels, each delivering a different second address tag to the sample (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, Para. [0076]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; 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, Para. [0014]).

Regarding claim 56, Chee discloses the method of claim 55, wherein the multiple sites in the sample are chosen by the first and second set of multiple addressing channels cooperatively delivering the first address tags and the second address tags, respectively, to each of the multiple sites, each site identified by a different combination of first and second address tags (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, Para. [0076]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; independently actuated nozzles can be used to deliver multiple reagents at the same time, Para. [0082]).

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Continuation of:

Regarding claim 57, Chee discloses a method of determining a spatial pattern of abundance, expression, and/or activity of one or more biological targets across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for each of one or more biological targets to multiple sites in a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]), wherein each probe comprises a target-binding moiety capable of binding to the probe's corresponding biological target (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); allowing each probe to bind to its corresponding biological target in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); delivering at least one adaptor to the multiple sites in the sample (Following ligation, the encoded probes are eluted, pooled, and, optionally, sequencing adapters are added to the encoded probes, Para. [0056]), wherein the at least one adaptor specifically binds to the probe and comprises an address tag that identifies each of the multiple sites to which the at least one adaptor is delivered (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, Para. [0062]), wherein the probe and/or the adaptor comprises an identity tag that identifies the probe's and/or adaptor's corresponding biological target or target-binding moiety (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, Para. [0042]); analyzing the at least one adaptor and the probe bound to the one or more biological targets, the analysis comprising: (1) determining abundance, expression, and/or activity of each of the one or more biological targets by assessing the amount of at least one adaptor bound to the probe bound to the biological target (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and (2) determining the identities of the identity tag, and the address tag of the at least one adaptor (the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]); and determining a spatial pattern of abundance and/or activity of the one or more biological targets across the multiple sites in the sample based on the analysis (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]), wherein the method does not depend on an imaging technique for determining spatial information of the one or more biological targets in the sample (In an optional embodiment, the assay system comprises imaging means to determine features and organization of the biological sample of interest, Para. [0060]; US 2011/024511 Claims: 1-57, do not explicitly cite an imagining technique, and because alternative elements are positively recited in the specification, they may be explicitly excluded in the claims, therefore the US 2011/024511 patent possessed the invention disclosed in the instant application's claims which include the negative limitation "the method does not depend on an imaging technique").

Regarding claim 58, Chee discloses a method of determining a spatial pattern of abundance, expression, and/or activity of one or more biological targets across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for each of one or more biological targets to multiple sites in a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]), wherein each probe comprises a target-binding moiety capable of binding to the probe's corresponding biological target (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); allowing each probe to bind to its corresponding biological target in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); delivering at least one adaptor to the multiple sites in the sample (Following ligation, the encoded probes are eluted, pooled, and, optionally, sequencing adapters are added to the encoded probes, Para. [0056]), wherein the at least one adaptor specifically binds to the probe and comprises an address tag that identifies each of the multiple sites to which the at least one adaptor is delivered, wherein the probe and/or the adaptor comprises an identity tag that identifies the probe's and/or adaptor's corresponding biological target or target-binding moiety (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, Para. [0062]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; independently actuated nozzles can be used to deliver multiple reagents at the same time, Para. [0082]); analyzing the at least one adaptor and the probe bound to the one or more biological targets by sequencing, wherein the amount of a sequencing product indicates abundance, expression, and/or activity of each of the one or more biological targets, the sequencing product comprising all or a portion of the address tag sequence and all or a portion of the identity tag sequence (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and determining a spatial pattern of abundance, expression, and/or activity of the one or more biological targets across the multiple sites in the sample based on the analysis (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); wherein the method does not depend on an imaging technique for determining spatial information of the one or more biological targets in the sample (In an optional embodiment, the assay system comprises imaging means to determine features and organization of the biological sample of interest, Para. [0060]; US 2011/024511 Claims: 1-57, do not explicitly cite an imagining technique, and because alternative elements are positively recited in the specification, they may be explicitly excluded in the claims, therefore the US 2011/024511 patent possessed the invention disclosed in the instant application's claims which include the negative limitation "the method does not depend on an imaging technique").

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding claim 59, Chee discloses a method of determining a spatial pattern of abundance, expression, and/or activity of one or more biological targets across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for each of one or more biological targets to multiple sites in a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]), wherein each probe comprises a target-binding moiety capable of binding to the probe's corresponding biological target (Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); allowing each probe to bind to its corresponding biological target in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); delivering at least one adaptor to the multiple sites in the sample, wherein the at least one adaptor specifically binds to the probe (Following ligation, the encoded probes are eluted, pooled, and, optionally, sequencing adapters are added to the encoded probes, Para. [0056]), wherein the probe and/or the adaptor comprises an identity tag that identifies the probe's and/or adaptor's corresponding biological target or target-binding moiety (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, Para. [0062]; delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]; independently actuated nozzles can be used to deliver multiple reagents at the same time, Para. [0082]); delivering an address tag to each of the multiple sites in the sample (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, Para. [0042]), wherein the address tag is to be coupled to the at least one adaptor bound to the probe bound to the biological target and identifies the site to which the address tag is delivered (a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); analyzing the adaptor/address tag conjugate, the analysis comprising: (1) determining abundance, expression, and/or activity of each of the one or more biological targets by assessing the amount of the adaptor/address tag conjugate bound to the probe bound to the biological target (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and (2) determining the identities of the identity tag, and the address tag of the adaptor/address tag conjugate; and determining a spatial pattern of abundance, expression, and/or activity of the one or more biological targets across the multiple sites in the sample based on the analysis (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]; the term includes the determination of the identity and ordering of a plurality of contiguous nucleotides in a nucleic acid, Para. [0033]), wherein the method does not depend on an imaging technique for determining spatial information of the one or more biological targets in the sample (in an optional embodiment, the assay system comprises imaging means to determine features and organization of the biological sample of interest, Para. [0080]; US 2011/024511 Claims: 1-57, do not explicitly cite an imagining technique, and because alternative elements are positively recited in the specification, they may be explicitly excluded in the claims, therefore the US 2011/024511 patent possessed the invention disclosed in the instant application's claims which include the negative limitation "the method does not depend on an imaging technique").

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding claim 60, Chee discloses a method of determining a spatial pattern of abundance, expression, and/or activity of one or more biological targets across multiple sites in a sample (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, Para. [0008]), comprising: delivering a probe for each of one or more biological targets to multiple sites in a sample (delivering encoded probes for the multiple biological targets to the multiple sites in the sample, Para. [0008]), wherein each probe comprises a target-binding moiety capable of binding to the probe's corresponding biological target Where each encoded probe comprises a probe region that may interact with the biological targets, Para. [0008]); allowing each probe to bind to its corresponding biological target in the sample (allowing the encoded probes to interact With the biological targets, Para. [0008]); delivering at least one adaptor to the multiple sites in the sample, wherein the at least one adaptor specifically binds to the probe (Following ligation, the encoded probes are eluted, pooled, and, optionally, sequencing adapters are added to the encoded probes, Para. [0056]), wherein the probe and/or the adaptor comprises an identity tag that identifies the probe's and/or adaptor's corresponding biological target or target-binding moiety (a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); delivering an address tag to each of the multiple sites in the sample (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, Para. [0042]), wherein the address tag is to be coupled to the at least one adaptor bound to the probe bound to the biological target and identifies the site to which the address tag is delivered (a coding tag that identifies a location of the site to which the encoded probe was delivered, Para. [0008]; 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, Para. [0062]; See FIG. 4a; Tag 410 can be a universal priming site for amplification of the assay products or an adaptor to enable identification of the address tag 406; as defined in Para. [0146] and FIG. 4a of the instant application); analyzing the adaptor/address tag conjugate by sequencing, wherein the amount of a sequencing product indicates abundance, expression, and/or activity of each of the one or more biological targets, the sequencing product comprising all or a portion of the address tag sequence and all or a portion of the identity tag sequence (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, Para. [0008]; Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]); and determining a spatial pattern of abundance, expression, and/or activity of the one or more biological targets across the multiple sites in the sample based on the analysis (Following hybridization, the relative amounts of a particular target mapping to different spatial locations in the sample can be determined by the relative abundances of the resolvable labels, Para. [0086]; an assay system to determine spatial patterns of abundance or activity or both of multiple nucleic acid targets at multiple sites in a sample, Para. [0014]).

Regarding claim 61, Chee discloses the method of claim 57, wherein at least two adaptors are delivered to each of the multiple sites in the sample (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, Para. [0056]; See FIG. 3), wherein the at least two adaptors each specifically binds to one probe that specifically binds to the biological target (shows two target-specific/encoding oligonucleotide constructs 420 and 422 (e.g., formed between steps 302 and 304 of FIG. 3) specifically bound to a target nucleic acid 402 of interest, Para. [0062]).

Regarding claim 62, Chee discloses the method of claim 61, wherein the at least two adaptors are joined (As seen in FIG. 3, each sequencing adapter comprises primer region 319 or 321, compatible With the primer regions 319 and 321 on the encoded probes. The ?nal 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, Para. [0056]; See FIG. 3).

Regarding claim 63, Chee discloses the method of claim 62, wherein the at least two adaptors are ligated by using a portion of the probe sequence as a splint (As seen in FIG. 3, each sequencing adapter comprises primer region 319 or 321, compatible With the primer regions 319 and 321 on the encoded probes. The ?nal 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, Para. [0056]; See FIG. 3).

Claims 1-5, 12-17, and 52-63 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: BU YIN
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE, SUITE 100
SAN DIEGO, CA 92130-2040

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 11 MAR 2015
Applicant's or agent's file reference 699932000640	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2014/064588	International filing date *(day/month/year)* 07 November 2014
Applicant PROGNOSYS BIOSCIENCES, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 699932000640	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2014/064588	International filing date *(day/month/year)* 07 November 2014	(Earliest) Priority Date *(day/month/year)* 08 November 2013
Applicant PROGNOSYS BIOSCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. 4

   ☒ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/064588

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☒ subsequently to this Authority for the purposes of search

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/064588

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-27, 31-59, 68-71, 82, 83, 88-107, 111, 113, 115
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/064588

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C40B 30/04 (2015.01)
CPC - C40B 30/04 (2015.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C40B 20/04, 30/04, 40/06, 50/06 (2015.01)
USPC - 506/9; 506/4; 506/16; 506/26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C40B 20/04, 30/04, 40/06, 50/06 (2015.01) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google Scholar, Google, PubMed

Search terms used: polynucleotide polypeptide conjugate, antibody, antigen, aptamer, probe, manufacture, hybridization

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0245101 A1 (CHEE et al) 06 October 2011 (06.10.2011) entire document	1-3, 28-30, 60-67, 72-74, 84-87, 108-110, 112, 114, 116
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Y		76-81
Y	US 2012/0258871 A1 (KOZLOV et al) 11 October 2012 (11.10.2012) entire document	75
Y	US 2013/0096033 A1 (PROGNOSYS BIOSCIENCES, INC) 18 April 2013 (18.04.2013) entire document	75-81

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2015	11 MAR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: BU YIN
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE, SUITE 100
SAN DIEGO, CA 92130-2040

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	11 MAR 2015
Applicant's or agent's file reference 699932000640	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2014/064588	07 November 2014	08 November 2013

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C40B 30/04 (2015.01)
CPC - C40B 30/04 (2015.01)

Applicant PROGNOSYS BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	11 February 2015	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/064588

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☒ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☒ subsequently to this Authority for the purposes of search

4. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/064588

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 4-27, 31-59, 68-71, 82, 83, 88-107, 111, 113, 115

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. see below are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 4-27, 31-59, 68-71, 82, 83, 88-107, 111, 113, and 115 are multiple dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 4-27, 31-59, 68-71, 82, 83, 88-107, 111, 113, 115

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and mannerceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and mannerceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/064588

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	75-81	YES
	Claims	1-3, 28-30, 60-67, 72-74, 84-87, 108-110, 112, 114, 116	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-3, 28-30, 60-67, 72-81, 84-87, 108-110, 112, 114 and 116	NO
Industrial applicability (IA)	Claims	1-3, 28-30, 60-67, 72-81, 84-87, 108-110, 112, 114 and 116	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-3, 28-30, 60-67, 72-74, 84-87, 108-110, 112, 114, and 116 lack novelty under PCT Article 33(2) as being anticipated by Chee et al. (hereafter Chee).

Regarding claim 1, Chee discloses a pair of polypeptide-polynucleotide conjugates (a binding pair comprising a protein and a different chemical moiety, Para. [0008]), comprising: a first polypeptide-polynucleotide conjugate comprising (providing a first set of binding constructs immobilized on a support surface, Para. [0009]): (a) a first polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a first epitope for specific binding of an antibody or antigen binding fragment thereof (In yet other aspects, the first binding agent is a peptide and the second binding agent is an antibody, Para. [0014]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a first primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a first identifying sequence (and a first nucleic acid tag unique to the first binding agent, Para. [0009]) that identifies the first polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0009]); and a second polypeptide-polynucleotide conjugate comprising (providing a second set of binding constructs in solution, Para. [0009]), (a) a second polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a second epitope for specific binding of the antibody or antigen binding fragment thereof (In yet other aspects, the first binding agent is a peptide and the second binding agent is an antibody, Para. [0014]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a second primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a second identifying sequence (and a second nucleic acid tag unique to the second binding agent, Para. [0009]) that identifies the second polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0009]), wherein the first and second engaging sequences are capable of engaging the first and second polynucleotides, and thereby engaging the first and second polypeptide-polynucleotide conjugates (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs thereby co-locating the first nucleic acid tags and the second nucleic acid tags, Para. [0009]).

Regarding claim 2, Chee discloses the pair of claim 1, wherein the first engaging sequence (The term "binding agent" as used herein refers to any binding agent that selectively binds to a molecule of interest, Para. [0033]) comprises a sequence hybridizable (The term also includes complementary nucleic acid molecules that selectively hybridize at or above a desired melting temperature, Para. [0034]) to the second engaging sequence, and/or the second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0009]) comprises a sequence hybridizable (The term also includes complementary nucleic acid molecules that selectively hybridize at or above a desired melting temperature, Para. [0034]) to the first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0009]).

Regarding claim 3, Chee discloses the pair of claim 1, wherein the first engaging sequence comprises a sequence complementary ("Complementary" or "substantially complementary" refers to the hybridization or base pairing or the formation of a duplex between nucleotides or nucleic acids, Para. [0035]) to all or a portion of the second engaging sequence (The term "binding pair" means any two molecules (binding agents) that are known to bind selectively to one another. In the case of two proteins, the proteins bind selectively to one another with a high affinity as described in more detail herein, Para. [0034]), and/or the second engaging sequence comprises a sequence complementary to all or a portion of the first engaging sequence.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding claim 28, Chee discloses a method for analyzing an antibody or antigen binding fragment thereof in a sample (a method for identifying binding agents that form a binding pair, Para. [0016]), comprising: (i) immobilizing a first polypeptide-polynucleotide conjugate on a substrate (comprising: providing a first set of binding constructs immobilized on a support surface, Para. [0016]), the first polypeptide-polynucleotide conjugate comprising: (a) a first polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a first epitope for specific binding of an antibody or antigen binding fragment thereof (the first and second binding agents (binding pair) are provided as antibodies or variable domains of antibodies that bind to different epitopes on a common molecule, Para. [0077]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a first primer sequence (a first primer region, Para. [0016]), a first identifying sequence (a first nucleic acid tag unique to the first binding agent, Para. [0016]) that identifies the first polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0016]), and a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0016]); (ii) contacting the substrate having the immobilized first polypeptide-polynucleotide conjugate (providing a first set of binding constructs immobilized on a support surface, Para. [0016]) with a sample containing or suspected of containing the antibody or antigen binding fragment thereof (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]), whereby the first epitope specifically binds to the antibody or antigen binding fragment thereof in the sample (the method further comprises the step of adding a third binding agent in the combining step, Para. [0035]); (iii) contacting the substrate having the immobilized first polypeptide-polynucleotide conjugate with a second polypeptide-polynucleotide conjugate (providing a second set of binding constructs in solution, Para. [0016]), the second polypeptide-polynucleotide conjugate comprising: (a) a second polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a second epitope for specific binding of the antibody or antigen binding fragment thereof (the first and second binding agents (binding pair) are provided as antibodies or variable domains of antibodies that bind to different epitopes on a common molecule, Para. [0077]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a second primer sequence (a second primer region, Para. [0016]), a second identifying sequence (a second nucleic acid tag unique to the second binding agent, Para. [0016]) that identifies the second polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0016]), and a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0016]), whereby the second epitope specifically binds to the antibody or antigen binding fragment thereof specifically bound to the first epitope (The presence and binding of both the first (A) and second (S) binding agents is necessary for the detection of the third molecule, Para. [0077]), and whereby the first and second polynucleotides are engaged via the first and second engaging sequences (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs, Para. [0016]); and (iv) analyzing the first and/or/or second polynucleotides engaged via the first and second engaging sequences (determining a sequence of at least one thousand binding event identifiers, where the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair, Para. [0016]), wherein the analysis in step (iv) indicates the presence, absence, and/or amount (and determining the frequency of each binding event identifier sequenced, Para. [0016]) of the antibody or antigen binding fragment thereof in the sample (In certain other assay schemes of the invention, however, the first and second binding agents may be analyzed for their ability to bind a third agent or analyte in addition to or in place of binding to one another, Para. [0076]).

