# COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

## BACKGROUND

We have previously described methods that enable tagging each of a population of fragmented genomes and then combining them together to create a 'population library' that can be processed and eventually sequenced as a mixture. The population tags enable analysis software to parse the sequence reads into files that can be attributed to a particular genome in the population. One limitation of the overall process stems from limitations of existing DNA sequencing technologies. In particular, if fragments in the regions of interest of the genome are longer than the lengths that can be sequenced by a particular technology, then such fragments will not be fully analyzed (since sequencing proceeds from an end of a fragment inward). Furthermore, a disadvantage of any sequencing technology dependent on fragmentation is that sequence changes in one part of a particular genomic region may not be able to be linked to sequence changes in other parts of the same genome (e.g., the same chromosome) because the sequence changes reside on different fragments. (See Figure 5 and its description below).

The present invention removes the limitations imposed by current sequencing technologies as well as being useful in a number of other nucleic acid analyses.

## SUMMARY OF THE INVENTION

Aspects of the present invention are drawn to processes for moving a region of interest in a polynucleotide from a first position to a second position with regard to a domain within the polynucleotide, also referred to as a "reflex method" (or reflex process, reflex sequence process, reflex reaction, and the like). In certain embodiments, the reflex method results in moving a region of interest into functional proximity to specific domain elements present in the polynucleotide (e.g., primer sites and/or MID). Compositions, kits and systems that find use in carrying out the reflex processes described herein are also provided.

## BRIEF DESCRIPTION OF THE DRAWINGS

The invention is best understood from the following detailed description when read in conjunction with the accompanying drawings. It is emphasized that, according to common practice, the various features of the drawings are not to scale. Indeed, the



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dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:

Figure 1: Panel A is a schematic diagram illustrating moving a first domain from one site to another in a nucleic acid molecule using a reflex sequence. Panel B is a schematic diagram depicting the relative position of primer pairs ($A_n$-$B_n$ primers) that find use in aspects of the reflex process described herein.

Figure 2 shows an exemplary embodiment of using binding partner pairs (biotin/streptavidin) to isolate single stranded polynucleotides of interest.

Figure 3 is a schematic diagram illustrating an exemplary embodiment for moving a primer site and a MID to a specific location in a nucleic acid of interest.

Figure 4 shows a schematic diagram illustrating an exemplary use of the reflex process for generating a sample enriched for fragments having a region of interest (e.g., from a population of randomly fragmented and asymmetrically tagged polynucleotides).

Figure 5 shows a comparison of methods for identifying nucleic acid polymorphisms in homologous nucleic acids in a sample (e.g., the same region derived from a chromosomal pair of a diploid cell or viral genomes/transcripts). The top schematic shows two nucleic acid molecules in a sample (1 and 2) having a different assortment of polymorphisms in polymorphic sites A, B and C (A1, B1, C1 and C2). Standard sequencing methods using fragmentation (left side) can identify the polymorphisms in these nucleic acids but do not retain linkage information. Employing the reflex process described herein to identify polymorphisms (right side) maintains linkage information.

Figure 6: Panel A is a schematic showing expected structures and sizes of nucleic acid species in the reflex process; Panel B is a polyacrylamide gel showing the nucleic acid species produced in the reflex process described in Example 1.

Figure 7: Panel A is a schematic showing the structure of the nucleic acid and competitor used in the reflex process; Panel B is a polyacrylamide gel showing the nucleic acid species produced in the reflex process described in Example 1.

Figure 8 shows a flow chart of a reflex process (left) in which the T7 exonuclease step is optional. The gel on the right shows the resultant product of the reflex process either without the T7 exonuclease step (lane 1) or with the T7 exonuclease step (lane 2).

Figure 9 shows an exemplary reflex process workflow with indications on the right as to where purification of reaction products is employed (e.g., using Agencourt beads to remove primer oligos).



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Figure 10 shows the starting material (left panel) and the resultant product generated (right panel) using a reflex process without using a T7 exonuclease step (as described in Example II). The reflex site in the starting material is a sequence normally present in the polynucleotide being processed (also called a "non-artificial" reflex site). This figure shows that the 755 base pair starting nucleic acid was processed to the expected 461 base pair product, thus confirming that a "non-artificial" reflex site is effective in transferring an adapter domain from one location to another in a polynucleotide of interest in a sequence specific manner.

Figure 11 shows a schematic and results of an experiment in which the reflex process is performed on a single large initial template (a "parent" fragment) to generate five different products ("daughter" products) each having a different region of interest (i.e., daughter products are produced having either region 1, 2, 3, 4 or 5).

Figure 12 shows a schematic and results of experiments performed to determine the prevalence of intramolecular rearrangement during the reflex process (as desired) vs. intermolecular rearrangement (MID switching).

Figure 13 shows a diagram of exemplary workflows for preparing material for and performing the reflex process.

## DEFINITIONS

Unless otherwise defined, 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. Still, certain elements are defined for the sake of clarity and ease of reference.

Terms and symbols of nucleic acid chemistry, biochemistry, genetics, and molecular biology used herein follow those of standard treatises and texts in the field, e.g. Kornberg and Baker, DNA Replication, Second Edition (W.H. Freeman, New York, 1992); Lehninger, Biochemistry, Second Edition (Worth Publishers, New York, 1975); Strachan and Read, Human Molecular Genetics, Second Edition (Wiley-Liss, New York, 1999); Eckstein, editor, Oligonucleotides and Analogs: A Practical Approach (Oxford University Press, New York, 1991); Gait, editor, Oligonucleotide Synthesis: A Practical Approach (IRL Press, Oxford, 1984); and the like.

"Amplicon" means the product of a polynucleotide amplification reaction. That is, it is a population of polynucleotides, usually double stranded, that are replicated from one or more starting sequences. The one or more starting sequences may be one or more copies of the same sequence, or it may be a mixture of different sequences. Amplicons



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may be produced by a variety of amplification reactions whose products are multiple replicates of one or more target nucleic acids. Generally, amplification reactions producing amplicons are "template-driven" in that base pairing of reactants, either nucleotides or oligonucleotides, have complements in a template polynucleotide that are required for the creation of reaction products. In one aspect, template-driven reactions are primer extensions with a nucleic acid polymerase or oligonucleotide ligations with a nucleic acid ligase. Such reactions include, but are not limited to, polymerase chain reactions (PCRs), linear polymerase reactions, nucleic acid sequence-based amplification (NASBAs), rolling circle amplifications, and the like, disclosed in the following references that are incorporated herein by reference: Mullis et al, U.S. patents 4,683,195; 4,965,188; 4,683,202; 4,800,159 (PCR); Gelfand et al, U.S. patent 5,210,015 (real-time PCR with "TAQMAN™" probes); Wittwer et al, U.S. patent 6,174,670; Kacian et al, U.S. patent 5,399,491 ("NASBA"); Lizardi, U.S. patent 5,854,033; Aono et al, Japanese patent publ. JP 4-262799 (rolling circle amplification); and the like. In one aspect, amplicons of the invention are produced by PCRs. An amplification reaction may be a "real-time" amplification if a detection chemistry is available that permits a reaction product to be measured as the amplification reaction progresses, e.g. "real-time PCR" described below, or "real-time NASBA" as described in Leone et al, Nucleic Acids Research, 26: 2150-2155 (1998), and like references. As used herein, the term "amplifying" means performing an amplification reaction. A "reaction mixture" means a solution containing all the necessary reactants for performing a reaction, which may include, but not be limited to, buffering agents to maintain pH at a selected level during a reaction, salts, co-factors, scavengers, and the like.