Regarding claim 29, Chee discloses the method of claim 28, wherein the substrate (a support surface comprising multiple anchors, Para. 0067]) comprises a microarray (the binding event identifiers could be amplified and hybridized to a microarray, Para. [0089]; wherein the support is a microarray, Claim 22) and/or a bead (a flowcell or a bead, Para. [0067]; wherein the support is a bead, Claim 23).

Regarding claim 30, Chee discloses the method of claim 28, wherein the first engaging sequence (The term "binding agent" as used herein refers to any binding agent that selectively binds to a molecule of interest, Para. [0033]) comprises a sequence hybridizable (The term also includes complementary nucleic acid molecules that selectively hybridize at or above a desired melting temperature, Para. [0034]) to the second engaging sequence, and/or the second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0016]) comprises a sequence hybridizable (The term also includes complementary nucleic acid molecules that selectively hybridize at or above a desired melting temperature, Para. [0034]) to the first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0016]).

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding claim 60, Chee discloses a method for analyzing an antibody or antigen binding fragment thereof in a sample (for detection of an agent or analyte using two sets of binding constructs, Para. [0087]), comprising: (i) immobilizing a first polypeptide-polynucleotide conjugate on a substrate (where the binding construct is ligated using a splint sequence 1333 to a anchor 1305 attached to a solid support, Para. [0087], Fig. 13), the first polypeptide-polynucleotide conjugate comprising (the first binding construct used in the assay is illustrated, Para. [0087]): (a) a first polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a first epitope for specific binding of an antibody or antigen binding fragment thereof (An antibody 1301 is attached to a nucleic acid portion of the first binding construct via a cleavable linker 1335, Para. [0087]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a first primer sequence (Sequence 1311 is a primer sequence, Para. [0087]), a first identifying sequence that identifies the first polypeptide (second unique nucleic acid tag 1323, the complement to second unique nucleic acid tag 1313, Para. [0088]), and a first engaging sequence (and primer/hybridization region 1325, the complement to primer/hybridization region 1315, Para. [0088]); (ii) providing a second polypeptide-polynucleotide conjugate (a second binding construct, Para. [0088]), the second polypeptide-polynucleotide conjugate comprising: (a) a second polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a second epitope for specific binding of the antibody or antigen binding fragment thereof (Binding of the binding agent 1303 of the second set of binding constructs to target agent 1337, Para. [0087]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a second primer sequence (a second binding construct, blocked at the 3' end 1329, Para. [0088]) a second identifying sequence that identifies the second polypeptide (The second binding construct comprises a unique nucleic acid tag 1313 that identifies the second binding agent present in the second binding construct, Para. [0088]), and a second engaging sequence (the complement to primer/hybridization region 1315, Para. [0088]), wherein the second polypeptide-polynucleotide conjugate forms a complex with the immobilized first polypeptide-polynucleotide conjugate (a second binding construct, blocked at the 3' end 1329 (black square) so that it cannot be extended, is bound to the first binding construct via target agent 1337, Para. [0088]); (iii) contacting the substrate having the complex between the first and second polypeptide-polynucleotide conjugates with a sample containing or suspected of containing the antibody or antigen binding fragment thereof (In the first part of the assay, a target agent 1337 is captured, Para. [0087]), wherein at least one molecule of the second polypeptide-polynucleotide conjugate specifically binds to the antibody or antigen binding fragment thereof specifically bound to the first polypeptide-polynucleotide conjugate (Binding of the binding agent 1303 of the second set of binding constructs to target agent 1337 may be done in solution prior to exposing the second set of binding constructs to the first set of binding constructs, Para. [0087]), thereby forming a ternary complex, (In the first part of the assay, a target agent 1337 is captured, Para. [0087]); (iv) washing the substrate under conditions that release molecules of the second polypeptide-polynucleotide conjugate that are not specifically bound to the antibody or antigen binding fragment thereof, while maintaining the ternary complex formed by specific binding (the cleavable linker 1335 attaching the first binding agent 1301 to the first binding construct is cleaved, and washing removes the second binding construct, the first antibody and target agent. The primer-extended construct attached to the support surface can now be assayed, Para. [0088]); (v) providing conditions under which the first and second polynucleotides are engaged via the first and second engaging sequences in the ternary complex formed by specific binding (The binding event identifiers comprise a combination of two unique nucleic acid tags, one present on each of the binding constructs, and the association of these unique nucleic acid tags, e.g., through incorporation into a single oligonucleotide. Para. [0089]); and (vi) analyzing the first and/or second polynucleotides engaged via the first and second engaging sequences, wherein the analysis in step (vi) indicates the presence, absence, and/or amount of the antibody or antigen binding fragment thereof in the sample (Numerous methods can be used to identify the binding event identifiers used in the assay systems of the invention, Para. [0089]).

Regarding claim 61, Chee discloses the method of claim 60, wherein the complex between the first and second polypeptide-polynucleotide conjugates in step (ii) (a second binding construct, blocked at the 3' end 1329 (black square) so that it cannot be extended, is bound to the first binding construct via target agent 1337, Para. [0088], Fig. 13) is formed by hybridization between the first and second polynucleotides (and primer/hybridization region 1325, the complement to primer/hybridization region 1315, Para. [0088], Fig. 13).

Regarding claim 62, Chee discloses the method of claim 61, wherein the washing step is performed under conditions that destabilize the hybridization between the first and second polynucleotides thereby releasing molecules of the second polypeptide-polynucleotide conjugate that are not specifically bound to the antibody or antigen binding fragment thereof (the cleavable linker 1335 attaching the first binding agent 1301 to the first binding construct is cleaved, and washing removes the second binding construct, the first antibody 1301 and target agent 1337, Para. [0088], Fig. 13).

Regarding claim 63, Chee discloses the method of claim 61, wherein the sequences involved in the hybridization between the first and second polynucleotides comprise one or more cleavable sites (An antibody 1301 is attached to a nucleic acid portion of the first binding construct via a cleavable linker 1335, Para. [0087], Fig. 13).

Regarding claim 64, Chee discloses the method of claim 63, wherein the sequences involved in the hybridization are cleaved at the one or more cleavable sites (In 13D, the cleavable linker 1335 attaching the first binding agent 1301 to the first binding construct is cleaved, Para. [0088], Fig. 13) before or during the washing step thereby destabilizing the hybridization between the first and second polynucleotides (and washing removes the second binding construct, the first antibody 1301 and target agent 1337, Para. [0088], Fig. 13).

Regarding claim 65, Chee discloses the method of claim 61, wherein the second polypeptide-polynucleotide conjugate is kept in physical proximity to the first polypeptide-polynucleotide conjugate by a cleavable linker (An antibody 1301 is attached to a nucleic acid portion of the first binding construct via a cleavable linker 1335, Para. [0087], Fig. 13) before or after the first and second polypeptide-polynucleotide conjugates form the complex in step (ii) (may be applied separately or simultaneously to the support surface (i.e., without a previous opportunity to interact), Para. [0087], Fig. 13).

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding claim 66, Chee discloses the method of claim 65, wherein the cleavable linker is between the first and second polypeptide-polynucleotide conjugates, or between the second polypeptide polynucleotide conjugate and the substrate (An antibody 1301 is attached to a nucleic acid portion of the first binding construct via a cleavable linker 1335, Para. [0087]), Fig. 13).

Regarding claim 67, Chee discloses the method of claim 66, wherein the cleavable linker is cleaved (In 13D, the cleavable linker 1335 attaching the first binding agent 1301 to the first binding construct is cleaved, Para. [0088]) before or during the washing step (and washing removes the second binding construct, the first antibody 1301 and target agent 1337, Para. [0088]), optionally under conditions that destabilize the hybridization between the first and second polynucleotides.

Regarding claim 72, Chee discloses a method for analyzing an antibody or antigen binding fragment thereof in a sample (a method for identifying binding agents that form a binding pair, Para. [0016]), comprising: (i) providing a first polypeptide-polynucleotide conjugate immobilized on a substrate (comprising: providing a first set of binding constructs immobilized on a support surface, Para. [0016]), the first polypeptide-polynucleotide conjugate comprising: (a) a first polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a first epitope for specific binding of an antibody or antigen binding fragment thereof (the first and second binding agents (binding pair) are provided as antibodies or variable domains of antibodies that bind to different epitopes on a common molecule, Para. [0077]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a primer sequence (a first primer region, Para. [0016]), a first identifying sequence (a first nucleic acid tag unique to the first binding agent, Para. [0016]) that identifies the first polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0016]), and a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0016]); (ii) contacting the substrate having the immobilized first polypeptide-polynucleotide conjugate (providing a first set of binding constructs immobilized on a support surface, Para. [0016]) with a sample containing or suspected of containing the antibody or antigen binding fragment thereof (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]), whereby the first epitope specifically binds to the antibody or antigen binding fragment thereof in the sample (the method further comprises the step of adding a third binding agent in the combining step, Para. [0035]); (iii) contacting the substrate having the immobilized first polypeptide-polynucleotide conjugate with a second polypeptide-polynucleotide conjugate (providing a second set of binding constructs in solution, Para. [0016]), the second polypeptide-polynucleotide conjugate comprising: (a) a second polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a second epitope for specific binding of the antibody or antigen binding fragment thereof (the first and second binding agents (binding pair) are provided as antibodies or variable domains of antibodies that bind to different epitopes on a common molecule, Para. [0077]); and (b) a second polynucleotide comprising a second identifying sequence (a second nucleic acid tag unique to the second binding agent, Para. [0016]) that identifies the second polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0016]), and a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0016]), whereby the second epitope specifically binds to the antibody or antigen binding fragment thereof specifically bound to the first epitope (The presence and binding of both the first (A) and second (S) binding agents is necessary for the detection of the third molecule, Para. [0077]), and whereby the first and second polynucleotides are engaged via the first and second engaging sequences (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs, Para. [0016]); and (iv) analyzing the first and/or second polynucleotides engaged via the first and second engaging sequences (determining a sequence of at least one thousand binding event identifiers, where the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair, Para. [0016]), wherein the analysis in step (iv) indicates the presence, absence, and/or amount (and determining the frequency of each binding event identifier sequenced, Para. [0016]) of the antibody or antigen binding fragment thereof in the sample (In certain other assay schemes of the invention, however, the first and second binding agents may be analyzed for their ability to bind a third agent or analyte in addition to or in place of binding to one another, Para. [0076]).

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding claim 73, Chee discloses a method for analyzing an antibody or antigen binding fragment thereof in a sample (a method for identifying binding agents that form a binding pair, Para. [0016]), comprising: (i) providing a first polypeptide-polynucleotide conjugate immobilized on a substrate (comprising: providing a first set of binding constructs immobilized on a support surface, Para. [0016]), the first polypeptide-polynucleotide conjugate comprising: (a) a first polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a first epitope for specific binding of an antibody or antigen binding fragment thereof (the first and second binding agents (binding pair) are provided as antibodies or variable domains of antibodies that bind to different epitopes on a common molecule, Para. [0077]); and (b) a first polynucleotide comprising a first identifying sequence (a first nucleic acid tag unique to the first binding agent, Para. [0016]) that identifies the first polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0016]), and a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0016]); (ii) contacting the substrate having the immobilized first polypeptide-polynucleotide conjugate (providing a first set of binding constructs immobilized on a support surface, Para. [0016]) with a sample containing or suspected of containing the antibody or antigen binding fragment thereof (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]), whereby the first epitope specifically binds to the antibody or antigen binding fragment thereof in the sample (the method further comprises the step of adding a third binding agent in the combining step, Para. [0035]); (iii) contacting the substrate having the immobilized first polypeptide-polynucleotide conjugate with a second polypeptide-polynucleotide conjugate (providing a second set of binding constructs in solution, Para. [0016]), the second polypeptide-polynucleotide conjugate comprising: (a) a second polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a second epitope for specific binding of the antibody or antigen binding fragment thereof (the first and second binding agents (binding pair) are provided as antibodies or variable domains of antibodies that bind to different epitopes on a common molecule, Para. [0077]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a primer sequence (a second primer region, Para. [0016]), a second identifying sequence (a second nucleic acid tag unique to the second binding agent, Para. [0016]) that identifies the second polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0016]), and a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0016]), whereby the second epitope specifically binds to the antibody or antigen binding fragment thereof specifically bound to the first epitope (The presence and binding of both the first (A) and second (S) binding agents is necessary for the detection of the third molecule, Para. [0077]), and whereby the first and second polynucleotides are engaged via the first and second engaging sequences (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs, Para. [0016]); and (iv) analyzing the first and/or second polynucleotides engaged via the first and second engaging sequences determining a sequence of at least one thousand binding event identifiers, where the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair, Para. [0016]), wherein the analysis in step (iv) indicates the presence, absence, and/or amount (and determining the frequency of each binding event identifier sequenced, Para. [0016]) of the antibody or antigen binding fragment thereof in the sample (In certain other assay schemes of the invention, however, the first and second binding agents may be analyzed for their ability to bind a third agent or analyte in addition to or in place of binding to one another, Para. [0076]).

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding claim 74, Chee discloses a method for analyzing a plurality (at least ten different binding agents, Para. [0009]) of antibodies or antigen binding fragments thereof in a sample (a method for identifying binding agents that form a binding pair, Para. [0009]), comprising: (i) immobilizing a plurality of first polypeptide-polynucleotide conjugates on a substrate (providing a first set of binding constructs immobilized on a support surface, Para. [0009]), each of the first polypeptide-polynucleotide conjugates comprising: (a) a first polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a first epitope for specific binding of an antibody or antigen binding fragment thereof in a plurality (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]) of antibodies or antigen binding fragments thereof (In yet other aspects, the first binding agent is a peptide and the second binding agent is an antibody, Para. [0014]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a first primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a first identifying sequence (and a first nucleic acid tag unique to the first binding agent, Para. [0009]) that identifies the first polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0009]); (ii) contacting the substrate having the immobilized plurality of first polypeptide-polynucleotide conjugates (providing a first set of binding constructs immobilized on a support surface, Para. [0016]) with a sample containing or suspected of containing at least one of the plurality (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]) of antibodies or antigen binding fragments (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]), whereby the at least one antibody or antigen binding fragment in the sample specifically binds to a first epitope of the immobilized plurality of first polypeptide-polynucleotide conjugates (the method further comprises the step of adding a third binding agent in the combining step, Para. [0035]); (iii) contacting the substrate having the immobilized plurality of first polypeptide-polynucleotide conjugates with a plurality of second polypeptide-polynucleotide conjugates (providing a second set of binding constructs in solution, Para. [0009]), each of the second polypeptide-polynucleotide conjugates comprising: (a) a second polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a second epitope for specific binding of an antibody or antigen binding fragment thereof in the plurality (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]) of antibodies or antigen binding fragments (In yet other aspects, the first binding agent is a peptide and the second binding agent is an antibody, Para. [0014]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a second primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a second identifying sequence (and a second nucleic acid tag unique to the second binding agent, Para. [0009]) that identifies the second polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0009]), whereby the at least one antibody or antigen binding fragment specifically bound to the first epitope specifically binds to a second epitope of the plurality of second polypeptide-polynucleotide conjugates (The presence and binding of both the first (A) and second (S) binding agents is necessary for the detection of the third molecule, Para. [0077]), and whereby the first and second polypeptide-polynucleotide conjugates specifically bound to the same antibody or antigen binding fragment are engaged via the first and second engaging sequences (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs thereby co-locating the first nucleic acid tags and the second nucleic acid tags, Para. [0009]); and (iv) analyzing the first and/or second polypeptide-polynucleotide conjugates engaged via the first and second engaging sequences (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), wherein the analysis in step (iv) indicates the presence, absence, and/or amount of the plurality of antibodies or antigen binding fragments thereof in the sample (and determining a sequence of each binding event identifier; wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair, Para. [0009]).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

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Regarding claim 84, Chee discloses a set of polypeptide-polynucleotide conjugates (detection of an agent or analyte using two sets of binding constructs, Para. [0087]), Fig. 13), comprising: a first polypeptide-polynucleotide conjugate (the first binding construct used in the assay, Para. [0087]) comprising: (a) a first polypeptide comprising a first epitope for specific binding of an antibody or antigen binding fragment thereof (An antibody 1301 is attached to a nucleic acid portion of the first binding construct via a cleavable linker 1335, Para. [0087]); and (b) a first polynucleotide comprising a first primer sequence (Sequence 1311 is a primer sequence, Para. [0087]), a first identifying sequence that identifies the first polypeptide, and a first engaging sequence (The binding construct further comprises a unique nucleic acid tag 1319 that identifies the binding agent, Para. [0087]); a second polypeptide-polynucleotide conjugate comprising: (a) a second polypeptide (a second binding construct, blocked at the 3' end 1329 (black square) so that it cannot be extended, Para. [0088]) comprising a second epitope for specific binding of the antibody or antigen binding fragment thereof (is bound to the first binding construct via target agent 1337, Para. [0088]); and (b) a second polynucleotide comprising a second identifying sequence that identifies the second polypeptide (The second binding construct comprises a unique nucleic acid tag 1313 that identifies the second binding agent present in the second binding construct, Para. [0088]), a second engaging sequence (a primer/hybridization region 1315, Para. [0088]), and optionally a second primer sequence; and a third polypeptide-polynucleotide conjugate comprising (In C, primer extension is carried out resulting in the first binding construct extended to comprise, Para. [0088]): (a) an antibody portion (first unique nucleic acid sequence tag 1319, Para. [0088]) that specifically binds to the Fe portion of the antibody or antigen binding fragment thereof (The binding construct further comprises a unique nucleic acid tag 1319 that identifies the binding agent (in this case, an antibody), Para. [0087]); and (2) a third polynucleotide that comprises a third primer sequence (primer 1311, Para. [0088]), a third identifying sequence that identifies the antibody portion (the complement to second unique nucleic acid tag 1313, Para. [0088]), and a third engaging sequence (the complement to primer/hybridization region 1315, Para. [0088]), wherein the first and second engaging sequences are capable of engaging the first and second polynucleotides (Binding of the binding agent 1303 of the second set of binding constructs to target agent 1337, Para. [0087]), wherein the first or second polynucleotide is capable of being extended by a polymerase after the first and second polynucleotides are engaged (The primer-extended construct attached to the support surface can now be assayed. For example, it can be amplified using either surface PCR, Para. [0088]), wherein the extended (primer extension is carried out resulting in the first binding construct extended, Para. [0088]) first or second polynucleotide is capable of engaging the third polynucleotide (the second set of binding constructs comprising binding agents 1303 and target agent 1337 may be applied separately or simultaneously to the support surface, Para. [0087]), and wherein the extended first or second polynucleotide is capable of being further extended by a polymerase (The primer-extended construct attached to the support surface can now be assayed. For example, it can be amplified using either surface PCR or an emulsion PCR, followed by sequencing, Para. [0088]).

Regarding claim 85, Chee discloses a pair of polynucleotide conjugates (a binding pair comprising a protein and a different chemical moiety, Para. [0008]), comprising: a first polynucleotide conjugate comprising (providing a first set of binding constructs immobilized on a support surface, Para. [0009]): (a) a first binder for specific binding of an analyte (In yet other aspects, the first binding agent is a peptide and the second binding agent is an antibody, Para. [0014]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a first primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a first identifying sequence (and a first nucleic acid tag unique to the first binding agent, Para. [0009]) that identifies the first binder (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0009]); and a second polynucleotide (an oligonucleotide, Para. [0039]) conjugate comprising (providing a second set of binding constructs in solution, Para. [0009]): (a) a second binder for specific binding of the analyte (In yet other aspects, the first binding agent is a peptide and the second binding agent is an antibody, Para. [0014]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a second primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a second identifying sequence (and a second nucleic acid tag unique to the second binding agent, Para. [0009]) that identifies the second binder (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0009]), wherein the first and second engaging sequences are capable of engaging the first and second polynucleotides, thereby engaging the first and second polynucleotide conjugates (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs thereby co-locating the first nucleic acid tags and the second nucleic acid tags, Para. [0009]).

Regarding claim 86, Chee discloses the pair of claim 85, wherein the first engaging sequence (The term "binding agent" as used herein refers to any binding agent that selectively binds to a molecule of interest, Para. [0033]) comprises a sequence hybridizable (The term also includes complementary nucleic acid molecules that selectively hybridize at or above a desired melting temperature, Para. [0034]) to the second engaging sequence, and/or the second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0009]) comprises a sequence hybridizable (The term also includes complementary nucleic acid molecules that selectively hybridize at or above a desired melting temperature, Para. [0034]) to the first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0009]).

Regarding claim 87, Chee discloses the pair of claim 85, wherein the first engaging sequence comprises a sequence complementary ("Complementary" or "substantially complementary" refers to the hybridization or base pairing or the formation of a duplex between nucleotides or nucleic acids, Para. [0035]) to all or a portion of the second engaging sequence (The term "binding pair" means any two molecules (binding agents) that are known to bind selectively to one another. In the case of two proteins, the proteins bind selectively to one another with a high affinity as described in more detail herein, Para. [0034]), and/or the second engaging sequence comprises a sequence complementary to all or a portion of the first engaging sequence.

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Regarding claim 108, Chee discloses a method for analyzing an analyte in a sample (a method for identifying binding agents that form a binding pair, Para. [0009]), comprising: (i) immobilizing a first polynucleotide conjugate on a substrate (providing a first set of binding constructs immobilized on a support surface, Para. [0009]), the first polynucleotide conjugate comprising: (a) a first binder for specific binding of an analyte (In yet alternative aspects, either the first or second binding agent is an aptamer, Para. [0014]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a first identifying sequence (and a first nucleic acid tag unique to the first binding agent, Para. [0009]) that identifies the first binder (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0009]), and optionally a first primer sequence; (ii) contacting the substrate having the immobilized first polynucleotide conjugate with a sample containing or suspected of containing the analyte (the method further comprises the step of adding a third binding agent in the combining step, Para. [0035]), whereby the first binder specifically binds to the analyte in the sample (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]); (iii) contacting the substrate having the immobilized first polynucleotide conjugate (providing a first set of binding constructs immobilized on a support surface, Para. [0016]) with a second polynucleotide conjugate (providing a second set of binding constructs in solution, Para. [0009]), the second polynucleotide conjugate comprising: (a) a second binder for specific binding of the analyte (In yet alternative aspects, either the first or second binding agent is an aptamer, Para. [0014]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a second identifying sequence (and a second nucleic acid tag unique to the second binding agent, Para. [0009]) that identifies the second binder (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0009]), and optionally a second primer sequence, whereby the second binder specifically binds to the analyte specifically bound to the first binder (The presence and binding of both the first (A) and second (S) binding agents is necessary for the detection of the third molecule, Para. [0077]), and whereby the first and second polynucleotides are engaged via the first and second engaging sequences (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs thereby co-locating the first nucleic acid tags and the second nucleic acid tags, Para. [0009]); and (iv) analyzing the first and/or second polynucleotides engaged via the first and second engaging sequences (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), wherein the analysis in step (iv) indicates the presence, absence, and/or amount of the analyte in the sample (and determining a sequence of each binding event identifier; wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair, Para. [0009]).

Regarding claim 109, Chee discloses a method for analyzing a plurality (at least ten different binding agents, Para. [0009]) of analytes in a sample (a method for identifying binding agents that form a binding pair, Para. [0009]), comprising: (i) immobilizing a plurality of first polynucleotide conjugates on a substrate (providing a first set of binding constructs immobilized on a support surface, Para. [0009]), each of the first polynucleotide conjugates comprising: (a) a first binder for specific binding of an analyte (In yet alternative aspects, either the first or second binding agent is an aptamer, Para. [0014]) in a plurality of analytes (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a first primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a first identifying sequence (and a first nucleic acid tag unique to the first binding agent, Para. [0009]) that identifies the first binder (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0009]); (ii) contacting the substrate having the immobilized plurality of first polynucleotide conjugates with a sample containing or suspected of containing at least one of the plurality of analytes (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]), whereby the at least one analyte in the sample specifically binds to a first binder of the immobilized plurality of first polynucleotide conjugates (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]); (iii) contacting the substrate having the immobilized plurality of first polynucleotide conjugates (providing a first set of binding constructs immobilized on a support surface, Para. [0016]) with a plurality (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]) of second polynucleotide conjugates (providing a second set of binding constructs in solution, Para. [0009]), each of the second polynucleotide conjugates comprising: (a) a second binder for specific binding of an analyte (In yet alternative aspects, either the first or second binding agent is an aptamer, Para. [0014]) in the plurality of analytes (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a second primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a second identifying sequence (and a second nucleic acid tag unique to the second binding agent, Para. [0009]) that identifies the second binder (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0009]), whereby the at least one analyte specifically bound to the first binder specifically binds to a second binder of the plurality of second polynucleotide conjugates (The presence and binding of both the first (A) and second (S) binding agents is necessary for the detection of the third molecule, Para. [0077]), and whereby the first and second polynucleotide conjugates specifically bound to the same anlayte are engaged via the first and second engaging sequences (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs thereby co-locating the first nucleic acid tags and the second nucleic acid tags, Para. [0009]); and (iv) analyzing the first and/or second polynucleotide conjugates engaged via the first and second engaging sequences (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), wherein the analysis in step (iv) indicates the presence, absence, and/or amount of the plurality of analytes in the sample (and determining a sequence of each binding event identifier; wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair, Para. [0009]).

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Regarding claim 109, Chee discloses a method for analyzing a plurality (at least ten different binding agents, Para. [0009]) of analytes in a sample (a method for identifying binding agents that form a binding pair, Para. [0009]), comprising: (i) immobilizing a plurality of first polynucleotide conjugates on a substrate (providing a first set of binding constructs immobilized on a support surface, Para. [0009]), each of the first polynucleotide conjugates comprising: (a) a first binder for specific binding of an analyte (In yet alternative aspects, either the first or second binding agent is an aptamer, Para. [0014]) in a plurality of analytes (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a first primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a first identifying sequence (and a first nucleic acid tag unique to the first binding agent, Para. [0009]) that identifies the first binder (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0009]); (ii) contacting the substrate having the immobilized plurality of first polynucleotide conjugates with a sample containing or suspected of containing at least one of the plurality of analytes (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]), whereby the at least one analyte in the sample specifically binds to a first binder of the immobilized plurality of first polynucleotide conjugates (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]); (iii) contacting the substrate having the immobilized plurality of first polynucleotide conjugates (providing a first set of binding constructs immobilized on a support surface, Para. [0016]) with a plurality (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]) of second polynucleotide conjugates (providing a second set of binding constructs in solution, Para. [0009]), each of the second polynucleotide conjugates comprising: (a) a second binder for specific binding of an analyte (In yet alternative aspects, either the first or second binding agent is an aptamer, Para. [0014]) in the plurality of analytes (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a second primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a second identifying sequence (and a second nucleic acid tag unique to the second binding agent, Para. [0009]) that identifies the second binder (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0009]), whereby the at least one analyte specifically bound to the first binder specifically binds to a second binder of the plurality of second polynucleotide conjugates (The presence and binding of both the first (A) and second (S) binding agents is necessary for the detection of the third molecule, Para. [0077]), and whereby the first and second polynucleotide conjugates specifically bound to the same anlayte are engaged via the first and second engaging sequences (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs thereby co-locating the first nucleic acid tags and the second nucleic acid tags, Para. [0009]); and (iv) analyzing the first and/or second polynucleotide conjugates engaged via the first and second engaging sequences (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), wherein the analysis in step (iv) indicates the presence, absence, and/or amount of the plurality of analytes in the sample (and determining a sequence of each binding event identifier; wherein the sequence of each binding event identifier identifies the binding pair and the binding agents that form the binding pair, Para. [0009]).

Regarding claim 110, Chee discloses the method of claim 109, wherein the plurality of first polynucleotide conjugates are immobilized (a first set of binding constructs comprising binding agents is associated with a support surface, e.g., immobilized on the support surface or provided in a discrete feature on the support surface, Para. [0049]) or directly synthesized on the substrate at a density that substantially reduces or prevents interaction between adjacent first polynucleotide conjugates on the substrate (Members of first binding construct set are immobilized on a surface 1121 so that each molecule is well spaced from another, Para. [0080]).

Regarding claim 112, Chee discloses the method of claim 108, wherein the density of the first polynucleotide conjugate molecules immobilized (a first set of binding constructs comprising binding agents is associated with a support surface, e.g., immobilized on the support surface or provided in a discrete feature on the support surface, Para. [0049]) or directly synthesized on the substrate is sufficiently low to: (1) substantially reduce or prevent interaction between adjacent first polynucleotide conjugate molecules on the substrate (Members of first binding construct set are immobilized on a surface 1121 so that each molecule is well spaced from another, Para. [0080]); (2) substantially reduce or prevent interaction between an analyte molecule bound by one first polynucleotide conjugate molecule and an adjacent first polynucleotide conjugate molecule on the substrate (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]); (3) substantially reduce or prevent interaction between a second polynucleotide conjugate molecule non-specifically bound to the substrate (For example, the first set of binding constructs 1117 may hybridize to anchor 1105 on surface 1121, e.g., the surface of a flowcell or a micro bead, but may not hybridize to anchors 1107, Para. [0080]) and an immobilized first polynucleotide conjugate molecule (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]); (4) substantially reduce or prevent interaction between a second polynucleotide conjugate molecule bound by an analyte molecule non-specifically bound to the substrate (For example, the first set of binding constructs 1117 may hybridize to anchor 1105 on surface 1121, e.g., the surface of a flowcell or a micro bead, but may not hybridize to anchors 1107, Para. [0080]), and an immobilized first polynucleotide conjugate molecule (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]); and/or (5) substantially reduce or prevent interaction between a second polynucleotide conjugate molecule specifically bound to an analyte molecule in a ternary complex with a first polynucleotide conjugate molecule, and an adjacent immobilized first polynucleotide conjugate molecule (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]).

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Regarding claim 114, Chee discloses the method of claim 108, wherein the second polynucleotide conjugate is provided in solution (This assay utilizes an anchored first set of binding constructs, a second set of binding constructs in solution, Para. [0079]), and the concentration of the second polynucleotide conjugate is sufficiently low to: (1) substantially reduce or prevent interaction between a second polynucleotide conjugate molecule non-specifically bound to the substrate and an immobilized first polynucleotide conjugate molecule (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]); and/or (2) substantially reduce or prevent interaction between a second polynucleotide conjugate molecule bound by an analyte molecule nonspecifically bound to the substrate, and an immobilized first polynucleotide conjugate molecule (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]).

Regarding claim 116, Chee discloses the method of claim 108, wherein the concentration of the second polynucleotide conjugate provided in solution (This assay utilizes an anchored first set of binding constructs, a second set of binding constructs in solution, Para. [0079]) and/or the ratio between the second polynucleotide conjugate and the first polynucleotide conjugate is sufficiently low to: (1) substantially reduce or prevent interaction between a second polynucleotide conjugate molecule non-specifically bound to the substrate and an immobilized first polynucleotide conjugate molecule (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]); and/or (2) substantially reduce or prevent interaction between a second polynucleotide conjugate molecule bound by an analyte molecule non-specifically bound to the substrate, and an immobilized first polynucleotide conjugate molecule (the binding agent of the first set of binding constructs (A) and the binding agent of the second set of binding constructs provided in solution (S) bind to a third agent or analyte (L) and do not bind directly to one another. Figure 8 and 8B, Para. [0076]).

Claim 75 lacks an inventive step under PCT Article 33(3) as being obvious over Chee et al (hereafter Chee), in view of Kozlov et al (hereafter Kozlov).

Regarding claim 75, Chee discloses the method of claim 74, but fails to explicitly disclose wherein the plurality of the first epitopes are overlapping epitopes, and/or the plurality of the second epitopes are overlapping epitopes. Kozlov is in the field of creating libraries of molecular tools for peptide analysis (methods for constructing peptide construct sets and methods of use of these peptide construct sets in assay systems for peptide analysis, Abstact) and discloses wherein the plurality of the first epitopes (the invention provides a set of at least 5,000 distinct peptide constructs, Para. [0013]) are overlapping epitopes (the peptide sequences of the peptide constructs are grouped into one or more sets of partially overlapping sequences, Para. [0015]), and/or the plurality of the second epitopes are overlapping epitopes. It would have been obvious to one of ordinary skill in the art at the time of invention to modify the multi-antigen analysis method of Chee to include use of overlapping epitopes as taught by Kozlov. The motivation would have been to create molecular tools in particular for use in high throughput peptide analysis (Abstract).

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Claims 76-81 lack an inventive step under PCT Article 33(3) as being obvious over Prognosys Biosciences, Inc., (hereafter Prognosys), in view of Chee et al (hereafter Chee).