The term "assessing" includes any form of measurement, and includes determining if an element is present or not. The terms "determining", "measuring", "evaluating", "assessing" and "assaying" are used interchangeably and includes quantitative and qualitative determinations. Assessing may be relative or absolute. "Assessing the presence of" includes determining the amount of something present, and/or determining whether it is present or absent. As used herein, the terms "determining," "measuring," and "assessing," and "assaying" are used interchangeably and include both quantitative and qualitative determinations.

Polynucleotides that are "asymmetrically tagged" have left and right adapter domains that are not identical. This process is referred to generically as attaching adapters asymmetrically or asymmetrically tagging a polynucleotide, e.g., a polynucleotide



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fragment. Production of polynucleotides having asymmetric adapter termini may be achieved in any convenient manner. Exemplary asymmetric adapters are described in: U.S. Patents 5,712,126 and 6,372,434; U.S. Patent Publications 2007/0128624 and 2007/0172839; and PCT publication WO/2009/032167; all of which are incorporated by reference herein in their entirety. In certain embodiments, the asymmetric adapters employed are those described in U.S. Patent Application Ser. No. 12/432,080, filed on April 29, 2009, incorporated herein by reference in its entirety.

As one example, a user of the subject invention may use an asymmetric adapter to tag polynucleotides. An "asymmetric adapter" is one that, when ligated to both ends of a double stranded nucleic acid fragment, will lead to the production of primer extension or amplification products that have non-identical sequences flanking the genomic insert of interest. The ligation is usually followed by subsequent processing steps so as to generate the non-identical terminal adapter sequences. For example, replication of an asymmetric adapter attached fragment(s) results in polynucleotide products in which there is at least one nucleic acid sequence difference, or nucleotide/nucleoside modification, between the terminal adapter sequences. Attaching adapters asymmetrically to polynucleotides (e.g., polynucleotide fragments) results in polynucleotides that have one or more adapter sequences on one end (e.g., one or more region or domain, e.g., a primer site) that are either not present or have a different nucleic acid sequence as compared to the adapter sequence on the other end. It is noted that an adapter that is termed an "asymmetric adapter" is not necessarily itself structurally asymmetric, nor does the mere act of attaching an asymmetric adapter to a polynucleotide fragment render it immediately asymmetric. Rather, an asymmetric adapter-attached polynucleotide, which has an identical asymmetric adapter at each end, produces replication products (or isolated single stranded polynucleotides) that are asymmetric with respect to the adapter sequences on opposite ends (e.g., after at least one round of amplification/primer extension).

Any convenient asymmetric adapter, or process for attaching adapters asymmetrically, may be employed in practicing the present invention. Exemplary asymmetric adapters are described in: U.S. Patents 5,712,126 and 6,372,434; U.S. Patent Publications 2007/0128624 and 2007/0172839; and PCT publication WO/2009/032167; all of which are incorporated by reference herein in their entirety. In certain embodiments, the asymmetric adapters employed are those described in U.S. Patent Application Ser. No. 12/432,080, filed on April 29, 2009, incorporated herein by reference in its entirety.



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"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 site on a single stranded nucleic acid. Complementary nucleotides are, generally, A and T (or A and U), or C and G. Two single stranded RNA or DNA molecules are said to be substantially complementary when the nucleotides of one strand, optimally aligned and compared and with appropriate nucleotide insertions or deletions, pair with at least about 80% of the nucleotides of the other strand, usually at least about 90% to 95%, and more preferably from about 98 to 100%. Alternatively, substantial complementarity exists when an RNA or DNA strand will hybridize under selective hybridization conditions to its complement. Typically, selective hybridization will occur when there is at least about 65% complementary over a stretch of at least 14 to 25 nucleotides, preferably at least about 75%, more preferably at least about 90% complementary. See, M. Kanehisa Nucleic Acids Res. 12:203 (1984), incorporated herein by reference.

"Duplex" means at least two oligonucleotides and/or polynucleotides that are fully or partially complementary undergo Watson-Crick type base pairing among all or most of their nucleotides so that a stable complex is formed. The terms "annealing" and "hybridization" are used interchangeably to mean the formation of a stable duplex. "Perfectly matched" in reference to a duplex means that the poly- or oligonucleotide strands making up the duplex form a double stranded structure with one another such that every nucleotide in each strand undergoes Watson-Crick base pairing with a nucleotide in the other strand. A stable duplex can include Watson-Crick base pairing and/or non-Watson-Crick base pairing between the strands of the duplex (where base pairing means the forming hydrogen bonds). In certain embodiments, a non-Watson-Crick base pair includes a nucleoside analog, such as deoxyinosine, 2, 6-diaminopurine, PNAs, LNA's and the like. In certain embodiments, a non-Watson-Crick base pair includes a "wobble base", such as deoxyinosine, 8-oxo-dA, 8-oxo-dG and the like, where by "wobble base" is meant a nucleic acid base that can base pair with a first nucleotide base in a complementary nucleic acid strand but that, when employed as a template strand for nucleic acid synthesis, leads to the incorporation of a second, different nucleotide base into the synthesizing strand (wobble bases are described in further detail below). A "mismatch" in a duplex between two oligonucleotides or polynucleotides means that a pair of nucleotides in the duplex fails to undergo Watson-Crick bonding.



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"Genetic locus," "locus," or "locus of interest" in reference to a genome or target polynucleotide, means a contiguous sub-region or segment of the genome or target polynucleotide. As used herein, genetic locus, locus, or locus of interest may refer to the position of a nucleotide, a gene or a portion of a gene in a genome, including mitochondrial DNA or other non-chromosomal DNA (e.g., bacterial plasmid), or it may refer to any contiguous portion of genomic sequence whether or not it is within, or associated with, a gene. A genetic locus, locus, or locus of interest can be from a single nucleotide to a segment of a few hundred or a few thousand nucleotides in length or more. In general, a locus of interest will have a reference sequence associated with it (see description of "reference sequence" below).

"Kit" refers to any delivery system for delivering materials or reagents for carrying out a method of the invention. In the context of reaction assays, such delivery systems include systems that allow for the storage, transport, or delivery of reaction reagents (e.g., probes, enzymes, etc. in the appropriate containers) and/or supporting materials (e.g., buffers, written instructions for performing the assay etc.) from one location to another. For example, kits include one or more enclosures (e.g., boxes) containing the relevant reaction reagents and/or supporting materials. Such contents may be delivered to the intended recipient together or separately. For example, a first container may contain an enzyme for use in an assay, while a second container contains probes.