Regarding claim 76, Prognosys discloses a method of manufacturing a system for analyzing an antibody or antigen binding fragment thereof (a method of manufacturing an array of products on a substrate, Para. [0010]), the method comprising (comprising providing partitioned reaction volumes on the substrate, Para. [0010]): (i) generating an array (an array of products, Para. [0010]) by immobilizing or directly synthesizing (immobilizing the products from the partitioned reaction volumes on capture moieties on the substrate, Para. [0010]) but fails to explicitly disclose a plurality of first polypeptide-polynucleotide conjugates on a substrate, each first polypeptide-polynucleotide conjugate comprising: (a) a first polypeptide comprising a first epitope for specific binding of an antibody or antigen binding fragment thereof; and (b) a first polynucleotide comprising a first primer sequence, a first identifying sequence that identifies the first polypeptide, and a first engaging sequence; (ii) generating a library comprising a plurality of second polypeptide-polynucleotide conjugates, each second polypeptide-polynucleotide conjugate comprising: (a) a second polypeptide comprising a second epitope for specific binding of an antibody or antigen binding fragment thereof; and (b) a second polynucleotide comprising a second primer sequence, a second identifying sequence that identifies the second polypeptide, and a second engaging sequence, wherein at least one pair of first and second polypeptide-polynucleotide conjugates is capable of specific binding to the same antibody molecule or antigen binding fragment thereof, wherein specific binding of the at least one pair to the same antibody molecule or antigen binding fragment thereof engages the first and second engaging sequences of the at least one pair. Chee is in the field of high throughput molecular assay platforms (a new assay format for high throughput molecular binding studies at a single molecule level, Abstract) and discloses a plurality of first polypeptide-polynucleotide conjugates on a substrate (providing a first set of binding constructs immobilized on a support surface, Para. [0009]), each first polypeptide-polynucleotide conjugate comprising: (a) a first polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a first epitope for specific binding of an antibody or antigen binding fragment thereof (In yet other aspects, the first binding agent is a peptide and the second binding agent is an antibody, Para. [0014]); and (b) a first polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a first primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a first identifying sequence (and a first nucleic acid tag unique to the first binding agent, Para. [0009]) that identifies the first polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a first engaging sequence (where each binding construct of the first set of binding constructs comprises a first binding agent, Para. [0009]); (ii) generating a library (either or both of the first and second sets of binding constructs comprises at least one hundred different binding agents....at least one million different binding agents or more, Para. [0011]) comprising a plurality of second polypeptide-polynucleotide conjugates (where either or both of the first and second sets of binding constructs comprises at least ten different binding agents, Para. [0009]), each second polypeptide-polynucleotide conjugate comprising (providing a second set of binding constructs in solution, Para. [0009]): (a) a second polypeptide (In some aspects, at least one of the first and second binding agents is a peptide, Para. [0013]) comprising a second epitope for specific binding of an antibody or antigen binding fragment thereof (In yet other aspects, the first binding agent is a peptide and the second binding agent is an antibody, Para. [0014]); and (b) a second polynucleotide ("Primer" means an oligonucleotide, Para. [0039]) comprising a second primer sequence (one or both of the first and second binding constructs further comprise a primer sequence, Para. [0012]), a second identifying sequence (and a second nucleic acid tag unique to the second binding agent, Para. [0009]) that identifies the second polypeptide (creating binding event identifiers from the co-located first and second nucleic acid tags, Para. [0009]), and a second engaging sequence (where each binding construct of the second set of binding constructs comprises a second binding agent, Para. [0009]), wherein at least one pair of first and second polypeptide-polynucleotide conjugates is capable of specific binding to the same antibody molecule or antigen binding fragment thereof (the method further comprises the step of adding a third binding agent in the combining step, Para. [0035]), wherein specific binding of the at least one pair to the same antibody molecule or antigen binding fragment thereof engages the first and second engaging sequences of the at least one pair (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs thereby co-locating the first nucleic acid tags and the second nucleic acid tags, Para. [0009]). It would have been obvious to one of ordinary skill in the art at the time of invention to modify the molecular analysis manufacturing method of Prognosys to include use of polypeptide-polynucleotide conjugates as taught by Chee. The motivation would have been to create a molecular assay platform which enables creation of binding event identifiers in a highly parallel way (Abstract).

Regarding claim 77, Prognosys discloses the method of claim 76, but fails to explicitly disclose wherein the plurality of first polypeptide-polynucleotide conjugates are immobilized or directly synthesized on the substrate at a density that substantially reduces or prevents interaction between adjacent first polypeptide-polynucleotide conjugates on the substrate. Chee is in the field of high throughput molecular assay platforms (a new assay format for high throughput molecular binding studies at a single molecule level, Abstract) and discloses wherein the plurality of first polypeptide-polynucleotide conjugates are immobilized (a first set of binding constructs comprising binding agents is associated with a support surface, e.g., immobilized on the support surface or provided in a discrete feature on the support surface, Para. [0049]) or directly synthesized on the substrate at a density that substantially reduces or prevents interaction between adjacent first polypeptide-polynucleotide conjugates on the substrate (Members of first binding construct set are immobilized on a surface 1121 so that each molecule is well spaced from another, Para. [0080]). It would have been obvious to one of ordinary skill in the art at the time of invention to modify the molecular analysis manufacturing method of Prognosys to include use of spaced polypeptide-polynucleotide conjugates as taught by Chee. The motivation would have been to create a molecular assay platform which enables creation of binding event identifiers in a highly parallel way (Abstract).

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Continuation of:

Regarding claim 78, Prognosys discloses the method of claim 76, further comprising contacting the array with the library (immobilizing the products from the partitioned reaction volumes from the master substrate on capture moieties disposed on the replica array that is in contact with the partitioned reaction volumes, Para. [0016]), but fails to explicitly disclose wherein at least one pair of first and second polypeptide-polynucleotide conjugates forms a conjugate complex. Chee is in the field of high throughput molecular assay platforms (a new assay format for high throughput molecular binding studies at a single molecule level, Abstract) and discloses wherein at least one pair of first and second polypeptide-polynucleotide conjugates forms a conjugate complex (combining the first and second sets of binding constructs under conditions to allow the first binding agents and the second binding agents to form binding pairs thereby co-locating the first nucleic acid tags and the second nucleic acid tags, Para. [0009]). It would have been obvious to one of ordinary skill in the art at the time of invention to modify the molecular array manufacturing method of Prognosys to include use of interacting polypeptide-polynucleotide conjugates as taught by Chee. The motivation would have been to create a molecular assay platform which enables creation of binding event identifiers in a highly parallel way (Abstract).

Regarding claim 79, Prognosys discloses the method of claim 78, but fails to explicitly disclose wherein the conjugate complex is formed by hybridization between the first and second polynucleotides of the at least one pair of first and second polypeptide-polynucleotide conjugates. Chee is in the field of high throughput molecular assay platforms (a new assay format for high throughput molecular binding studies at a single molecule level, Abstract) and discloses wherein the conjugate complex is formed (a second binding construct, blocked at the 3' end 1329 (black square) so that it cannot be extended, is bound to the first binding construct via target agent 1337, Para. [0088], Fig. 13) by hybridization between the first and second polynucleotides of the at least one pair of first and second polypeptide-polynucleotide conjugates (and primer/hybridization region 1325, the complement to primer/hybridization region 1315, Para. [0088], Fig. 13). It would have been obvious to one of ordinary skill in the art at the time of invention to modify the molecular array manufacturing method of Prognosys to include use of hybridizing polypeptide-polynucleotide conjugates as taught by Chee. The motivation would have been to create a molecular assay platform which enables creation of binding event identifiers in a highly parallel way (Abstract).

Regarding claim 80, Prognosys discloses the method of claim 79, but fails to explicitly disclose wherein the sequences involved in the hybridization between the first and second polynucleotides comprise one or more cleavable sites. Chee is in the field of high throughput molecular assay platforms (a new assay format for high throughput molecular binding studies at a single molecule level, Abstract) and discloses wherein the sequences involved in the hybridization between the first and second polynucleotides comprise one or more cleavable sites (An antibody 1301 is attached to a nucleic acid portion of the first binding construct via a cleavable linker 1335, Para. [0087], Fig. 13). It would have been obvious to one of ordinary skill in the art at the time of invention to modify the molecular array manufacturing method of Prognosys to include use of cleavable polypeptide-polynucleotide conjugates as taught by Chee. The motivation would have been to create a molecular assay platform which enables creation of binding event identifiers in a highly parallel way (Abstract).

Regarding claim 81, Prognosys discloses the method of claim 78, but fails to explicitly disclose wherein the second polypeptide-polynucleotide conjugate of the at least one pair that forms a conjugate complex is immobilized on the substrate via a cleavable linker. Chee is in the field of high throughput molecular assay platforms (a new assay format for high throughput molecular binding studies at a single molecule level, Abstract) and discloses wherein the second polypeptide-polynucleotide conjugate of the at least one pair that forms a conjugate complex is immobilized on the substrate (where the binding construct is ligated using a splint sequence 1333 to a anchor 1305 attached to a solid support. Para. [0087]) via a cleavable linker (the cleavable linker 1335 attaching the first binding agent 1301 to the first binding construct is cleaved, and washing removes the second binding construct, the first antibody 1301 and target agent 1337, Para. [0088], Fig. 13). It would have been obvious to one of ordinary skill in the art at the time of invention to modify the molecular array manufacturing method of Prognosys to include use of cleavable polypeptide-polynucleotide conjugates as taught by Chee. The motivation would have been to create a molecular assay platform which enables creation of binding event identifiers in a highly parallel way (Abstract).

Claims 1-4, 28-30, 60-67, 72-81, 84-87, 108-110, 112, 114 and 116 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Search History:

Limited Classification Search

The Patent Analyst performed a limited classification search within the following US, IPC, CPC classification areas:

U.S. Class/Subclasses: 506/9; 506/4; 506/16; 506/26

IPC (8) Class/Subclasses: C40B 20/04, 30/04, 40/06, 50/06 (2015.01)

CPC Class/Subclasses: C40B 20/04, 30/04, 40/06, 50/06 (2015.01)

See Global Search Results.

Global Patent Literature Text Search

The Patent Analyst performed the following global text search, which was not limited by classification but may or may not have been limited by other criteria:

ORBIT

Number	Search String	Results
1	Prognosys biosciences	11
2	Igor Kozlov (168) with (peptide or nucleotide*)	8
3	John Andrew Altin	1
4	Petr Chapek	0
5	Mark Chee	98
6	(nucleotide*) AND (peptide*) AND (conjugate* OR probe*)	
7	Line 6 and 506004000 in US	0
8	Line 6 and 506016000 in US	6
9	Line 6 and 506026000 in US	0
10	Line 6 and 506009000 in US	11
11	Line 6 and C40B-030/04 in IPC/CPC	11/2
12	Line 6 and C40B-020/04 in IPC/CPC	0/0
13	Line 6 and C40B-040/06 in IPC/CPC	9/7
14	Line 6 and C40B-050/06 in IPC/CPC	4/2

GOOGLE PATENT http://www.google.com/advanced_patent_search

Text String	No. of Hits
peptide nucleotide pairs for antibody detection	12,300
polynucleotide polypeptide conjugate antibody antigen aptamer probe manufacture hybridization	15,800
polynucleotide polypeptide conjugate antibody probe hybridization	1 million
Polynucleotide-polypeptide conjugate	2.7 million

Computer Accessed Text Databases Searched

The Patent Analyst searched the following computer accessed text databases:

GOOGLE: www.google.com

Text String	No. of Hits
peptide nucleotide pairs for antibody detection	6 million
Polynucleotide-polypeptide conjugate	13 million
polynucleotide polypeptide conjugate antibody probe hybridization	4 million

GOOGLE SCHOLAR: www.scholar.google.com

Text String	No. of Hits
peptide nucleotide pairs for antibody detection	93,000
polynucleotide polypeptide conjugate antibody probe hybridization	8,170

PUBMED: http://www.ncbi.nlm.nih.gov/pubmed/advanced

Number	Query	Items found
1	Peptide nucleotide conjugates	2
2	Chee kozlov	6

Date search was completed: 11 February 2015

RM/JJ

Docket No.: 699932000200
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Mark S. CHEE	Confirmation No.: 2142
Application No.: 13/080,616	Art Unit: 1634
Filed: April 5, 2011	Examiner: James Martinell
For: SPATIALLY ENCODED BIOLOGICAL ASSAYS	

AMENDMENT AND REQUEST FOR CONTINUED EXAMINATION

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

Dear Commissioner:

Prior to examination on the merits, Applicant respectfully requests entry of this amendment in the above-captioned application, submitted together with a Request for Continued Examination (RCE), and in response to the final Office Action dated October 21, 2014, for which a response was filed February 23, 2015 with the petition for an extension of time of one (1) month and the required fee, and in response to the Advisory Action dated March 17, 2015, and following the telephonic interview between Examiner Martinell and Applicant's representatives Bu Yin (the undersigned) and Peng Chen on March 24, 2015. An additional two-month extension of time is hereby requested, extending the response date to April 21, 2015. Accordingly, this RCE is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 11 of this paper.

Curio EX1012-p. 483
Curio v Prognosys

AMENDMENTS TO THE CLAIMS

1. (currently amended): A method to determine a spatial pattern of abundance or activity or both of a biological target in a sample, comprising the following steps:

delivering encoded probes for a biological target to multiple sites in a sample affixed to a support, wherein each encoded probe comprises a probe region capable of specific binding to the biological target and a coding tag comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered;

allowing the encoded probes to interact with the biological target;

separating encoded probes specifically bound to the biological target from encoded probes not specifically bound to the biological target;

determining ~~a sequence of the encoded probes specifically bound to the biological target, wherein the sequence comprises~~ all or a portion of the coding tag oligonucleotide sequence of the encoded probe specifically bound to the biological target by performing a polynucleotide sequencing reaction of the encoded probe, thereby identifying the location of the site to which the encoded probe is delivered; and

associating the abundance or activity or both of the biological target to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the biological target in the sample.

2. (previously presented): The method of claim 1, wherein the biological target is a nucleic acid and the encoded probes are oligonucleotides.

3. (previously presented): The method of claim 2, wherein there are two encoded probes for the nucleic acid target at each of the multiple sites in the sample.

4. (previously presented): The method of claim 1, wherein the biological target is a protein, the probe regions of the encoded probes are proteins, and the coding tags comprise oligonucleotides.

5. (previously presented): The method of claim 4, wherein the biological target comprises an enzyme.

6. (previously presented): The method of claim 1, wherein each of the probe regions of the encoded probes comprises an antibody, an aptamer, and/or a small molecule that is capable of specific binding to the biological target.

7-8. (canceled)

9. (previously presented): The method of claim 1, further comprising an amplification step between the separating step and the determining step.

10. (previously presented): The method of claim 1, wherein the determining step is performed by nucleic acid sequencing or high-throughput sequencing or high-throughput digital nucleic acid sequencing.

11. (canceled)

12. (previously presented): The method of claim 1, wherein multiple biological targets in the sample are assayed and the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 100, 1,000, 10,000, 100,000, or 1,000,000.

13-19. (canceled)

20. (previously presented): The method of claim 1, wherein the sequences of at least one hundred thousand, at least five hundred thousand, or at least one million encoded probes are determined in parallel.

21-23. (canceled)

24. (previously presented): The method of claim 1, wherein software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step and the associating step.

25. (previously presented): The method of claim 1, wherein the probe regions of the encoded probes are proteins and the separating step is accomplished by capturing encoded probes specifically bound to the biological target using an affinity capture agent.

26. (previously presented): The method of claim 1, wherein the probe regions of the encoded probes are nucleic acids and the separating step is accomplished by washing the sample.

27. (currently amended): A method to determine a spatial pattern of abundance or activity or both of a nucleic acid target in a sample, comprising the following steps:

delivering an oligonucleotide probe capable of specific hybridization with a nucleic acid target to multiple sites in a sample affixed to a support;

allowing the oligonucleotide probe to hybridize with the nucleic acid target;

washing unhybridized oligonucleotide probe from the sample;

delivering one or more encoding agents to the multiple sites in the sample, wherein the one or more encoding agents delivered to each site comprise an oligonucleotide that identifies the location of the site in the sample;

coupling the one or more encoding agents and the oligonucleotide probe delivered to each site to form an encoded probe specifically hybridized with the nucleic acid target at the site;

determining ~~a sequence of the encoded probes specifically bound to the nucleic acid target, wherein the sequence comprises~~ all or a portion of the one or more encoding agent oligonucleotide sequences of the encoded probe specifically hybridized with the nucleic acid target by performing a polynucleotide sequencing reaction of the encoded probe, thereby identifying the location of the site to which the one or more encoding agents are delivered; and

associating the abundance or activity or both of nucleic acid target to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the nucleic acid target in the sample.

28. (previously presented): The method of claim 27, wherein multiple nucleic acid targets in the sample are assayed and the product of the multiple nucleic acid targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 10,000, 100,000, or 1,000,000.

29-33. (canceled)

34. (previously presented): The method of claim 27, wherein the sequences of at least one hundred thousand or at least one million encoded probes are determined in parallel.

35. (canceled)

36. (previously presented): The method of claim 27, wherein two oligonucleotide probes are delivered for the nucleic acid target.

37. (previously presented): The method of claim 27, wherein the coupling step is performed by ligation.

38. (previously presented): The method of claim 27, wherein the coupling step is performed by extension followed by ligation.

39. (previously presented): The method of claim 27, further comprising an amplification step between the coupling step and the determining step.

40-54. (canceled)

55. (currently amended): A method of determining a spatial pattern of abundance or activity or both of a biological target in a sample, comprising:

delivering a probe capable of specific binding to a biological target to multiple sites in a sample affixed to a support;

allowing the probe to interact with the biological target at each of the multiple sites in the sample;

delivering an encoding agent to each of the multiple sites in the sample, wherein the encoding agent delivered to each site comprises an oligonucleotide that identifies the location of the site in the sample;

coupling the encoding agent to the probe delivered to each of the multiple sites to form an encoded probe at each of the multiple sites;

determining ~~a sequence of the encoded probes specifically bound to the biological target, wherein the sequence comprises~~ all or a portion of the encoding agent oligonucleotide sequence of the encoded probe specifically bound to the biological target by performing a polynucleotide sequencing reaction of the encoded probe, thereby identifying the location of the site to which the encoding agent is delivered; and

associating the abundance or activity or both of the biological target at each of the multiple sites to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the biological target in the sample.

56. (previously presented): The method of claim 55, wherein one or more biological targets in the sample are assayed in parallel.

57. (previously presented): The method of claim 56, wherein for each biological target, one or more probes capable of specific binding to the biological target are delivered to the multiple sites in the sample.

58. (previously presented): The method of claim 55, wherein at least two encoding agents are delivered to each of the multiple sites in the sample and are coupled to the probe delivered to the site to form an encoded probe comprising the at least two encoding agents.

59. (previously presented): The method of claim 55, wherein the biological target comprises a nucleic acid and the probe comprises an oligonucleotide.

60. (previously presented): The method of claim 55, wherein the biological target comprises a protein and the probe comprises a protein.

61. (previously presented): The method of claim 55, wherein the biological target comprises an enzyme, and the probe comprises a substrate or putative substrate for the enzyme.

62. (previously presented): The method of claim 55, wherein the probe comprises an affinity capture agent, antibody, aptamer, or small molecule.

63. (previously presented): The method of claim 55, further comprising amplifying all or a portion of a sequence of the encoded probe.

64. (previously presented): The method of claim 55, wherein the determining step is performed by nucleic acid sequencing or high-throughput sequencing.

65. (previously presented): The method of claim 55, wherein multiple biological targets in the sample are assayed and the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 100, 1,000, 10,000, 100,000, or 1,000,000.

66. (previously presented): The method of claim 55, wherein the sequences of at least one hundred thousand, at least five hundred thousand, or at least one million encoded probes are determined in parallel.

67. (previously presented): The method of claim 55, wherein the probe for the biological target and/or the encoding agent are delivered to the multiple sites in the sample according to a known spatial pattern.

68. (previously presented): The method of claim 55, wherein software programmed hardware performs at least two steps of the delivering steps, the coupling step, the determining step, and the associating step.

69. (previously presented): The method of claim 55, further comprising separating probes specifically bound to the biological target from probes not specifically bound to the biological target.

70. (previously presented): The method of claim 69, wherein the separating step is accomplished by washing the sample.

71. (previously presented): The method of claim 55, wherein the coupling step is performed by ligation, or performed by extension followed by ligation.

72. (previously presented): The method of claim 55, wherein the biological target is a nucleic acid and the probe is capable of specific hybridization with the nucleic acid target, wherein the probe sequence identifies the nucleic acid target.

73. (previously presented): The method of claim 72, wherein in the determining step, the encoded probe sequence being determined comprises all or a portion of the probe sequence and all or a portion of the encoding agent oligonucleotide sequence.

74. (previously presented): The method of claim 73, further comprising quantification of the encoded probe sequence being determined, wherein:

the determined probe sequence identifies the nucleic acid target;

the determined encoding agent oligonucleotide sequence identifies the location of the site at which the probe specific hybridizes with the nucleic acid target; and

the quantity of the encoded probe sequence indicates the amount of the probe specifically hybridized with the nucleic acid target at the site in the sample, and thereby indicates the abundance or activity of the nucleic acid target at the site in the sample.

75. (previously presented): The method of claim 55, wherein the biological target is a protein, the probe is capable of specific binding to the protein target and comprises an oligonucleotide sequence that identifies the protein target.

76. (previously presented): The method of claim 75, wherein in the determining step, the encoded probe sequence being determined comprises all or a portion of the probe oligonucleotide sequence and all or a portion of the encoding agent oligonucleotide sequence.

77. (previously presented): The method of claim 76, further comprising quantification of the encoded probe sequence being determined, wherein:

the determined probe oligonucleotide sequence identifies the protein target;

the determined encoding agent oligonucleotide sequence identifies the location of the site at which the probe specific binds to the protein target; and

the quantity of the encoded probe sequence indicates the amount of the probe specifically binds to the protein target at the site in the sample, and thereby indicates the abundance or activity of the protein target at the site in the sample.

REMARKS

Summary of Telephonic Interview of March 24, 2015

Applicant thanks Examiner Martinell for his time and courtesy shown during the telephonic interview of March 24, 2015, with Applicant's representatives Peng Chen and Bu Yin (the undersigned). The parties discussed the pending claims in reference to Figures 4 and 5 of the original specification, and the rejections under 35 U.S.C. § 103(a) in view of the cited references. The Examiner indicated that amendments to the independent claims by including a sequencing reaction step would be entered and considered.

Claim Status and Amendment

Claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-77 are pending. Claims 7, 8, 11, 13-19, 21-23, 29-33, and 40-54 are canceled. Claims 1, 27, and 55 are amended, support for which is found throughout the specification as originally filed, including in the original claims, for example, at paragraphs [00010], [00014], [00015], [00029], [00033], [00039], and [00049] of the original specification. No new matter is added. Reconsideration and allowance of the claims as amended are respectfully requested.

Conclusion

As submitted in Applicant's February 23, 2015 response, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection

with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 699932000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 20, 2015

Respectfully submitted,

Electronic signature: / Bu Yin /

Bu Yin
Registration No.: 68,930
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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/080,616	Filing Date 04/05/2011	☐ 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 $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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

AMENDMENT **04/20/2015**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 44	Minus	** 57	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***4	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ 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.

** 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 number found in the appropriate box in column 1.

LIE
/GLORIA ANTHONY/

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

25225 7590 06/01/2015

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EXAMINER	
MARTINELL, JAMES	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
06/01/2015	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):

PatentDocket@mofo.com
EOfficeSD@mofo.com

Office Action Summary	Application No. 13/080,616	Applicant(s) CHEE, MARK S.	
	Examiner JAMES MARTINELL	Art Unit 1634	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *4/20/15*.

☐ 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) *1-6,9,10,12,20,24-28,34,36-39 and 55-77* 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) *1-6,9,10,12,20,24-28,34,36-39 and 55-77* 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 *4/5/11* 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 *4/20/15*.

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

4) ☐ Other: _____.

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

Regarding the Information Disclosure Statement filed (April 20, 2015), References Nos. 15-17 (Response to Second Examination report for CN 201180017696.3, filed 17 September 2014; Third Examination Report for CN 201180017696.3, mailed 27 January 2015; and Response to Third Examination report for CN 201180017696.3, filed 13 April 2015) have not been considered because there are no English language translations or statements of relevance in the file (see MPEP 609 and 37 CFR § 1.98(a)(3)).

Claim55 is objected to because of the following informalities: In claim 55, line 8, "comprise" should be changed to "comprises". Appropriate correction is required.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-77 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Roth et al (U.S. Patent Application Publication 2006/0046313 A1) in view of Brenner et al (U.S. Patent Application Publication 2007/0172873 A1). This rejection is repeated for reasons already of record (e.g., Office action mailed October 21, 2014, Pages 2-4). It is noted that Applicant's arguments (response filed August 11, 2014, pages 14-21 and Interview Summary mailed March 31, 2015) are directed toward limitations that were not in the version of the claims filed on April 20, 2015. For example, no pooling step is seen in the instant claims. Roth et al teaches an assay system to determine spatial patterns of abundance or activity or both of multiple biological targets at multiple sites in a sample (paragraphs 0032 and 0140), wherein the assay system performs the steps of providing a sample affixed to a support (paragraph 0033), delivering encoded probes for the multiple biological targets to the multiple sites in the sample is 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 (paragraph 0033), allowing the encoded probes to interact with the biological targets (paragraph 0033), separating the encoded probes that interact with the biological targets from encoded probes that do not interact with the biological targets (paragraph 0033), determining all or a portion of a sequence of the encoded probes (paragraphs 0104 and 0122), and associating the abundance or activity or both of the multiple biological targets to the locations of the sites in the sample (paragraph 0033). Roth et al also teach the use of oligonucleotide probes (*e.g.*, paragraphs 0033 and 0102-0103), washing unhybridized probes from the probes bound the targets (paragraphs 0033 and 0102-0103), delivering one or more encoding agents to locations of the multiple sites in the sample according to a known spatial pattern wherein the combination of encoding agents delivered to each site is different (paragraphs 0086 and 0097), coupling the encoding agents and the oligonucleotide probes to form encoded probes (paragraph 0086), determining all or a portion of a sequence of the encoded probes using high throughput sequencing (paragraphs 0104 and 0122) and associating the abundance or activity or both of multiple biological targets to the locations of multiple sites in the sample (paragraphs 0033, 0104, and 0122). Roth et al further teaches the biological targets are nucleic acids and the encoded probes are oligonucleotides (paragraphs 0102-0103), that there are two encoded probes for each of the multiple nucleic acid targets (paragraphs 0047 and 0091), probe regions of the encoded probes comprise antibodies, the probe regions of the encoded probes are aptamers (paragraph 0069), the probe regions of the encoded probes are small molecules (paragraph 0069), an amplification step between the separating step and the determining step (paragraph 0105), the determining step is performed by nucleic acid sequencing (paragraph 0104 and 0122), sequencing is high throughput digital nucleic acid sequencing (paragraphs 0039 and 0122-0124), the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 1,000,000 (paragraphs 0097-0098 and 0138), the sequences of at least 1,000,000 encoding probes are determined in parallel (paragraphs 0097-0098, 0104, and 0138), the known spatial pattern is determined by histological features of the sample (paragraphs 0036 and 0038), software programmed hardware

performs at least two steps of the delivering step, the separation step, the determining step, and the associating step (paragraphs 0123-0124). Roth et al teaches the probe regions of the encoded probes are proteins (paragraph 0092) and the separating step is accomplished by encoded probes that interact with the biological targets being captured by an affinity capture agent (paragraph 0027), Separation of interacting probes and non-interacting probes is by washing (paragraphs 0084-0085). Roth et al also teaches two oligonucleotide probes are delivered for each of the multiple nucleic acid targets (paragraph 0083) and the coupling step is performed by ligation (paragraph 0083). Brenner et al teaches the attachment of oligonucleotide tags to a variety of types of biological macromolecules for the purpose of identification by sequencing the oligonucleotide tags (*e.g.*, paragraphs 0030-0031). It would have been obvious for one of ordinary skill in the art at the time the invention was made to have prepared 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 coding tags comprise oligonucleotides, in view of Roth et al teaching the coding tags are unique and fluorescent for scanning based detection (paragraphs 0031 and 0055), and in light of Brenner et al teaching the attachment of oligonucleotide tags to a variety of types of biological macromolecules for the purpose of identification by sequencing the oligonucleotide tags (*e.g.*, paragraphs 0030-0031). All that is achieved is the known and expected result. Applicants have asserted (Interview Summary mailed |3 31, 2015) that the references do not teach a sequencing step to determine the tag sequence and identity. This argument is not persuasive because Brenner et al clearly teaches such a sequencing step in at least the following locations: paragraphs 0012, 0033, and 0063).

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

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4745	(((high adj density) or (high adj resolution)) near5 (array$ or microarray$)) near10 (dna or (nucleic adj adic) or protein or antibod$)	US-PGPUB; USPAT	OR	ON	2015/05/27 19:55
L2	3023278	@rlad<"20110405"	US-PGPUB; USPAT	OR	ON	2015/05/27 19:56
L3	3730	l1 and l2	US-PGPUB; USPAT	OR	ON	2015/05/27 19:56
L4	408179	@pd>"20141016"	US-PGPUB; USPAT	OR	ON	2015/05/27 19:56
L5	72	l3 and l4	US-PGPUB; USPAT	OR	ON	2015/05/27 19:56

5/27/2015 7:58:55 PM
C:\Users\jmartinell\Documents\EAST\Workspaces\13-080616-c.wsp

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	SALLY MERKLING	1773

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

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

CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014	10/16/2014	05/28/2015					
	1	÷	✓	✓	✓					
	2	÷	✓	✓	✓					
	3	÷	✓	✓	✓					
	4	÷	✓	✓	✓					
	5	÷	✓	✓	✓					
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	34	÷	✓	✓	✓					
	35	÷	✓	-	-					
	36	÷	✓	✓	✓					

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CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014	10/16/2014	05/28/2015					
	37	÷	✓	✓	✓					
	38	÷	✓	✓	✓					
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	68			✓	✓					
	69			✓	✓					
	70			✓	✓					
	71			✓	✓					
	72			✓	✓					

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	**Art Unit**
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014	10/16/2014	05/28/2015					
	73			✓	✓					
	74			✓	✓					
	75			✓	✓					
	76			✓	✓					
	77			✓	✓					

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	Art Unit
	JAMES MARTINELL	1634

CPC- SEARCHED		
Symbol	Date	Examiner
C12Q1/6837, 6874; C12Q2565/501, 513, 50, 514, 518, 519, 525, 531, 537, 543, 549; G01N21/6452, 8903; 33/53	4/3/14	JM
Updated	10/16/14	JM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST text search (printout attached)	4/3/14	JM
EAST text search (printout attached)	10/16/14	JM
EAST text search (printout attached))	5/27/15	JM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/JAMES MARTINELL/ Primary Examiner.Art Unit 1634

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-7,393,665	07-01-2008	Brenner	
	2.	US-7,407,757	08-2008	Brenner	
	3.	US-7,537,897	05-26-2009	Brenner et al.	
	4.	US-7,579,153	08-25-2009	Brenner et al.	
	5.	US-7,635,566	12-22-2009	Brenner	
	6.	US-8,337,851	12-25-2012	Aukerman et al.	
	7.	US-8,343,500	01-01-2013	Wraith et al.	
	8.	US-2003/0162216	08-28-2003	Gold et al.	
	9.	US-2012/0195810	08-02-2012	Cohen et al.	
	10.	US-2013/0109595	05-02-2013	Routenberg	
	11.	US-2013/0096033	04-18-2013	Routenberg	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	12.	WO-2014/210223	12-2014	Chee et al.		
	13.	WO-2014/210225	12-2014	Chee et al.		

Examiner Signature	/James Martinell/	Date Considered	05/28/2015

*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	14.	Response to Office Action for CA 2794522, dated 17 September 2014	
	15.	Response to Second Examination Report for CN 201180017696.3, filed 17 September 2014	
	16.	Third Examination Report for CN 201180017696.3, mailed 27 January 2015	
	17.	Response to Third Examination Report for CN 201180017696.3, filed 13 April 2015	
	18.	European Examination Report for EP 11766613.1, dated 22 August 2014	
	19.	Response to European Examination Report for EP 11766613.1, filed 8 January 2015	
	20.	Office Action for US 13/442,637, mailed 22 January 2015	
	21.	Extended European Search Report for EP 12767937.1-1403, mailed 18 November 2014	
	22.	International Search Report and Written Opinion of PCT/US14/29691, mailed 19 August 2014	

/James Martinell/ 05/28/2015

sd-660351

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

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/080,616
				Filing Date	April 5, 2011
				First Named Inventor	Mark S. CHEE
				Art Unit	1634
				Examiner Name	J. Martinell
Sheet	2	of	2	Attorney Docket Number	699932000200

	23.	International Search Report and Written Opinion of PCT/US14/44191, mailed 7 November 2014	
	24.	International Search Report and Written Opinion of PCT/US14/44196, mailed 7 November 2014	
	25.	International Search Report and Written Opinion of PCT/US14/64588, mailed 11 March 2015	
	26.	ALEXANDER VALENCIA et al., "mRNA-display-based selections for proteins with desired functions: A protease-substrate case study," Biotechnology Progress, 2008, 24(3): 561-569	
	27.	OSADA et al., "Epitope mapping using ribosome display in a resconstituted cell-free protein synthesis system," Journal of Biochemistry, 2009, 145(5):693-700	
	28.	ROUNTENBERG et al., "Microfluidic probe: a new tool for integrating microfluidic environments and electronic wafer-probing," Lab Chip, 29 October 2009, 10: 123-127	
	29.	WEICHHART et al., "Functional selection of vaccine candidate peptides from Staphylococcus aureus whole-genome expression libraries in vitro," Infection and Immunity, 2003, 71(8):4333-4641	

Examiner Signature	/James Martinell/	Date Considered	05/28/2015

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

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

sd-660351

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

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: November 30, 2015 Electronic Signature for Nicole San Nicolas: /Nicole San Nicolas/

Docket No.: 699932000200
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Mark S. CHEE Application No.: 13/080,616 Filed: April 5, 2011 For: SPATIALLY ENCODED BIOLOGICAL ASSAYS	Confirmation No.: 2142 Art Unit: 1634 Examiner: James Martinell

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. 1.111

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

Dear Commissioner:

INTRODUCTORY COMMENTS

This is in response to an Office action herein, mailed June 1, 2015, time for response to which was set to expire September 1, 2015. Filed herein is a fee for an extension of time of three months, extending the deadline for a response to December 1, 2015. Accordingly, this response is timely filed. Reconsideration and allowance of the pending claims, as amended, in light of the remarks presented herein are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 10 of this paper.

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Curio v Prognosys

AMENDMENTS TO THE CLAIMS

1. (currently amended): A method to determine ~~a spatial pattern of~~ the abundance or activity or both of a biological target in a sample, comprising the following steps:

delivering encoded probes for a biological target to multiple sites in a sample affixed to a support, wherein each encoded probe comprises a probe region capable of specific binding to the biological target and a coding tag comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered;

allowing the encoded probes to interact with the biological target;

separating encoded probes specifically bound to the biological target from encoded probes not specifically bound to the biological target;

pooling encoded probes specifically bound to the biological target;

determining all or a portion of the coding tag oligonucleotide sequence of the encoded probe ~~specifically bound to the biological target~~ in the pool by performing a polynucleotide sequencing reaction of the encoded probe, thereby identifying the location of the site to which the encoded probe is delivered; and

associating the abundance or activity or both of the biological target to the locations of the multiple sites in the sample ~~to determine a spatial pattern of abundance or activity or both of the biological target in the sample~~.

2. (previously presented): The method of claim 1, wherein the biological target is a nucleic acid and the encoded probes are oligonucleotides.

3. (previously presented): The method of claim 2, wherein there are two encoded probes for the nucleic acid target at each of the multiple sites in the sample.

4. (previously presented): The method of claim 1, wherein the biological target is a protein, the probe regions of the encoded probes are proteins, and the coding tags comprise oligonucleotides.

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5. (previously presented): The method of claim 4, wherein the biological target comprises an enzyme.

6. (previously presented): The method of claim 1, wherein each of the probe regions of the encoded probes comprises an antibody, an aptamer, and/or a small molecule that is capable of specific binding to the biological target.