"Ligation" means to form a covalent bond or linkage between the termini of two or more nucleic acids, e.g. oligonucleotides and/or polynucleotides, in a template-driven reaction. The nature of the bond or linkage may vary widely and the ligation may be carried out enzymatically or chemically. As used herein, ligations are usually carried out enzymatically to form a phosphodiester linkage between a 5' carbon of a terminal nucleotide of one oligonucleotide with 3' carbon of another oligonucleotide. A variety of template-driven ligation reactions are described in the following references, which are incorporated by reference: Whiteley et al, U.S. patent 4,883,750; Letsinger et al, U.S. patent 5,476,930; Fung et al, U.S. patent 5,593,826; Kool, U.S. patent 5,426,180; Landegren et al, U.S. patent 5,871,921; Xu and Kool, Nucleic Acids Research, 27: 875-881 (1999); Higgins et al, Methods in Enzymology, 68: 50-71 (1979); Engler et al, The Enzymes, 15: 3-29 (1982); and Namsaraev, U.S. patent publication 2004/0110213.

"Multiplex Identifier" (MID) as used herein refers to a tag or combination of tags associated with a polynucleotide whose identity (e.g., the tag DNA sequence)



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can be used to differentiate polynucleotides in a sample. In certain embodiments, the MID on a polynucleotide is used to identify the source from which the polynucleotide is derived. For example, a nucleic acid sample may be a pool of polynucleotides derived from different sources, (e.g., polynucleotides derived from different individuals, different tissues or cells, or polynucleotides isolated at different times points), where the polynucleotides from each different source are tagged with a unique MID. As such, a MID provides a correlation between a polynucleotide and its source. In certain embodiments, MIDs are employed to uniquely tag each individual polynucleotide in a sample. Identification of the number of unique MIDs in a sample can provide a readout of how many individual polynucleotides are present in the sample (or from how many original polynucleotides a manipulated polynucleotide sample was derived; see, e.g., U.S. Patent No. 7,537,897, issued on May 26, 2009, incorporated herein by reference in its entirety). MIDs can range in length from 2 to 100 nucleotide bases or more and may include multiple subunits, where each different MID has a distinct identity and/or order of subunits. Exemplary nucleic acid tags that find use as MIDs are described in U.S. Patent 7,544,473, issued on June 6, 2009, and titled "Nucleic Acid Analysis Using Sequence Tokens", as well as U.S. Patent 7,393,665, issued on July 1, 2008, and titled "Methods and Compositions for Tagging and Identifying Polynucleotides", both of which are incorporated herein by reference in their entirety for their description of nucleic acid tags and their use in identifying polynucleotides. In certain embodiments, a set of MIDs employed to tag a plurality of samples need not have any particular common property (e.g., Tm, length, base composition, etc.), as the methods described herein can accommodate a wide variety of unique MID sets. It is emphasized here that MIDs need only be unique within a given experiment. Thus, the same MID may be used to tag a different sample being processed in a different experiment. In addition, in certain experiments, a user may use the same MID to tag a subset of different samples within the same experiment. For example, all samples derived from individuals having a specific phenotype may be tagged with the same MID, e.g., all samples derived from control (or wildtype) subjects can be tagged with a first MID while subjects having a disease condition can be tagged with a second MID (different than the first MID). As another example, it may be desirable to tag different samples derived from the same source with different MIDs (e.g., samples derived over time or derived from different sites within a tissue). Further, MIDs can be generated in a



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variety of different ways, e.g., by a combinatorial tagging approach in which one MID is attached by ligation and a second MID is attached by primer extension. Thus, MIDs can be designed and implemented in a variety of different ways to track polynucleotide fragments during processing and analysis, and thus no limitation in this regard is intended.

"Nucleoside" as used herein includes the natural nucleosides, including 2'-deoxy and 2'-hydroxyl forms, e.g. as described in Kornberg and Baker, DNA Replication, 2nd Ed. (Freeman, San Francisco, 1992). "Analogs" in reference to nucleosides includes synthetic nucleosides having modified base moieties and/or modified sugar moieties, e.g. described by Scheit, Nucleotide Analogs (John Wiley, New York, 1980); Uhlman and Peyman, Chemical Reviews, 90: 543-584 (1990), or the like, with the proviso that they are capable of specific hybridization. Such analogs include synthetic nucleosides designed to enhance binding properties, reduce complexity, increase specificity, and the like. Polynucleotides comprising analogs with enhanced hybridization or nuclease resistance properties are described in Uhlman and Peyman (cited above); Crooke et al, Exp. Opin. Ther. Patents, 6: 855-870 (1996); Mesmaeker et al, Current Opinion in Structual Biology, 5: 343-355 (1995); and the like. Exemplary types of polynucleotides that are capable of enhancing duplex stability include oligonucleotide N3'→P5' phosphoramidates (referred to herein as "amidates"), peptide nucleic acids (referred to herein as "PNAs"), oligo-2'-O-alkylribonucleotides, polynucleotides containing C-5 propynylpyrimidines, locked nucleic acids ("LNAs"), and like compounds. Such oligonucleotides are either available commercially or may be synthesized using methods described in the literature.

"Polymerase chain reaction," or "PCR," means a reaction for the in vitro amplification of specific DNA sequences by the simultaneous primer extension of complementary strands of DNA. In other words, PCR is a reaction for making multiple copies or replicates of a target nucleic acid flanked by primer sites, such reaction comprising one or more repetitions of the following steps: (i) denaturing the target nucleic acid, (ii) annealing primers to the primer sites, and (iii) extending the primers by a nucleic acid polymerase in the presence of nucleoside triphosphates. Usually, the reaction is cycled through different temperatures optimized for each step in a thermal cycler instrument. Particular temperatures, durations at each step, and rates of change between steps depend on many factors well-known to those of ordinary skill in the art, e.g. exemplified by the references: McPherson et al, editors, PCR: A Practical Approach and PCR2: A Practical Approach (IRL Press, Oxford, 1991 and 1995, respectively). For example, in a conventional



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PCR using Taq DNA polymerase, a double stranded target nucleic acid may be denatured at a temperature >90°C, primers annealed at a temperature in the range 50-75°C, and primers extended at a temperature in the range 72-78°C. The term "PCR" encompasses derivative forms of the reaction, including but not limited to, RT-PCR, real-time PCR, nested PCR, quantitative PCR, multiplexed PCR, and the like. Reaction volumes range from a few hundred nanoliters, e.g. 200 nL, to a few hundred μL, e.g. 200 μL. "Reverse transcription PCR," or "RT-PCR," means a PCR that is preceded by a reverse transcription reaction that converts a target RNA to a complementary single stranded DNA, which is then amplified, e.g. Tecott et al, U.S. patent 5,168,038, which patent is incorporated herein by reference. "Real-time PCR" means a PCR for which the amount of reaction product, i.e. amplicon, is monitored as the reaction proceeds. There are many forms of real-time PCR that differ mainly in the detection chemistries used for monitoring the reaction product, e.g. Gelfand et al, U.S. patent 5,210,015 ("TAQMAN™"); Wittwer et al, U.S. patents 6,174,670 and 6,569,627 (intercalating dyes); Tyagi et al, U.S. patent 5,925,517 (molecular beacons); which patents are incorporated herein by reference. Detection chemistries for real-time PCR are reviewed in Mackay et al, Nucleic Acids Research, 30: 1292-1305 (2002), which is also incorporated herein by reference. "Nested PCR" means a two-stage PCR wherein the amplicon of a first PCR becomes the sample for a second PCR using a new set of primers, at least one of which binds to an interior location of the first amplicon. As used herein, "initial primers" in reference to a nested amplification reaction mean the primers used to generate a first amplicon, and "secondary primers" mean the one or more primers used to generate a second, or nested, amplicon. "Multiplexed PCR" means a PCR wherein multiple target sequences (or a single target sequence and one or more reference sequences) are simultaneously carried out in the same reaction mixture, e.g. Bernard et al, Anal. Biochem., 273: 221-228 (1999)(two-color real-time PCR). Usually, distinct sets of primers are employed for each sequence being amplified.

"Quantitative PCR" means a PCR designed to measure the abundance of one or more specific target sequences in a sample or specimen. Quantitative PCR includes both absolute quantitation and relative quantitation of such target sequences. Quantitative measurements are made using one or more reference sequences that may be assayed separately or together with a target sequence. The reference sequence may be endogenous or exogenous to a sample or specimen, and in the latter case, may comprise one or more competitor templates. Typical endogenous reference sequences include segments of transcripts of the following genes: β-actin, GAPDH, $\beta_2$-microglobulin, ribosomal RNA, and the like. Techniques for



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quantitative PCR are well-known to those of ordinary skill in the art, as exemplified in the following references that are incorporated by reference: Freeman et al, Biotechniques, 26: 112-126 (1999); Becker-Andre et al, Nucleic Acids Research, 17: 9437-9447 (1989); Zimmerman et al, Biotechniques, 21: 268-279 (1996); Diviacco et al, Gene, 122: 3013-3020 (1992); Becker-Andre et al, Nucleic Acids Research, 17: 9437-9446 (1989); and the like.

"Polynucleotide" or "oligonucleotide" is used interchangeably and each means a linear polymer of nucleotide monomers. Monomers making up polynucleotides and oligonucleotides are capable of specifically binding to a natural polynucleotide by way of a regular pattern of monomer-to-monomer interactions, such as Watson-Crick type of base pairing, base stacking, Hoogsteen or reverse Hoogsteen types of base pairing, wobble base pairing, or the like. As described in detail below, by "wobble base" is meant a nucleic acid base that can base pair with a first nucleotide base in a complementary nucleic acid strand but that, when employed as a template strand for nucleic acid synthesis, leads to the incorporation of a second, different nucleotide base into the synthesizing strand. Such monomers and their internucleosidic linkages may be naturally occurring or may be analogs thereof, e.g. naturally occurring or non-naturally occurring analogs. Non-naturally occurring analogs may include peptide nucleic acids (PNAs, e.g., as described in U.S. Patent 5,539,082, incorporated herein by reference), locked nucleic acids (LNAs, e.g., as described in U.S. Patent 6,670,461, incorporated herein by reference), phosphorothioate internucleosidic linkages, bases containing linking groups permitting the attachment of labels, such as fluorophores, or haptens, and the like. Whenever the use of an oligonucleotide or polynucleotide requires enzymatic processing, such as extension by a polymerase, ligation by a ligase, or the like, one of ordinary skill would understand that oligonucleotides or polynucleotides in those instances would not contain certain analogs of internucleosidic linkages, sugar moieties, or bases at any or some positions. Polynucleotides typically range in size from a few monomeric units, e.g. 5-40, when they are usually referred to as "oligonucleotides," to several thousand monomeric units. Whenever a polynucleotide or oligonucleotide is represented by a sequence of letters (upper or lower case), such as "ATGCCTG," it will be understood that the nucleotides are in 5'→3' order from left to right and that "A" denotes deoxyadenosine, "C" denotes deoxycytidine, "G" denotes deoxyguanosine, and "T" denotes thymidine, "I" denotes deoxyinosine, "U" denotes uridine, unless otherwise indicated or obvious from context. Unless otherwise noted the terminology and atom numbering conventions will follow those disclosed in Strachan and Read, Human Molecular Genetics 2 (Wiley-Liss, New York,



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1999). Usually polynucleotides comprise the four natural nucleosides (e.g. deoxyadenosine, deoxycytidine, deoxyguanosine, deoxythymidine for DNA or their ribose counterparts for RNA) linked by phosphodiester linkages; however, they may also comprise non-natural nucleotide analogs, e.g. including modified bases, sugars, or internucleosidic linkages. It is clear to those skilled in the art that where an enzyme has specific oligonucleotide or polynucleotide substrate requirements for activity, e.g. single stranded DNA, RNA/DNA duplex, or the like, then selection of appropriate composition for the oligonucleotide or polynucleotide substrates is well within the knowledge of one of ordinary skill, especially with guidance from treatises, such as Sambrook et al, Molecular Cloning, Second Edition (Cold Spring Harbor Laboratory, New York, 1989), and like references.

"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. Usually primers are extended by a DNA polymerase. Primers are generally of a length compatible with their use in synthesis of primer extension products, and are usually are in the range of between 8 to 100 nucleotides in length, such as 10 to 75, 15 to 60, 15 to 40, 18 to 30, 20 to 40, 21 to 50, 22 to 45, 25 to 40, and so on, more typically in the range of between 18-40, 20-35, 21-30 nucleotides long, and any length between the stated ranges. Typical primers can be in the range of between 10-50 nucleotides long, such as 15-45, 18-40, 20-30, 21-25 and so on, and any length between the stated ranges. In some embodiments, the primers are usually not more than about 10, 12, 15, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, or 70 nucleotides in length.

Primers are usually single-stranded for maximum efficiency in amplification, but may alternatively be double-stranded. If double-stranded, the primer is usually first treated to separate its strands before being used to prepare extension products. This denaturation step is typically affected by heat, but may alternatively be carried out using alkali, followed by neutralization. Thus, a "primer" is complementary to a template, and complexes by hydrogen bonding or hybridization with the template to give a primer/template complex for initiation of synthesis by a polymerase, which is extended by the addition of covalently bonded bases linked at its 3' end complementary to the template in the process of DNA synthesis.



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A "primer pair" as used herein refers to first and second primers having nucleic acid sequence suitable for nucleic acid-based amplification of a target nucleic acid. Such primer pairs generally include a first primer having a sequence that is the same or similar to that of a first portion of a target nucleic acid, and a second primer having a sequence that is complementary to a second portion of a target nucleic acid to provide for amplification of the target nucleic acid or a fragment thereof. Reference to "first" and "second" primers herein is arbitrary, unless specifically indicated otherwise. For example, the first primer can be designed as a "forward primer" (which initiates nucleic acid synthesis from a 5' end of the target nucleic acid) or as a "reverse primer" (which initiates nucleic acid synthesis from a 5' end of the extension product produced from synthesis initiated from the forward primer). Likewise, the second primer can be designed as a forward primer or a reverse primer.

"Primer site" (e.g., a sequencing primer site, and amplification primer site, etc.) as used herein refers to a domain in a polynucleotide that includes the sequence of a primer (e.g., a sequencing primer) and/or the complementary sequence of a primer. When present in single stranded form (e.g., in a single stranded polynucleotide), a primer site can be either the identical sequence of a primer or the complementary sequence of a primer. When present in double stranded form, a primer site contains the sequence of a primer hybridized to the complementary sequence of the primer. Thus, a primer site is a region of a polynucleotide that is either identical to or complementary to the sequence of a primer (when in a single stranded form) or a double stranded region formed between a primer sequence and its complement. Primer sites may be present in an adapter attached to a polynucleotide. The specific orientation of a primer site can be inferred by those of ordinary skill in the art from the structural features of the relevant polynucleotide and/or context in which it is used.