7-8. (canceled)

9. (previously presented): The method of claim 1, further comprising an amplification step between the separating step and the determining step.

10. (previously presented): The method of claim 1, wherein the determining step is performed by nucleic acid sequencing or high-throughput sequencing or high-throughput digital nucleic acid sequencing.

11. (canceled)

12. (previously presented): The method of claim 1, wherein multiple biological targets in the sample are assayed and the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 100, 1,000, 10,000, 100,000, or 1,000,000.

13-19. (canceled)

20. (previously presented): The method of claim 1, wherein the sequences of at least one hundred thousand, at least five hundred thousand, or at least one million encoded probes are determined in parallel.

21-23. (canceled)

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24. (previously presented): The method of claim 1, wherein software programmed hardware performs at least two steps of the delivering step, the separation step, the determining step and the associating step.

25. (previously presented): The method of claim 1, wherein the probe regions of the encoded probes are proteins and the separating step is accomplished by capturing encoded probes specifically bound to the biological target using an affinity capture agent.

26. (previously presented): The method of claim 1, wherein the probe regions of the encoded probes are nucleic acids and the separating step is accomplished by washing the sample.

27. (currently amended): A method to determine ~~a spatial pattern of~~ the abundance or activity or both of a nucleic acid target in a sample, comprising the following steps:

delivering an oligonucleotide probe capable of specific hybridization with a nucleic acid target to multiple sites in a sample affixed to a support;

allowing the oligonucleotide probe to hybridize with the nucleic acid target;

washing unhybridized oligonucleotide probe from the sample;

delivering one or more encoding agents to the multiple sites in the sample, wherein the one or more encoding agents delivered to each site comprise an oligonucleotide that identifies the location of the site in the sample;

coupling the one or more encoding agents and the oligonucleotide probe delivered to each site to form an encoded probe specifically hybridized with the nucleic acid target at the site;

pooling encoded probes specifically hybridized with the nucleic acid target;

determining all or a portion of the one or more encoding agent oligonucleotide sequences of the encoded probe ~~specifically hybridized with the nucleic acid target~~ in the pool by performing a polynucleotide sequencing reaction of the encoded probe, thereby identifying the location of the site to which the one or more encoding agents are delivered; and

associating the abundance or activity or both of nucleic acid target to the locations of the multiple sites in the sample ~~to determine a spatial pattern of abundance or activity or both of the nucleic acid target in the sample~~.

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28. (previously presented): The method of claim 27, wherein multiple nucleic acid targets in the sample are assayed and the product of the multiple nucleic acid targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 10,000, 100,000, or 1,000,000.

29-33. (canceled)

34. (previously presented): The method of claim 27, wherein the sequences of at least one hundred thousand or at least one million encoded probes are determined in parallel.

35. (canceled)

36. (previously presented): The method of claim 27, wherein two oligonucleotide probes are delivered for the nucleic acid target.

37. (previously presented): The method of claim 27, wherein the coupling step is performed by ligation.

38. (previously presented): The method of claim 27, wherein the coupling step is performed by extension followed by ligation.

39. (previously presented): The method of claim 27, further comprising an amplification step between the coupling step and the determining step.

40-54. (canceled)

55. (currently amended): A method of determining ~~a spatial pattern of~~ the abundance or activity or both of a biological target in a sample, comprising:

delivering a probe capable of specific binding to a biological target to multiple sites in a sample affixed to a support;

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allowing the probe to interact with the biological target at each of the multiple sites in the sample;

delivering an encoding agent to each of the multiple sites in the sample, wherein the encoding agent delivered to each site comprises an oligonucleotide that identifies the location of the site in the sample;

coupling the encoding agent to the probe delivered to each of the multiple sites to form an encoded probe at each of the multiple sites;

pooling encoded probes specifically bound to the biological target;

determining all or a portion of the encoding agent oligonucleotide sequence of the encoded probe ~~specifically bound to the biological target~~ in the pool by performing a polynucleotide sequencing reaction of the encoded probe, thereby identifying the location of the site to which the encoding agent is delivered; and

associating the abundance or activity or both of the biological target at each of the multiple sites to the locations of the multiple sites in the sample ~~to determine a spatial pattern of abundance or activity or both of the biological target in the sample~~.

56. (previously presented): The method of claim 55, wherein one or more biological targets in the sample are assayed in parallel.

57. (previously presented): The method of claim 56, wherein for each biological target, one or more probes capable of specific binding to the biological target are delivered to the multiple sites in the sample.

58. (previously presented): The method of claim 55, wherein at least two encoding agents are delivered to each of the multiple sites in the sample and are coupled to the probe delivered to the site to form an encoded probe comprising the at least two encoding agents.

59. (previously presented): The method of claim 55, wherein the biological target comprises a nucleic acid and the probe comprises an oligonucleotide.

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60. (previously presented): The method of claim 55, wherein the biological target comprises a protein and the probe comprises a protein.

61. (previously presented): The method of claim 55, wherein the biological target comprises an enzyme, and the probe comprises a substrate or putative substrate for the enzyme.

62. (previously presented): The method of claim 55, wherein the probe comprises an affinity capture agent, antibody, aptamer, or small molecule.

63. (previously presented): The method of claim 55, further comprising amplifying all or a portion of a sequence of the encoded probe.

64. (previously presented): The method of claim 55, wherein the determining step is performed by nucleic acid sequencing or high-throughput sequencing.

65. (previously presented): The method of claim 55, wherein multiple biological targets in the sample are assayed and the product of the multiple biological targets being assayed and the multiple sites in the sample is greater than 20, 50, 75, 100, 1,000, 10,000, 100,000, or 1,000,000.

66. (previously presented): The method of claim 55, wherein the sequences of at least one hundred thousand, at least five hundred thousand, or at least one million encoded probes are determined in parallel.

67. (previously presented): The method of claim 55, wherein the probe for the biological target and/or the encoding agent are delivered to the multiple sites in the sample according to a known spatial pattern.

68. (previously presented): The method of claim 55, wherein software programmed hardware performs at least two steps of the delivering steps, the coupling step, the determining step, and the associating step.

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69. (previously presented): The method of claim 55, further comprising separating probes specifically bound to the biological target from probes not specifically bound to the biological target.

70. (previously presented): The method of claim 69, wherein the separating step is accomplished by washing the sample.

71. (previously presented): The method of claim 55, wherein the coupling step is performed by ligation, or performed by extension followed by ligation.

72. (previously presented): The method of claim 55, wherein the biological target is a nucleic acid and the probe is capable of specific hybridization with the nucleic acid target, wherein the probe sequence identifies the nucleic acid target.

73. (previously presented): The method of claim 72, wherein in the determining step, the encoded probe sequence being determined comprises all or a portion of the probe sequence and all or a portion of the encoding agent oligonucleotide sequence.

74. (previously presented): The method of claim 73, further comprising quantification of the encoded probe sequence being determined, wherein:

the determined probe sequence identifies the nucleic acid target;

the determined encoding agent oligonucleotide sequence identifies the location of the site at which the probe specific hybridizes with the nucleic acid target; and

the quantity of the encoded probe sequence indicates the amount of the probe specifically hybridized with the nucleic acid target at the site in the sample, and thereby indicates the abundance or activity of the nucleic acid target at the site in the sample.

75. (previously presented): The method of claim 55, wherein the biological target is a protein, the probe is capable of specific binding to the protein target and comprises an oligonucleotide sequence that identifies the protein target.

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76. (previously presented): The method of claim 75, wherein in the determining step, the encoded probe sequence being determined comprises all or a portion of the probe oligonucleotide sequence and all or a portion of the encoding agent oligonucleotide sequence.

77. (previously presented): The method of claim 76, further comprising quantification of the encoded probe sequence being determined, wherein:

the determined probe oligonucleotide sequence identifies the protein target;

the determined encoding agent oligonucleotide sequence identifies the location of the site at which the probe specific binds to the protein target; and

the quantity of the encoded probe sequence indicates the amount of the probe specifically binds to the protein target at the site in the sample, and thereby indicates the abundance or activity of the protein target at the site in the sample.

78. (new): The method of claim 1, wherein in the associating step, the abundance or activity or both of the biological target is associated to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the biological target in the sample.

79. (new): The method of claim 27, wherein in the associating step, the abundance or activity or both of the nucleic acid target is associated to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the nucleic acid target in the sample.

80. (new): The method of claim 55, wherein in the associating step, the abundance or activity or both of the biological target is associated to the locations of the multiple sites in the sample to determine a spatial pattern of abundance or activity or both of the biological target in the sample.

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REMARKS

Claim Status and Amendments

Claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-77 are pending. Claims 1, 27, and 55 are amended, and new claims 78-80 are added. Support for the amendments herein is found throughout the specification as originally filed, including in the original claims. Exemplary for the amendments can be found at paragraphs [0023], [0024], [0028], [0032], [0039], [0049]-[0051], [0069], and [0071]. For example, in some aspects, "[t]he 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." The original specification at paragraph [0023]. In some aspects, after an encoding agent is ligated to a target-specific oligonucleotide that hybridizes to the target nucleic acid in the biological sample, the ligated constructs (*i.e.*, encoded probes) "are then eluted from the biological sample, pooled, and . . . are sequenced by, *e.g.*, high throughput or 'next generation' sequencing." The original specification at paragraph [0049].

No new matter is added by way of the amendments herein. After entry of the amendments, claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-80 will be pending. Reconsideration and allowance of the claims as amended are respectfully requested.

Claim Objection

Claim 55 stands objected to because line 8 of the claim allegedly contains a typographical error in which "comprise" allegedly should be changed to "comprises." Applicant notes that the same objection was raised in the final Office Action dated October 21, 2014, and was addressed in Applicant's amendment and response submitted February 23, 2015.

With respect, Applicant submits that line 8 of claim 55 already recites "comprises." As a result, the objection appears moot. Withdrawal is respectfully requested.

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The Rejections under 35 U.S.C. § 103(a)

Claims 1-6, 9, 10, 12, 20, 24-28, 34, 36-39, and 55-77 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Roth *et al.*, US2006/0046313 (hereinafter "Roth") in view of Brenner *et al.*, US2007/0172873 (hereinafter "Brenner"). Applicant respectfully requests reconsideration.

The Office bears the initial burden to make a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, (Fed. Cir. 1993); *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). To make a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). There must be shown some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the teachings of the references to arrive at something within the claims, with a reasonable expectation of success. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398; 82 U.S.P.Q.2d 1385; 127 S. Ct. 1727 (2007); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Office must provide some articulated reason why the claimed invention would have been obvious to one of ordinary skill in the art. MPEP § 2142; *KSR*, 82 U.S.P.Q.2d at 1396. The fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEP § 2143.01. Furthermore, if a modification renders a reference unsatisfactory for its intended purpose, or changes the principle of operation of a reference, the teachings of that reference do not render the claimed invention obvious. MPEP § 2143.01. Finally, in the analysis of prior art references, it is improper to exercise hindsight to select bits and pieces from the references to create a motivation to modify that is not found in the references, but only in the applicant's disclosure. *In re Dow Chemical Co.* 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Here, a *prima facie* case of obviousness has not been established.

Instant claim 1 recites, *inter alia*:

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delivering encoded probes for a biological target to multiple sites in a sample affixed to a support, wherein each encoded probe comprises a probe region capable of specific binding to the biological target and a coding tag comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered;

allowing the encoded probes to interact with the biological target;

separating encoded probes specifically bound to the biological target from encoded probes not specifically bound to the biological target;

pooling encoded probes specifically bound to the biological target;

determining all or a portion of the coding tag oligonucleotide sequence of the encoded probe in the pool by performing a polynucleotide sequencing reaction of the encoded probe, thereby identifying the location of the site to which the encoded probe is delivered; and

associating the abundance or activity or both of the biological target to the locations of the multiple sites in the sample.

Similar to claim 1, independent claims 27 and 55 also recite, *inter alia*:

(1) an encoded probe that identifies the location of the site to which the encoded probe (or encoding agent) is delivered in a sample;

(2) that the encoded probe comprises an oligonucleotide that identifies the location of the site to which the encoded probe (or encoding agent) is delivered in the sample; and

(3) pooling the encoded probes specifically bound to the biological target (or specifically hybridized with the nucleic acid target) for sequence determination.

Therefore, claims 27 and 55 are not separately argued.

Roth discloses the use of probes labeled with Composite Organic-Inorganic Nanoparticles (COINs) for biological assays. COINs are typically clusters of several primary metal crystal particles with Raman-active organic compounds trapped in the junctions of the primary particles or embedded in the metal atoms, and intrinsically produce Surface Enhanced Raman Scattering (SERS) signals upon laser irradiation. *See* Roth at the abstract and at paragraph [0063]. Since most biological targets are not Raman-active, upon binding of a COIN-labeled probe to a biological target, shifts in the Raman spectrum can be used to assay the binding. *Id.*

The Office appears to acknowledge that Roth fails to teach any coding tag comprising an oligonucleotide, because Brenner is cited as allegedly teaching attachment of oligonucleotide tags to a variety of biological macromolecules for the purpose of identification by sequencing the oligonucleotide tags. Even assuming this is the case, however, the cited art still fails to teach or even suggest each and every claim element.

A. The cited art fails to teach or suggest any encoded probe that identifies the location of the site to which the encoded probe is delivered in a sample

Roth teaches lysing tissue samples in order to form "arrays of cell lysates." Roth at paragraph [0033], which is cited by the Office. These cell lysates contain the target molecules to be detected by the COIN-labeled probes. *See* Roth at paragraph [0033], and Figure 3 reproduced below. The cell lysates are "immobilized at (for example, spotted onto) individual defined locations" on an array, and the cell lysate spots are then contacted with a mixture of COIN-labeled probes. *Id.* For example, as shown in Figure 3, extracted cell proteins **330**, **331**, and **332** identify locations X_1X_1, X_1X_2, and X_2X_2, respectfully. *Id.* Since all of the cell lysate spots X_1X_1, X_1X_2, and X_2X_2 are contacted with the mixture of COIN-labeled probes, each COIN-labeled probe in the mixture does not identify the location to which it is delivered. Rather, the "defined locations" on the array are identified by the immobilized extracted cell proteins (*i.e.*, the targets), not by the COINs or COIN-labeled probes.

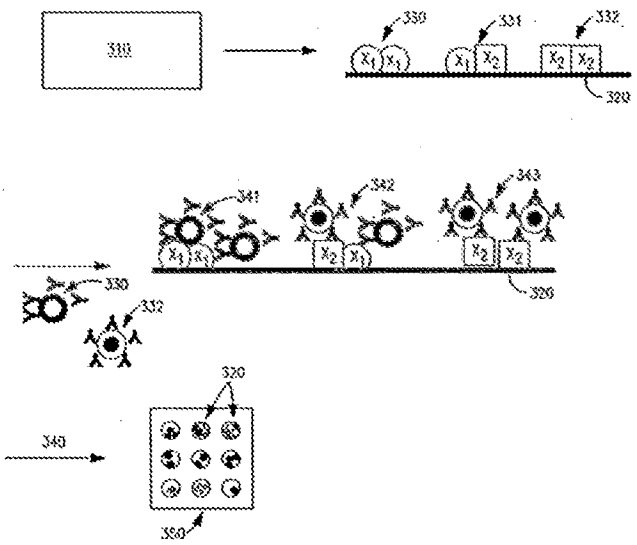


FIG. 3

COINs intrinsically produce SERS signals upon laser irradiation, and may be used to label any probe for an analyte. *See* Roth at the abstract and paragraph [0092]. The Office has not identified any teaching or suggestion that the COINs of Roth are encoded with spatial information of where the COINs or COIN-labeled probes are delivered, much less that the COINs comprise an oligonucleotide that identifies a location to which the COINs or COIN-labeled probes are delivered.

In view of the above, the Office has not identified any teaching or suggestion in Roth of any COIN that identifies the location of the site to which a COIN-labeled probe is delivered.

Brenner discloses methods and compositions for counting molecules in a sample, wherein each molecule is labeled with an oligonucleotide tag. *See* Brenner at the abstract. The tagged molecules are in a mixture, and the number of different tag sequences in the mixture is counted by sorting the tags into separate aliquots. *See* Brenner at Figure 1B. The Office has not identified anything in Brenner that teaches or even suggests that its oligonucleotide tags identify the location in a sample to which a tag or tagged molecule is delivered. In fact, Brenner's oligonucleotide tags or tagged molecules are not delivered to any specific location -- they simply exist in a mixture waiting to be sorted by their sequence identity.

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In sum, the skilled artisan would have no reason to combine the teachings of Roth and Brenner, because neither reference teaches or even suggests any encoded probe that identifies the location to which it is delivered. The Office has not shown that the skilled artisan would have arrived at the present claim with any reasonable expectation of success. For this reason alone, a *prima facie* case has not been established.

B. The cited art fails to teach or suggest any encoded probe comprising an oligonucleotide that identifies the location of the site to which the encoded probe is delivered in a sample

As discussed above, the Office has not identified any teaching or suggestion in Roth of any COIN that identifies the location of the site to which a COIN-labeled probe is delivered, let alone that the COIN comprises any oligonucleotide that identifies the location.

As a first matter, the COINs are composite organic-inorganic nanoparticles, which the Office has not shown to comprise any oligonucleotide. Although Roth at paragraph [0140] teaches "a COIN-labeled oligonucleotide that is complementary to the target nucleic acid sequence," such disclosure merely teaches that the probe region can be an oligonucleotide, not that the COIN (the alleged coding tag) is an oligonucleotide. Furthermore, the Office has not identified any teaching or suggestion that the oligonucleotide portion of Roth's COIN-labeled oligonucleotide probe identifies the location to which the probe is delivered.

Brenner allegedly teaches labeling a molecule with an oligonucleotide tag for the purpose of identification by sequencing the oligonucleotide tag. However, Brenner's oligonucleotide tags or tagged molecules are not delivered to any specific location. As discussed above, Brenner is concerned with counting the number of oligonucleotide tags in a mixture by sequencing, and the Office has not shown that Brenner's oligonucleotide tags encode any spatial information. Thus, even assuming Roth's COINs could comprise an oligonucleotide tag as disclosed in Brenner, the skilled artisan still would not arrive at the present claim with a reasonable expectation of success. This is because neither Roth's COIN nor Brenner's oligonucleotide tag

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identifies the location of the site to which a COIN-labeled probe or an oligonucleotide-tagged molecule is delivered. In fact, Roth specifically teaches that it is the SERS signals, not any oligonucleotide sequence of the COINs, that are collected, associated with the positions on the array, and used to characterize the target proteins. *See* Roth at paragraph [0032].

In view of the above, the skilled artisan would have no reason to combine the teachings of Roth and Brenner, let alone arrive at the present claim with a reasonable expectation of success. A *prima facie* case has not been established, and the rejection should be withdrawn.

C. The cited art fails to teach or suggest pooling the encoded probes specifically bound to the biological target for sequence determination

Instant claim 1 recites, *inter alia*, a step of pooling encoded probes specifically bound to the biological target for sequence determination. A sequence of the encoded probes in the pool is then determined, and a sequence of the coding tag oligonucleotide identifies the location to which its encoded probe is delivered. The Examiner has not identified any teaching or even suggestion in the cited art of the claim elements.

Roth teaches immobilizing extracted cell proteins at individual defined locations on an array, and the cell lysate spots are then contacted with a mixture of COIN-labeled probes for detection of surface enhances Raman scattering (SERS) signals from the immobilized complexes at the defined locations. *See* Roth at paragraph [0033] and Figure 3. Thus, Roth requires that its COIN-labeled probes (the alleged encoded probes) remain immobilized at the individual defined locations during signal detection, such that SERS signals from each location can be detected from that location. Such disclosure is fundamentally different from the present claims, which recite pooling encoded probes for sequence determination, wherein the sequence is then used to identify the location to which an encoding agent or encoded probe is delivered. In fact, if one were to pool Roth's COIN-labeled probes, the probes from the individual locations would be mixed together -- it would be impossible to isolate the SERS signals from individual locations and to "map" the SERS signals back to the individual location. This is because the COIN or COIN-probe, if not

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immobilized at a known location, contains no information to identify that location. In contrast, in the present claims, when the encoded probes are pooled, each encoded probe comprises an oligonucleotide of which sequence can be determined to identify the location to which the encoding agent or encoded probe is delivered.

Even assuming Brenner teaches attachment of oligonucleotide tags to a variety of biological macromolecules for the purpose of identification by sequencing the oligonucleotide tags, the Office still has not articulated any reason or motivation that the skilled artisan would have to combine and/or modify Roth and Brenner in order to arrive at the present claims, which recite a step of pooling the encoded probes for sequence determination. In fact, as detailed below, the skilled artisan would have been dissuaded from doing so.

D. There is no reason to combine the cited references

As discussed above, the Office acknowledges that Roth fails to teach or even suggest sequencing any oligonucleotide in the COINs, and that is why Brenner is cited. However, the mere fact that references can be combined or modified, or the mere statement that modifications of the cited art to meet the claimed invention would have been within the capabilities of one of ordinary skill in the art, is not sufficient to establish *prima facie* obviousness. MPEP § 2143.01, subsections III and IV. Therefore, the test of obviousness is not whether modifying the Roth method in view of Brenner could have been done, but whether a skilled artisan would have had a reason to do it with a reasonable expectation of success to arrive at the present claims. Here, the Office has not carried its burden to make a *prima facie* case.

First, the Office's proposed modification requires that Roth's COIN comprises an oligonucleotide, and that sequencing of the COIN is performed for the purpose of identifying the location of a COIN-labeled probe on an array. The skilled artisan, however, would have no reason to deviate from the specific teachings of Roth by getting rid of the detection of SERS signals and instead using sequencing as the readout. After all, the Roth method relies on the detection of SERS signals and the distinguishable Raman signature (the "COIN signature") that is characteristic of the

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binding to a biological target the sample. *See* Roth at paragraph [0012] and Figure 2. The Office has not shown why its proposed modification would have been desirable. If anything, such a modification would have contradicted the principle of operation of Roth and/or rendered the Roth method unsatisfactory for its intended purpose. The Office is respectfully reminded that if a proposed modification changes the principle of operation of a reference, or renders the reference unsatisfactory for its intended purpose, the teachings of that reference do not render the claimed invention obvious. MPEP § 2143.01.

Second, as discussed above, Roth requires that its COIN-labeled probes (the alleged encoded probes) remain immobilized at the individual defined locations during signal detection, such that SERS signals from each location can be detected from an individual location and "mapped" back to that location. To arrive at the present claims, the skilled artisan would have to pool Roth's COIN-labeled probes such that the probes from the individual locations would be mixed together. Since the COIN or COIN-probe, if not already immobilized at a known location, contains no information to identify that location, the modification of Roth would render it impossible to isolate the SERS signals from individual locations and to "map" the SERS signals back to the individual location. Thus, the modification would have rendered the Roth method completely unsatisfactory for its intended purpose. The Office is again respectfully reminded that if a proposed modification changes the principle of operation of a reference, or renders the reference unsatisfactory for its intended purpose, the teachings of that reference do not render the claimed invention obvious. MPEP § 2143.01.

In sum, Brenner fails to remedy the deficiencies of Roth, and a *prima facie* case has not been established. Applicant's arguments also apply to claims dependent from claim 1, and claims 27 and 55 and dependent claims therefrom. Withdrawal of the rejections is respectfully requested.

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CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 699932000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 30, 2015

Respectfully submitted,

Electronic signature: / Bu Yin /

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Electronic Patent Application Fee Transmittal

Application Number:	13080616
Filing Date:	05-Apr-2011
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Filer:	Bu Yin/NICOLE SAN NICOLAS
Attorney Docket Number:	699932000200

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
			Total in USD ($)	**700**

Electronic Acknowledgement Receipt

EFS ID:	24213085
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/NICOLE SAN NICOLAS
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	30-NOV-2015
Filing Date:	05-APR-2011
Time Stamp:	19:06:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$700
RAM confirmation Number	7498
Deposit Account	031952
Authorized User	YIN, BU
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		699932000200_resp_to_NFOA.pdf	162041 ee9926027844e44252ad4413ee983f6d87679c46	yes	19

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Amendment Copy Claims/Response to Suggested Claims	2	9
Applicant Arguments/Remarks Made in an Amendment	10	19

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30481 97ec6e24884e9a629ed2c722be667c62fdb1ae3b	no	2

Warnings:

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Total Files Size (in bytes):	192522

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

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

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

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/080,616	Filing Date 04/05/2011	☐ 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 $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ 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

AMENDMENT **11/30/2015**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 46	Minus	** 57	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***4	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ 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.
** 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 number found in the appropriate box in column 1.

LIE
/MARGARET BYARS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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SAN DIEGO, CA 92130-2040

EXAMINER
MARTINELL, JAMES

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/18/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

TITLE OF INVENTION: SPATIALLY ENCODED BIOLOGICAL ASSAYS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	05/18/2016

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

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

HOW TO REPLY TO THIS NOTICE:

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

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

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

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

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

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

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Curio EX1012-p. 532
Curio v Prognosys

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

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

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

25225 7590 02/18/2016
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

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

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

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

TITLE OF INVENTION: SPATIALLY ENCODED BIOLOGICAL ASSAYS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	05/18/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
MARTINELL, JAMES	1634	435-006110

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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

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

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

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

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

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

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

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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

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Curio v Prognosys

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.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

25225 7590 02/18/2016

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EXAMINER	
MARTINELL, JAMES	

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1634	

DATE MAILED: 02/18/2016

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

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

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

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

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Curio v Prognosys

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

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

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 13/080,616	Applicant(s) CHEE, MARK S.	
	Examiner JAMES MARTINELL	Art Unit 1634	AIA (First Inventor to File) Status No

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment filed 11/30/15*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-6,9,10,12,20,24-28,34,36-39 and 55-80*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

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

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JAMES MARTINELL/
Primary Examiner, Art Unit 1634

UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET

CONFIRMATION NO. 2142

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/080,616	04/05/2011	435	1634	699932000200

APPLICANTS

INVENTORS

Mark S. Chee, Encinitas, CA;

**** CONTINUING DATA ***************************

This appln claims benefit of 61/321,124 04/05/2010

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **

04/15/2011

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /JAMES MARTINELL/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	5	57	4

ADDRESS

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040
UNITED STATES

TITLE

SPATIALLY ENCODED BIOLOGICAL ASSAYS

FILING FEE RECEIVED		
1534	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	JAMES MARTINELL	1634

CPC						
Symbol					**Type**	**Version**
C40B		60	/	04	F	2013-01-01
C12Q		1	/	6837	I	2013-01-01
C40B		30	/	04	I	2013-01-01
G01N		33	/	6845	I	2013-01-01
G01N		2458	/	10	A	2013-01-01
C12Q		1	/	6809	I	2013-01-01
C12Q		1	/	6834	I	2013-01-01
C12Q		1	/	6841	I	2013-01-01
C12Q		1	/	6869	I	2013-01-01
			/			
			/			
			/			
			/			
			/			
			/			

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
C12Q		1	/	6837	I	1	1	2013-01-01
C12Q		2565	/	515	A	1	2	2013-01-01
C12Q		1	/	6869	I	2	1	2013-01-01
C12Q		2535	/	122	A	2	2	2013-01-01
C12Q		2543	/	10	A	2	3	2013-01-01
C12Q		2563	/	179	A	2	4	2013-01-01
C12Q		1	/	6841	I	3	1	2013-01-01
C12Q		2535	/	122	A	3	2	2013-01-01
C12Q		2543	/	10	A	3	3	2013-01-01
C12Q		2563	/	179	A	3	4	2013-01-01
C12Q		1	/	6834	I	4	1	2013-01-01
C12Q		2535	/	122	A	4	2	2013-01-01

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 46	
/JAMES MARTINELL/ Primary Examiner.Art Unit 1634 (Primary Examiner)	02/07/2016 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	JAMES MARTINELL	1634

C12Q		2543	/	10	A	4	3	2013-01-01
C12Q		2563	/	179	A	4	4	2013-01-01
C12Q		1	/	6809	I	5	1	2013-01-01
C12Q		2535	/	122	A	5	2	2013-01-01
C12Q		2543	/	10	A	5	3	2013-01-01
C12Q		2563	/	179	A	5	4	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	46	
/JAMES MARTINELL/ Primary Examiner.Art Unit 1634	02/07/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	JAMES MARTINELL	1634

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
435	6.11	C	1	2	Q	1 / 68 (2006.0)						
CROSS REFERENCE(S)		G	0	1	N	33 / 53 (2006.01.01)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											
435	7.1											

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	46	
/JAMES MARTINELL/ Primary Examiner.Art Unit 1634	02/07/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	JAMES MARTINELL	1634

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

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	-	17	-	33	-	49	33	65						
2	2	-	18	17	34	-	50	34	66						
3	3	-	19	-	35	-	51	35	67						
4	4	10	20	18	36	-	52	36	68						
5	5	-	21	19	37	-	53	37	69						
6	6	-	22	20	38	-	54	38	70						
-	7	-	23	21	39	23	55	39	71						
-	8	11	24	-	40	24	56	40	72						
7	9	12	25	-	41	25	57	41	73						
8	10	13	26	-	42	26	58	42	74						
-	11	15	27	-	43	27	59	43	75						
9	12	16	28	-	44	28	60	44	76						
-	13	-	29	-	45	29	61	45	77						
-	14	-	30	-	46	30	62	14	78						
-	15	-	31	-	47	31	63	22	79						
-	16	-	32	-	48	32	64	46	80						

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 46	
/JAMES MARTINELL/ Primary Examiner.Art Unit 1634 (Primary Examiner)	02/07/2016 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	Art Unit
	JAMES MARTINELL	1634

CPC- SEARCHED		
Symbol	Date	Examiner
C12Q1/6837, 6874; C12Q2565/501, 513, 50, 514, 518, 519, 525, 531, 537, 543, 549; G01N21/6452, 8903; 33/53	4/3/14	JM
Updated	10/16/14	JM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST text search (printout attached)	4/3/14	JM
EAST text search (printout attached)	10/16/14	JM
EAST text search (printout attached))	5/27/15	JM
EAST text search (2 sets of printouts attached)	2/7/16	JM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	PGPUBS (2 sets of printouts attached)	2/7/16	JM

	/JAMES MARTINELL/ Primary Examiner.Art Unit 1634

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	119	((array$ or microarray$ or support$ or surface) near5 (dna or (nucleic adj acid) or protein or antibod$)) same (probe near5 pool$6) same (probe near5 sequenc$6)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2016/02/07 13:09
L2	3105829	@rlad<"20110405"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2016/02/07 13:09
L3	97	l1 and l2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2016/02/07 13:09

2/7/2016 1:14:26 PM
C:\Users\jmartinell\Documents\EAST\Workspaces\13-080616-e.wsp

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	6064	(((high adj density) or (high adj resolution)) near5 (array$ or microarray$)) near10 (dna or (nucleic adj acid) or protein or antibod$)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2016/02/07 12:46
L2	3105829	@rlad<"20110405"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2016/02/07 12:47
L3	4604	l1 and l2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2016/02/07 12:47
L4	5080601	@pd>"20141016"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2016/02/07 12:47
L5	217	l3 and l4	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2016/02/07 12:47

2/7/2016 12:58:47 PM
C:\Users\jmartinell\Documents\EAST\Workspaces\13-080616-d.wsp

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	SALLY MERKLING	1773

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

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

CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014	10/16/2014	05/28/2015	02/07/2016				
1	1	÷	✓	✓	✓	=				
2	2	÷	✓	✓	✓	=				
3	3	÷	✓	✓	✓	=				
4	4	÷	✓	✓	✓	=				
5	5	÷	✓	✓	✓	=				
6	6	÷	✓	✓	✓	=				
	7	÷	✓	-	-	-				
	8	÷	✓	-	-	-				
7	9	÷	✓	✓	✓	=				
8	10	÷	✓	✓	✓	=				
	11	÷	✓	-	-	-				
9	12	÷	✓	✓	✓	=				
	13	÷	✓	-	-	-				
	14	÷	✓	-	-	-				
	15	÷	✓	-	-	-				
	16	÷	✓	-	-	-				
	17	÷	✓	-	-	-				
	18	÷	✓	-	-	-				
	19	÷	✓	-	-	-				
10	20	÷	✓	✓	✓	=				
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	23	÷	✓	-	-	-				
11	24	÷	✓	✓	✓	=				
12	25	÷	✓	✓	✓	=				
13	26	÷	✓	✓	✓	=				
15	27	÷	✓	✓	✓	=				
16	28	÷	✓	✓	✓	=				
	29	÷	✓	-	-	-				
	30	÷	✓	-	-	-				
	31	÷	✓	-	-	-				
	32	÷	✓	-	-	-				
	33	÷	✓	-	-	-				
17	34	÷	✓	✓	✓	=				
	35	÷	✓	-	-	-				
18	36	÷	✓	✓	✓	=				

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
	SALLY MERKLING	1773

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014	10/16/2014	05/28/2015	02/07/2016				
19	37	÷	✓	✓	✓	=				
20	38	÷	✓	✓	✓	=				
21	39	÷	✓	✓	✓	=				
	40	÷	N	-	-	-				
	41	÷	N	-	-	-				
	42	÷	N	-	-	-				
	43	÷	N	-	-	-				
	44	÷	N	-	-	-				
	45	÷	N	-	-	-				
	46	÷	N	-	-	-				
	47	÷	N	-	-	-				
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23	55	÷		✓	✓	=				
24	56	÷		✓	✓	=				
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28	60			✓	✓	=				
29	61			✓	✓	=				
30	62			✓	✓	=				
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33	65			✓	✓	=				
34	66			✓	✓	=				
35	67			✓	✓	=				
36	68			✓	✓	=				
37	69			✓	✓	=				
38	70			✓	✓	=				
39	71			✓	✓	=				
40	72			✓	✓	=				

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13080616	CHEE, MARK S.
	Examiner	**Art Unit**
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✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/11/2013	04/04/2014	10/16/2014	05/28/2015	02/07/2016				
41	73			✓	✓	=				
42	74			✓	✓	=				
43	75			✓	✓	=				
44	76			✓	✓	=				
45	77			✓	✓	=				
14	78					=				
22	79					=				
46	80					=				

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

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

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

25225 7590 02/18/2016
MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

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

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

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

TITLE OF INVENTION: SPATIALLY ENCODED BIOLOGICAL ASSAYS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	05/18/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
MARTINELL, JAMES	1634	435-006110

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☒ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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