"Readout" means a parameter, or parameters, which are measured and/or detected that can be converted to a number or value. In some contexts, readout may refer to an actual numerical representation of such collected or recorded data. For example, a readout of fluorescent intensity signals from a microarray is the address and fluorescence intensity of a signal being generated at each hybridization site of the microarray; thus, such a readout may be registered or stored in various ways, for example, as an image of the microarray, as a table of numbers, or the like.

"Reflex site", "reflex sequence" and equivalents are used to indicate sequences in a polynucleotide that are employed to move a domain intramolecularly from its initial location



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to a different location in the polynucleotide. The sequence of a reflex site can be added to a polynucleotide of interest (e.g., present in an adapter ligated to the polynucleotide), be based on a sequence naturally present within the polynucleotide of interest (e.g., a genomic sequence in the polynucleotide), or a combination of both. The reflex sequence is chosen so as to be distinct from other sequences in the polynucleotide (i.e., with little sequence homology to other sequences likely to be present in the polynucleotide, e.g., genomic or sub-genomic sequences to be processed). As such, a reflex sequence should be selected so as to not hybridize to any sequence except its complement under the conditions employed in the reflex processes herein described. As described later in this application, the complement to the reflex sequence is inserted on the same strand of the polynucleotide (e.g., the same strand of a double-stranded polynucleotide or on the same single stranded polynucleotide) in a particular location so as to facilitate an intramolecular binding event on such particular strand. Reflex sequences employed in the reflex process described herein can thus have a wide range of lengths and sequences. Reflex sequences may range from 5 to 200 nucleotide bases in length.

"Solid support", "support", and "solid phase support" are used interchangeably and refer to a material or group of materials having a rigid or semi-rigid surface or surfaces. In many embodiments, at least one surface of the solid support will be substantially flat, although in some embodiments it may be desirable to physically separate synthesis regions for different compounds with, for example, wells, raised regions, pins, etched trenches, or the like. According to other embodiments, the solid support(s) will take the form of beads, resins, gels, microspheres, or other geometric configurations. Microarrays usually comprise at least one planar solid phase support, such as a glass microscope slide.

"Specific" or "specificity" in reference to the binding of one molecule to another molecule, such as a labeled target sequence for a probe, means the recognition, contact, and formation of a stable complex between the two molecules, together with substantially less recognition, contact, or complex formation of that molecule with other molecules. In one aspect, "specific" in reference to the binding of a first molecule to a second molecule means that to the extent the first molecule recognizes and forms a complex with another molecule in a reaction or sample, it forms the largest number of the complexes with the second molecule. Preferably, this largest number is at least fifty percent. Generally, molecules involved in a specific binding event have areas on their surfaces or in cavities giving rise to specific recognition between the molecules binding to each other. Examples of specific binding include antibody-antigen interactions, enzyme-substrate interactions, formation of



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duplexes or triplexes among polynucleotides and/or oligonucleotides, biotin-avidin or biotin-streptavidin interactions, receptor-ligand interactions, and the like. As used herein, "contact" in reference to specificity or specific binding means two molecules are close enough that weak noncovalent chemical interactions, such as Van der Waal forces, hydrogen bonding, base-stacking interactions, ionic and hydrophobic interactions, and the like, dominate the interaction of the molecules.

As used herein, the term "$T_m$" is used in reference to the "melting temperature." The melting temperature is the temperature (e.g., as measured in °C) 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 known in the art (see e.g., Anderson and Young, Quantitative Filter Hybridization, in Nucleic Acid Hybridization (1985). Other references (e.g., Allawi, H.T. & SantaLucia, J., 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 $T_m$.

"Sample" means a quantity of material from a biological, environmental, medical, or patient source in which detection, measurement, or labeling of target nucleic acids is sought. On the one hand it is meant to include a specimen or culture (e.g., microbiological cultures). On the other hand, it is meant to include both biological and environmental samples. A sample may include a specimen of synthetic origin. Biological samples may be animal, including human, fluid, solid (e.g., stool) or tissue, as well as liquid and solid food and feed products and ingredients such as dairy items, vegetables, meat and meat by-products, and waste. Biological samples may include materials taken from a patient including, but not limited to cultures, blood, saliva, cerebral spinal fluid, pleural fluid, milk, lymph, sputum, semen, needle aspirates, and the like. Biological samples may be obtained from all of the various families of domestic animals, as well as feral or wild animals, including, but not limited to, such animals as ungulates, bear, fish, rodents, etc. Environmental samples include environmental material such as surface matter, soil, water and industrial samples, as well as samples obtained from food and dairy processing instruments, apparatus, equipment, utensils, disposable and non-disposable items. These examples are not to be construed as limiting the sample types applicable to the present invention.

The terms "upstream" and "downstream" in describing nucleic acid molecule orientation and/or polymerization are used herein as understood by one of skill in the art. As such, "downstream" generally means proceeding in the 5' to 3' direction, i.e., the direction in which a nucleotide polymerase normally extends a sequence, and "upstream" generally



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means the converse. For example, a first primer that hybridizes "upstream" of a second primer on the same target nucleic acid molecule is located on the 5' side of the second primer (and thus nucleic acid polymerization from the first primer proceeds towards the second primer).

It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely", "only" and the like in connection with the recitation of claim elements, or the use of a "negative" limitation.

## DETAILED DESCRIPTION OF THE INVENTION

The invention is drawn to compositions and methods for intramolecular nucleic acid rearrangement that find use in various applications of genetic analysis, including sequencing, as well as general molecular biological manipulations of polynucleotide structures.

Before the present invention is described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated 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 or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

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. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, some potential and preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in



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connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction.

It must be noted 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" includes a plurality of such nucleic acids and reference to "the compound" includes reference to one or more compounds and equivalents thereof known to those skilled in the art, and so forth.

The practice of the present invention may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology, which are within the skill of the art. Such conventional techniques include polymer array synthesis, hybridization, ligation, and detection of hybridization using a label. Specific illustrations of suitable techniques can be had by reference to the example herein below. 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 *Genome Analysis: A Laboratory Manual Series* (Vols. I-IV), *Using Antibodies: A Laboratory Manual, Cells: A Laboratory Manual, PCR Primer: A Laboratory Manual, and Molecular Cloning: A Laboratory Manual* (all from Cold Spring Harbor Laboratory Press), Stryer, L. (1995) *Biochemistry* (4th Ed.) Freeman, New York, Gait, "*Oligonucleotide Synthesis: A Practical Approach*" 1984, IRL Press, London, Nelson and Cox (2000), Lehninger, A., *Principles of Biochemistry* 3rd Ed., W. H. Freeman Pub., New York, N.Y. and Berg et al. (2002) *Biochemistry,* 5th Ed., W. H. Freeman Pub., New York, N.Y., all of which are herein incorporated in their entirety by reference for all purposes.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

As summarized above, aspects of the present invention are drawn to the use of a 'reflex' sequence present in a polynucleotide (e.g., in an adapter structure of the polynucleotide, in a genomic region of the polynucleotide, or a combination of both) to move a domain of the polynucleotide intra-molecularly from a first location to a second location. The reflex process described herein finds use in any number of applications, e.g.,



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placing functional elements of a polynucleotide (e.g., sequencing primer sites and/or MID tags) into proximity to a desired sub-region of interest.