1 Morrison & Foerster LLP
2
3

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

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

(A) NAME OF ASSIGNEE: Prognosys Biosciences, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): San Diego, CA

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

4a. The following fee(s) are submitted:
☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☒ Advance Order - # of Copies 2

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 03-1952 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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

Authorized Signature /Bu Yin/ Date May 18, 2016
Typed or printed name Bu Yin Registration No. 68,930

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Curio EX1012 p. 548
Curio v Prognosys

Electronic Patent Application Fee Transmittal

Application Number:	13080616
Filing Date:	05-Apr-2011
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Filer:	Bu Yin/Jennifer Jung
Attorney Docket Number:	699932000200

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	2501	1	480	480

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Printed Copy of Patent - No Color	8001	2	3	6
		Total in USD ($)		**486**

Electronic Acknowledgement Receipt

EFS ID:	25820017
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
Title of Invention:	SPATIALLY ENCODED BIOLOGICAL ASSAYS
First Named Inventor/Applicant Name:	Mark S. Chee
Customer Number:	25225
Filer:	Bu Yin/Jennifer Jung
Filer Authorized By:	Bu Yin
Attorney Docket Number:	699932000200
Receipt Date:	18-MAY-2016
Filing Date:	05-APR-2011
Time Stamp:	19:05:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$486
RAM confirmation Number	5676
Deposit Account	031952
Authorized User	YIN, BU

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	69993_IDS_Transmittal.pdf	22284 f9b071bcbcb54ad15d43728ea9b0512f54d72e79	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	69993_SB08.pdf	26056 887997d8e942f56fd48e30531fcb4f36ec8aeb2e	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	AUOA10012015.pdf	224200 16fd7501bfea2dcae71d0e197f040f16a7933ca7	no	2
Warnings:					
Information:					
4	Non Patent Literature	CAOA04282015.pdf	122446 c92b89e4f1f97f10babf91d06321b9e8ba22b9f9	no	3
Warnings:					
Information:					
5	Non Patent Literature	CNNOA08252015.pdf	346349 b35fd693c534c7e0988374c4136adb76a873841d	no	1
Warnings:					
Information:					
6	Non Patent Literature	JPNOA01262016.pdf	211384 cb5bade483a8c33fe50fec7acbf5bea70b3e90a5	no	2
Warnings:					
Information:					
7	Non Patent Literature	JPOA06232015.pdf	727255 49274f6a919dbabe5248e2695515b4c9552e6ede	no	3
Warnings:					
Information:					

8	Non Patent Literature	RspCAOA10272015.pdf	3958769 ae2beb56239d0f98359a9807125db1c988bc1311	no	14
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Information:					
9	Non Patent Literature	RspJPOA12182015.pdf	5011880 a2e289fbf26cc9f14cc83ce93b5677d4c5bb077f	no	19
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Information:					
10	Non Patent Literature	RspUSOA07222015.pdf	2442089 699427cc8747537ed5dd676a7ce3e73f8419dde2	no	34
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Information:					
11	Non Patent Literature	USOA02232016.pdf	236869 2bee72ff1b6f19cd2c82ec5f556098d72b796e0e	no	7
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Information:					
12	Non Patent Literature	USOA03012016.pdf	1420768 9b7241f4f9a5149816468479f26a5837c69ac58c	no	12
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Information:					
13	Non Patent Literature	USOA10082015.PDF	415390 885417c227df3f41c844fcbaf5c00903557a26a5	no	10
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Information:					
14	Change of Address	69993_FeeAddress.pdf	21806 a2758f4eb9b716d369ec1c804e2e288f0bfe6519	no	1
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Information:					
15	Issue Fee Payment (PTO-85B)	69993_Issue_Fee_Payment.pdf	209474 192d447d3f12558d70968f4ab72b67758f9d0a60	no	1
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Information:					
16	Fee Worksheet (SB06)	fee-info.pdf	32253 121c1c836057bfe9852202112f3f6acbce225822	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	15429272

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.

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: May 18, 2016
Electronic Signature for Jennifer Jung: /Jennifer Jung/

Patent
Docket No. 699932000200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mark S. CHEE

Application No.: 13/080,616 | Confirmation No.: 2142

Filed: April 5, 2011 | Art Unit: 1634

For: SPATIALLY ENCODED BIOLOGICAL ASSAYS | Examiner: J. Martinell

COMMUNICATION REGARDING REFERENCES

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

Dear Sir:

Applicant brings to the Examiner's attention the documents listed on the attached Form PTO/SB/08a/b. The documents listed on the attached Form PTO/SB/08a/b are actions and responses directed to corresponding applications. It is understood that the Office is under no obligation to consider the documents at this time, and, while Applicant believes that the documents are in no way destructive of patentability of the allowed claims, in the interest of completeness, they are submitted herewith.

sd-681618

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing (699932000200).

Dated: May 18, 2016

Respectfully submitted,

Electronic signature: /Bu Yin/
Bu Yin
Registration No.: 68,930
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego, California 92130-2040
(858) 720-7912

sd-681618

ALTERNATIVE TO PTO/SB/08A/B
(Based on PTO 08-08 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. CHEE
Art Unit	1634
Examiner Name	J. Martinell
Attorney Docket Number	699932000200

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
						☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1.	Examiner's Report for CA 2,794,522, mailed 28 April 2015, 3 pages	☐
	2.	Notification of Reasons for Rejection (translation) for JP 2013-503861, mailed 23 June 2015, 3 pages	☐
	3.	Notification to Go Through Registration Formalities (translation) for CN 201180017696.3, issued 25 August 2015, 1 page	☐
	4.	Response to Examiner's Report for CA 2,794,522, filed 27 October 2015, 14 pages	☐
	5.	Response to Notification of Reasons for Rejection for JP 2013-503861, filed 18 December 2015, 19 pages	☐
	6.	Notice of Allowance for JP 2013-503861, issued 26 January 2016, 2 pages	☐
	7.	First Examination Report for AU 2014203638, issued 1 October 2015, 2 pages	☐
	8.	Office Action in US 14/723,332, mailed 23 February 2016, 7 pages	☐
	9.	Response to Office Action in US 13/442, 637, dated 22 July 2015, 34 pages	☐
	10.	Office Action in US 13/442, 637, dated 8 October 2015, 10 pages	☐
	11.	Office Action in US 14/068,921, mailed 1 March 2016, 12 pages	☐

Examiner Signature		Date Considered	

sd-681595

PTO/SB/47 (03-09)
Approved for use through 05/31/2015. OMB 0651-0016
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.

"FEE ADDRESS" INDICATION FORM

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P.O. Box 1450
Alexandria, VA 22313-1450

- OR -

Fax to:
571-273-6500

INSTRUCTIONS: The issue fee must have been paid for application(s) listed on this form. In addition, only an address represented by a Customer Number can be established as the fee address for maintenance fee purposes (hereafter, fee address). A fee address should be established when correspondence related to maintenance fees should be mailed to a different address than the correspondence address for the application. **When to check the first box below:** If you have a Customer Number to represent the fee address. **When to check the second box below:** If you have no Customer Number representing the desired fee address, in which case a completed Request for Customer Number (PTO/SB/125) must be attached to this form. For more information on Customer Numbers, see the Manual of Patent Examining Procedure (MPEP) § 403.

For the following listed application(s), please recognize as the "Fee Address" under the provisions of 37 CFR 1.363 the address associated with:

[X] Customer Number: 000197

OR

[ ] The attached Request for Customer Number (PTO/SB/125) form.

PATENT NUMBER (if known)	APPLICATION NUMBER
8,906,379	

Completed by (check one):

[ ] Applicant/Inventor — /Bu Yin/ (Signature)

[X] Attorney or Agent of record — 68,930 (Reg. No.) — Bu Yin (Typed or printed name)

[ ] Assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96) — (858) 720-7912 (Requester's telephone number)

[ ] Assignee recorded at Reel _____ Frame _____ — May 18, 2016 (Date)

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more that one signature is required, see below*.

[X] * **Total of** 1 **forms are submitted.**

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: May 18, 2016 Electronic Signature for Jennifer Jung: /Jennifer Jung/

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.
13/080,616	04/05/2011	Mark S. Chee	699932000200	2142

7590 05/25/2016

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
MARTINELL, JAMES	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
05/25/2016	ELECTRONIC

NOTICE OF NON-COMPLIANT INFORMATION DISCLOSURE STATEMENT

An Information Disclosure Statement (IDS) filed 05.18.16 in the above-identified application fails to meet the requirements of 37 CFR 1.97(d) for the reason(s) specified below. Accordingly, the IDS will be placed in the file, but the information referred to therein has not been considered.

The IDS is not compliant with 37 CFR 1.97(d) because:

☑ The IDS lacks a statement as specified in 37 CFR 1.97(e).

☐ The IDS lacks the fee set forth in 37 CFR 1.17(p).

☐ The IDS was filed after the issue fee was paid. Applicant may wish to consider filing a petition to withdraw the application from issue under 37 CFR 1.313(c) to have the IDS considered. See MPEP 1308.

for NRHB
571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Data Management

FORM PTOM327-B (Rev. 02/08)

Curio EX1012-p. 559
Curio v Prognosys

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/080,616	06/21/2016	9371598	699932000200	2142

25225 7590 06/01/2016

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 783 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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

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

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

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

Mark S. Chee, Encinitas, CA;

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

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Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	REQUEST ID
13/080,616	9371598	1634	79738

PAIR Correspondence Address/Fee Address Change

The following fields have been changed to Customer Number 159367 on 01/22/2019 via Private PAIR in view of the certification copied below that authorized the change.

- Correspondence Address

The address for Customer Number 159367 is:
159367
FISH & RICHARDSON P.C.
10x Genomics
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

An attorney or Agent of Record registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature:	/James J. Mullen, III/
Name:	James J. Mullen, III
Registration Number:	44957

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	REQUEST ID
13/080,616	9371598	1634	79738

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- Maintenance Fee Address

The address for Customer Number 159367 is:
159367
FISH & RICHARDSON P.C.
10x Genomics
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

An attorney or Agent of Record registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature:	/James J. Mullen, III/
Name:	James J. Mullen, III
Registration Number:	44957

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

Curio EX1012-p. 564
Curio v Prognosys

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

61850684.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	Unknown
Application No.	:	15/187,661	Examiner	:	Unknown
Filed	:	June 20, 2016	Conf. No.	:	1038
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.** and **Prognosys Biosciences, Inc.**, acting on behalf of **10X Genomics, Inc.** and **Prognosys Biosciences, Inc.**, hereby revokes all powers of attorney previously granted in the application.

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

The undersigned for **10X Genomics, Inc.** and **Prognosys Biosciences, Inc.**, acting on behalf of **10X Genomics, Inc.** and **Prognosys Biosciences, Inc.**, hereby appoints **10X Genomics, Inc.**'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 Biosciences, Inc.** 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 Biosciences, Inc.** 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 Biosciences, Inc.**'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 Biosciences, Inc.** and the Firm, or, for that matter, between the Firm and any other person. Moreover, communications between **Prognosys Biosciences, Inc.** and the Firm will not be withheld from **10X Genomics, Inc.**.

10X Genomics, Inc. 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 Biosciences, Inc.**, 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.

Curio EX1012-p. 567
Curio v Prognosys

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

61886512.doc

Curio EX1012-p. 568
Curio v Prognosys

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	1636
Application No.	:	16/276,235	Examiner	:	Unknown
Filed	:	February 14, 2019	Conf. No.	:	7944
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.** and **Prognosys Biosciences, Inc.**, acting on behalf of **10X Genomics, Inc.** and **Prognosys Biosciences, Inc.**, hereby revokes all powers of attorney previously granted in the application.

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

The undersigned for **10X Genomics, Inc.** and **Prognosys Biosciences, Inc.**, acting on behalf of **10X Genomics, Inc.** and **Prognosys Biosciences, Inc.**, hereby appoints **10X Genomics, Inc.**'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 Biosciences, Inc.** 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 Biosciences, Inc.** 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 Biosciences, Inc.**'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 Biosciences, Inc.** and the Firm, or, for that matter, between the Firm and any other person. Moreover, communications between **Prognosys Biosciences, Inc.** and the Firm will not be withheld from **10X Genomics, Inc.**.

10X Genomics, Inc. 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 Biosciences, Inc.**, 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

CVL/jxw

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

61886515.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	1636
Application No.	:	16/276,260	Examiner	:	Unknown
Filed	:	February 14, 2019	Conf. No.	:	8647
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.** and **Prognosys Biosciences, Inc.**, acting on behalf of **10x Genomics, Inc.** and **Prognosys Biosciences, Inc.**, hereby revokes all powers of attorney previously granted in the application.

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

The undersigned for **10x Genomics, Inc.** and **Prognosys Biosciences, Inc.**, acting on behalf of **10x Genomics, Inc.** and **Prognosys Biosciences, Inc.**, hereby appoints **10x Genomics, Inc.**'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

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PTO Customer Number: 159367

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10x Genomics, Inc. 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 Biosciences, Inc.**, 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.

Curio EX1012-p. 573
Curio v Prognosys

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

61886516.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark Chee	Art Unit	:	Unknown
Patent No.	:	9,868,979	Examiner	:	Unknown
Issue Date	:	January 16, 2018	Conf. No.	:	9096
Application No.	:	14/900,602			
Filed	:	December 21, 2015			
Title	:	SPATIALLY ENCODED BIOLOGICAL ASSAYS USING A MICROFLUIDIC DEVICE			

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

REVOCATION AND NEW POWER OF ATTORNEY

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

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

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

PTO Customer Number: 159367

By executing this Power of Attorney, **Prognosys Biosciences, Inc.** 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 Biosciences, Inc.** is

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10x Genomics, Inc. 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 Biosciences, Inc.**, 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

61886518.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	Unknown
Patent No.	:	9,879,313	Examiner	:	Unknown
Issue Date	:	January 30, 2018	Conf. No.	:	5726
Application No.	:	14/900,604			
Filed	:	December 21, 2015			
Title	:	METHODS AND SYSTEMS FOR DETERMINING SPATIAL PATTERNS OF BIOLOGICAL TARGETS IN A SAMPLE			

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

REVOCATION AND NEW POWER OF ATTORNEY

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

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

PTO Customer Number: 159367

By executing this Power of Attorney, **Prognosys Biosciences, Inc.** 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 Biosciences, Inc.** 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 Biosciences, Inc.**'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 Biosciences, Inc.** and the Firm, or, for that matter, between the Firm and any other person. Moreover, communications between **Prognosys Biosciences, Inc.** and the Firm will not be withheld from **10x Genomics, Inc.**.

10x Genomics, Inc. 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 Biosciences, Inc.**, despite your execution of this Power of Attorney.

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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

61886532.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Mark S. Chee	Art Unit	:	Unknown
Application No.	:	15/831,158	Examiner	:	Unknown
Filed	:	December 4, 2017	Conf. No.	:	5500
Title	:	METHODS AND SYSTEMS FOR DETERMINING SPATIAL PATTERNS OF BIOLOGICAL TARGETS IN A SAMPLE			

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

REVOCATION AND NEW POWER OF ATTORNEY

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

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

PTO Customer Number: 159367

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10x Genomics, Inc. 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 Biosciences, Inc.**, 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.

Curio EX1012-p. 582
Curio v Prognosys

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

61886523.doc

Electronic Acknowledgement Receipt

EFS ID:	35965479
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
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:	69993-20002.00
Receipt Date:	09-MAY-2019
Filing Date:	05-APR-2011
Time Stamp:	13:26:42
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	PrognosysnonclientPOAs.pdf	2336907 4a16d7b258c5ce8211aab57536e85442414 28c14	no	21

Warnings:

Information:	
Total Files Size (in bytes):	2336907

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
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/080,616	04/05/2011	Mark S. Chee	47706-0004001

CONFIRMATION NO. 2142

POA ACCEPTANCE LETTER

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

OC00000108209579

Date Mailed: 05/16/2019

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/09/2019.

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**.

/ldvan/

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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/080,616	04/05/2011	Mark S. Chee	69993-20002.00

CONFIRMATION NO. 2142

POWER OF ATTORNEY NOTICE

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

OC000000108209568

Date Mailed: 05/16/2019

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/09/2019.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

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

/ldvan/

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

Application Number	13/080,616
Filing Date	April 5, 2011
First Named Inventor	Mark S. Chee
Title	SPATIALLY ENCODED BIOLOGICAL ASSAYS
Art Unit	
Examiner Name	
Attorney Docket Number	47706-0004001

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.

61938666.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)

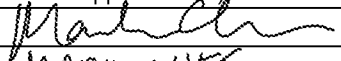
☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ 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		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:	36188380
Application Number:	13080616
International Application Number:	
Confirmation Number:	2142
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:	47706-0004001
Receipt Date:	03-JUN-2019
Filing Date:	05-APR-2011
Time Stamp:	18:45:33
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	145238 2f4d83b6c6ab5155ec0509d73157fd5db9d3f858	no	2

Warnings:

Information:	
Total Files Size (in bytes):	145238

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.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/080,616	04/05/2011	Mark S. Chee	47706-0004001

CONFIRMATION NO. 2142

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

POA ACCEPTANCE LETTER

OC00000108755767

Date Mailed: 06/10/2019

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**.

/cvorachack/

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
13/080,616	04/05/2011	Mark S. Chee	47706-0004001	90876

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 07/02/2019 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

X Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Cameron Luitjens/
Name:	Cameron Luitjens
Registration Number:	58674