Nucleic Acids

The reflex process (as described in detail below) can be employed for the manipulation and analysis of nucleic acid sequences of interest from virtually any nucleic acid source, including but not limited to genomic DNA, complementary DNA (cDNA), RNA (e.g., messenger RNA, ribosomal RNA, short interfering RNA, microRNA, etc.), plasmid DNA, mitochondrial DNA, synthetic DNA, etc. Furthermore, any organism, organic material or nucleic acid-containing substance can be used as a source of nucleic acids to be processed in accordance with the present invention including, but not limited to, plants, animals (e.g., reptiles, mammals, insects, worms, fish, etc.), tissue samples, bacteria, fungi (e.g., yeast), phage, viruses, cadaveric tissue, archaeological/ancient samples, etc. In certain embodiments, the nucleic acids in the nucleic acid sample are derived from a mammal, where in certain embodiments the mammal is a human.

In certain embodiments, the nucleic acid sequences are enriched prior to the reflex sequence process. By enriched is meant that the nucleic acid is subjected to a process that reduces the complexity of the nucleic acids, generally by increasing the relative concentration of particular nucleic acid species in the sample (e.g., having a specific locus of interest, including a specific nucleic acid sequence, lacking a locus or sequence, being within a specific size range, etc.). There are a wide variety of ways to enrich nucleic acids having a specific characteristic(s) or sequence, and as such any convenient method to accomplish this may be employed. The enrichment (or complexity reduction) can take place at any of a number of steps in the process, and will be determined by the desires of the user. For example, enrichment can take place in individual parental samples (e.g., untagged nucleic acids prior to adaptor ligation) or in multiplexed samples (e.g., nucleic acids tagged with primer sites, MID and/or reflex sequences and pooled; MID are described in further detail below).

In certain embodiments, nucleic acids in the nucleic acid sample are amplified prior to analysis. In certain of these embodiments, the amplification reaction also serves to enrich a starting nucleic acid sample for a sequence or locus of interest. For example, a starting nucleic acid sample can be subjected to a polymerase chain reaction (PCR) that amplifies one or more region of interest. In certain embodiments, the amplification reaction is an exponential amplification reaction, whereas in certain other embodiments, the amplification reaction is a linear amplification reaction. Any convenient method for performing



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amplification reactions on a starting nucleic acid sample can be used in practicing the subject invention. In certain embodiments, the nucleic acid polymerase employed in the amplification reaction is a polymerase that has proofreading capability (e.g., phi29 DNA Polymerase, Thermococcus litoralis DNA polymerase, Pyrococcus furiosus DNA polymerase, etc.).

In certain embodiments, the nucleic acid sample being analyzed is derived from a single source (e.g., a single organism, virus, tissue, cell, subject, etc.), whereas in other embodiments, the nucleic acid sample is a pool of nucleic acids extracted from a plurality of sources (e.g., a pool of nucleic acids from a plurality of organisms, tissues, cells, subjects, etc.), where by "plurality" is meant two or more. As such, in certain embodiments, a nucleic acid sample can contain nucleic acids from 2 or more sources, 3 or more sources, 5 or more sources, 10 or more sources, 50 or more sources, 100 or more sources, 500 or more sources, 1000 or more sources, 5000 or more sources, up to and including about 10,000 or more sources.

In certain embodiments, nucleic acid fragments that are to be pooled with nucleic acid fragments derived from a plurality of sources (e.g., a plurality of organisms, tissues, cells, subjects, etc.), where by "plurality" is meant two or more. In such embodiments, the nucleic acids derived from each source includes a multiplex identifier (MID) such that the source from which the each tagged nucleic acid fragment was derived can be determined. In such embodiments, each nucleic acid sample source is correlated with a unique MID, where by unique MID is meant that each different MID employed can be differentiated from every other MID employed by virtue of at least one characteristic, e.g., the nucleic acid sequence of the MID. Any type of MID can be used, including but not limited to those described in co-pending U.S. Patent Application Serial Number 11/656,746, filed on January 22, 2007, and titled "Nucleic Acid Analysis Using Sequence Tokens", as well as U.S. Patent 7,393,665, issued on July 1, 2008, and titled "Methods and Compositions for Tagging and Identifying Polynucleotides", both of which are incorporated herein by reference in their entirety for their description of nucleic acid tags and their use in identifying polynucleotides. In certain embodiments, a set of MIDs employed to tag a plurality of samples need not have any particular common property (e.g., $T_m$, length, base composition, etc.), as the asymmetric tagging methods (and many tag readout methods, including but not limited to sequencing of the tag or measuring the length of the tag) can accommodate a wide variety of unique MID sets.



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In certain embodiments, each individual polynucleotide (e.g., double-stranded or single-stranded, as appropriate to the methodological details employed) in a sample to be analyzed is tagged with a unique MID so that the fate of each polynucleotide can be tracked in subsequent processes (where, as noted above, unique MID is meant to indicate that each different MID employed can be differentiated from every other MID employed by virtue of at least one characteristic, e.g., the nucleic acid sequence of the MID). For example (and as described below), having each nucleic acid tagged with a unique MID allows analysis of the sequence of each individual nucleic acid using the reflex sequence methods described herein. This allows the linkage of sequence information for large nucleic acid fragments that cannot be sequenced in a single sequencing run.

Reflex Sequence Process

As summarized above, aspects of the present invention include methods and compositions for moving a domain in a polynucleotide from a first location to a second location in the polynucleotide. An exemplary embodiment is shown in Figure 1A.

Figure 1A shows a single stranded polynucleotide 100 comprising, in a 5' to 3' orientation, a first domain (102; the domain to be moved); a reflex sequence 104; a nucleic acid sequence 106 having a site distal to the first domain (Site A), and a complement of the reflex sequence 108 (positioned at the 3' terminus of the polynucleotide). The steps of the reflex method described below will move the first domain into closer proximity to Site A. It is noted here that the prime designation in Figure 1A denotes a complementary sequence of a domain. For example, First Domain' is the complement of the First Domain.

In Step 1, the reflex sequence and its complement in the polynucleotide are annealed intramolecularly to form polynucleotide structure 112, with the polynucleotide folding back on itself and hybridizing to form a region of complementarity (i.e., double stranded reflex/reflex' region). In this configuration, the 3' end of the complement of the reflex sequence can serve as a nucleic acid synthesis priming site. Nucleic acid synthesis from this site is then performed in extension Step 2 producing a complement of the first domain at the 3' end of the nucleic acid extension (shown in polynucleotide 114; extension is indicated with dotted arrow labeled "extend").

Denaturation of polynucleotide 114 (e.g., by heat) generates linear single stranded polynucleotide 116. As shown in Figure 1, resultant polynucleotide 116 contains a complement of the first domain at a position proximal to Site A (i.e., separated by only the complement of the reflex sequence). This resultant polynucleotide may be used for any



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subsequent analysis or processing steps as desired by the user (e.g., sequencing, as a template for amplification (linear, PCR, etc.), sequence specific extraction, etc.).

In alternative embodiments, the first domain and reflex sequence are removed from the 5' end of the double-stranded region of polynucleotide 114 (shown in polynucleotide 118; removal is shown in the dotted arrow labeled "remove"). Removal of this region may be accomplished by any convenient method, including, but not limited to, treatment (under appropriate incubation conditions) of polynucleotide structure 114 with T7 exonuclease or by treatment with Lambda exonuclease; the Lambda exonuclease can be employed so long as the 5' end of the polynucleotide is phosphorylated. If the region is removed enzymatically, resultant polynucleotide 118 is used in place of polynucleotide 116 in subsequent steps (e.g., copying to reverse polarity).

In certain embodiments, polynucleotide 116 or 118 is used as a template to produce a double stranded polynucleotide, for example by performing a nucleic acid synthesis reaction with a primer that primes in the complement of the first domain. This step is sometimes referred to as copying to reverse polarity of a single stranded polynucleotide, and in some instances, the double-stranded intermediate product of this copying is not shown (see, e.g., Figure 3). For example, copying to reverse the polarity of polynucleotide 116 results in single-stranded polynucleotide 120 having, in a 5' to 3' orientation, the first domain (122); the reflex sequence (124); the complement of polynucleotide 106 (oriented with the complement of Site A (Site A'; 126) proximal to the reflex sequence); the complement of the reflex sequence (128); and the complement of the first domain (130).

In certain embodiments, the first domain in the polynucleotide comprises one or more elements that find use in one or more subsequent processing or analysis steps. Such sequences include, but are not limited to, restriction enzyme sites, PCR primer sites, linear amplification primer sites, reverse transcription primer sites, RNA polymerase promoter sites (such as for T7, T3 or SP6 RNA polymerase), MID tags, sequencing primer sites, etc. Any convenient element can be included in the first domain and, in certain embodiments, is determined by the desires of the user of the methods described herein.

As an exemplary embodiment, suppose we want to sequence a specific polynucleotide region from multiple genomes in a pooled sample where the polynucleotide region is too long to sequence in a single reaction. For example, sequencing a polynucleotide region that is 2 kilobases or more in length using Roche 454 (Branford, CT) technology, in which the length of a single sequencing run is about 400 bases. In this scenario, we can design a set of left hand primers ($A_n$) and right hand primers ($B_n$) specific



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for the polynucleotide region that are positioned in such a way that we can obtain direct sequences of all parts of the insert, as shown in Figure 1B. Note that the polynucleotide shown in Figure 1B (140) has a domain (142) containing a primer site and an MID denoting from which original sample(s) the polynucleotide is derived. Site 142 thus represents an example of a First Domain site such identified as 122 in the Figure 1A. The polynucleotide also includes a reflex site (144), which can be part of the polynucleotide region itself (e.g., a genomic sequence), added in a ligated adapter domain along with the primer site and the MID (an artificial sequence), or a combination of both (a sequence spanning the adapter/polynucleotide junction).

It is noted here that polynucleotide 140 can be categorized as a precursor to polynucleotide 100 in Figure 1A, as it does not include a 3' reflex sequence complementary to the reflex site (domain 108 in Figure 1A). As detailed below, polynucleotide 140 can be converted to a polynucleotide having the structural configuration of polynucleotide 100, a polynucleotide suitable as a substrate for the reflex process described herein (e.g., by primer extension using a $B_n$ primer and reversal of polarity).

In an exemplary embodiment, each $A_n$-$B_n$ primer pair defines a nucleic acid region that is approximately 400 bases in length or less. This size range is within the single-sequencing run read length of the current Roche 454 sequencing platform; a different size range for the defined nucleic acid region may be utilized for a different sequencing platform. Thus, each product from each reflex process can be sequenced in a single run. It is noted here that primer pairs as shown in Figure 1B can be used to define regions 1 to 5 shown in Figure 3 (described in further detail below).

In certain embodiments, to obtain the first part of the sequence of the polynucleotide region (i.e., in the original structure, that part of the polynucleotide closest to the first domain), we only need a right hand primer (e.g., $B_0$) and we do not need to transfer the MID as it is within reach of this sequencing primer (i.e., the MID is within 400 bases of sequencing primer $B_0$). All other $B_n$ primers have the reflex sequence added to their 5' ends ("R" element shown on B primers) so that they read 5' reflex-$B_n$. However, in certain embodiments, the $B_0$ primer does include the reflex sequence and is used in the reflex process (along with a corresponding $A_0$ primer) as detailed below.

As described above, we obtain a single stranded polynucleotide having, in the 5' to 3' orientation, a primer site (e.g., for Roche 454 sequencing), an MID, a reflex sequence and the polynucleotide to be sequenced. Numerous methods for obtaining single-stranded polynucleotides of interest have been described and are known in the art, including in U.S.



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Patent 7,217,522, issued on May 15, 2007; U.S. Patent Application 11/377,462, filed on March 16, 2006; and U.S. Patent Application 12/432,080, filed on April 29, 2009; each of which is incorporated by reference herein in their entirety. For example, a single stranded product can be produced using linear amplification with a primer specific for the primer site of the template. In certain embodiments, the primer includes a binding moiety to facilitate isolation of the single stranded nucleic acid of interest, e.g., to immobilize the top strand on a binding partner of the binding moiety immobilized on a solid support. Removal of a hybridized, non-biotinylated strand by denaturation using heat or high pH (or any other convenient method) serves to isolate the biotinylated strand. Binding moieties and their corresponding binding partners are sometimes referred to herein as binding partner pairs. Any convenient binding partner pairs may be used, including but not limited to biotin/avidin (or streptavidin), antigen/antibody pairs, etc.

It is noted here that while the figures and description of the reflex process provided herein depict manipulations with regard to a single stranded polynucleotide, it is not necessarily required that the single stranded polynucleotide described or depicted in the figures be present in the sample in an isolated form (i.e., isolated from its complementary strand). In other words, double stranded polynucleotides may be used where only one strand is described/depicted, which will generally be determined by the user.

The implementation of a single strand isolation step using the methods described above or variations thereof (or any other convenient single strand isolation step) will generally be based on the desires of the user. One example of isolating single stranded polynucleotides is shown in Figure 2. In this Figure, a starting double stranded template (with 5' to 3' orientation shown as an arrow) is denatured and primed with a biotinylated synthesis primer specific for the primer site. After extension of the primer (i.e., nucleic acid synthesis), the sample is contacted with a solid support having streptavidin bound to it. The biotin moiety (i.e., the binding partner of streptavidin) on the extended strands will bind to the solid-phase streptavidin. Denaturation and washing is then performed to remove all non-biotinylated polynucleotide strands. If desired, the bound polynucleotide, which can be used in subsequent reflex process steps (e.g., as a template for $B_n$ primer extension reactions), may be eluted from the streptavidin support. Alternatively, the bound polynucleotide may be employed in subsequent steps of the desired process while still bound to the solid support (e.g., in solid phase extension reactions using $B_n$ primers). This process, with minor variations depending on the template being used and the identity of the desired single stranded polynucleotide, may be employed at any of a number of steps in which a single



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stranded product is to be isolated. It is noted that in certain embodiments, substrate bound biotinylated polynucleotide can be used to produce and isolate non-biotinylated single stranded products (i.e., by eluting the non-biotinylated products while leaving the biotinylated templates bound to the streptavidin on the solid support). Thus, the specifics of how binding partners are used to isolate single stranded polynucleotides of interest will vary depending on experimental design parameters.

Additional single-stranded isolation/production methods include asymmetric PCR, strand-specific enzymatic degradation, and the use of in-vitro transcription followed by reverse transcriptase (IVT-RT) with subsequent destruction of the RNA strand. As noted above, any convenient single stranded production/isolation method may be employed.

To the single stranded polynucleotide shown in Figure 1B we anneal one of the $B_n$ primers having the appended reflex sequence, denoted with a capital "R" (e.g., $B_1$) and extend the primer under nucleic acid synthesis conditions to produce a copy of the polynucleotide that has a reflex sequence at its 5' end. A single stranded copy of this polynucleotide is then produced to reverse polarity using a primer specific for the primer site in the first domain' (complement of the first domain 102). The resulting nucleic acid has structure 100 shown in Figure 1A, where the first domain 102 includes the primer site and the MID. Site A (110) in Figure 1 is determined by the specificity of the 5' reflex-$B_n$ primer used.

The reflex process (e.g., as shown in Figure 1) is then performed to produce a product in which the primer site and the MID are now in close proximity to the desired site (or region of interest (ROI)) within the original polynucleotide (i.e., the site defined by the primer used, e.g., $B_1$). The resulting polynucleotide can be used in subsequent analyses as desired by the user (e.g., Roche 454 sequencing technology).

It is noted here that, while not shown in Figure 1A and 1B, any convenient method for adding adapters to a polynucleotide to be processed as described herein may be used in the practice of the reflex process (adapters containing, e.g., primer sites, polymerase sites, MIDs, restriction enzyme sites, and reflex sequences). For example, adapters can be added at a particular position by ligation. For double stranded polynucleotides, an adapter can be configured to be ligated to a particular restriction enzyme cut site. Where a single stranded polynucleotide is employed, a double stranded adapter construct that possesses an overhang configured to bind to the end of the single-stranded polynucleotide can be used. For example, in the latter case, the end of a single stranded polynucleotide can be modified to include specific nucleotide bases that are complementary to the overhang in the double



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stranded adaptor using terminal transferase and specific nucleotides. In other embodiments, PCR or linear amplification methods using adapter-conjugated primers is employed to add an adapter at a site of interest. Again, any convenient method for producing a starting polynucleotide may be employed in practicing the methods of the subject invention.

In certain embodiments, the nucleic acid may be sequenced directly using a sequencing primer specific for the primer site. This sequencing reaction will read through the MID and desired site in the insert.

In certain embodiments, the polynucleotide may be isolated (or fractionated) using an appropriate $A_n$ primer (e.g., when using $B_1$ as the first primer, primer $A_1$ can be used). In certain embodiments, the $A_n$ primed polynucleotide is subjected to nucleic acid synthesis conditions to produce a copy of the fragment produced in the reflex process. In certain of these embodiments, the $A_n$ primer has appended on its 5' end a primer site that can be used in subsequent steps, including sequencing reactions. Providing a primer site in the $A_n$ primer allows amplifying and/or sequencing from both ends of the resultant fragment: from the primer site in the first domain 102 and the primer site in the $A_n$ primer (not shown in Figure 1B). Because of the position of the primer sites and their distance apart (i.e., less than one sequencing run apart), sequencing from both ends will usually capture the sequence of the desired site (or ROI) and the sequence of the MID, which can be used for subsequent bioinformatic analyses, e.g., to positively identify the sample of origin. It is noted here that while sequencing in both directions is possible, it is not necessary, as sequencing from either primer site alone will capture the sequence of the ROI as well as its corresponding MID sequence.

Note that in certain embodiments, the first fragment obtained by amplification/extension from primer $B_0$ directly, the polarity of the ROI in the resulting fragment is reversed as compared to the ROI in fragments obtained by primers $B_1$-$B_n$. This is because the $B_0$-generated fragment, unlike the $B_1$-$B_n$ generated fragments, has not been subjected to a reflex process which reverses the orientation of the ROI sequence with respect to the first domain/reflex sequence (as described above). Therefore, the $B_0$ primer may have appended to it a primer site (e.g., at its 5' end) that can be used for subsequent amplification and/or sequencing reactions (e.g., in Roche 454 sequencing system) rather than a reflex sequence as with primers $B_1$-$B_n$. However, in certain embodiments, as noted above, the reflex process may be used with a corresponding $B_0$-$A_0$ primer pair as described above, i.e., using a $B_0$ primer having a 5' reflex sequence and a corresponding $A_0$ primer with its corresponding 5' adapter domain (e.g., a primer site).



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It is noted here that because the particular sections of sequence to be analyzed are defined by the $A_n$-$B_n$ primer pairs (as shown and described above), a much higher sequence specificity is achieved as compared to using previous extraction methods that employ only a single oligo binding event (e.g., using probes on a microarray).

Figure 3 provides a detailed flow chart for an exemplary embodiment that employs reflex sequences for use in sequencing multiple specific regions in a polynucleotide (i.e., regions 1, 2, 3, 4 and 5 in an 11kb region of lambda DNA).

A single parent DNA fragment 202 is generated that includes adapter domains (i.e., a Roche 454 sequencing primer site, a single MID, and a reflex sequence) and the sequence of interest. In the example shown, the sequence of interest is from lambda DNA and the reflex sequence is present on the top strand (with its complement shown in the bottom strand). Any convenient method for producing this parent DNA fragment may be used, including amplification with a primer that includes the adapter domains (e.g., using PCR), cloning the fragment into a vector that includes the adapter domains (e.g., a vector with the adapter domains adjacent to a cloning site), or by attaching adapters to polynucleotide fragments (e.g., fragment made by random fragmentation, by sequence-specific restriction enzyme digestion, or combinations thereof). While only a single fragment with a single MID is shown, the steps in Figure 3 are applicable to samples having multiple different fragments each with a different MID, e.g., a sample having a population of homologous fragments from any number of different sources (e.g., different individuals). Figure 3 describes the subsequent enzymatic steps involved in creating the five daughter fragments in which regions 1, 2, 3, 4 and 5 (shown in polynucleotide 204) are rearranged to be placed within a functional distance of the adapter domains (i.e., close enough to the adapter domains to be sequenced in a single Roche 454 sequencing reaction). Note that certain steps are shown for region 4 only (206).

In step 1, the five regions of interest are defined within the parent fragment (labeled 1 to 5 in polynucleotide 204) and corresponding primer pairs are designed for each. The distance of each region of interest from the reflex sequence is shown below polynucleotide 204. The primer pairs are designed as described and shown in Figure 1B (i.e., the $A_n$-$B_n$ primer pairs). For clarity, only primer sites for region 4 are shown in Figure 3 ("primer sites" surrounding region 4). In step 2, sequence specific primer extensions are performed (only region 4 is shown) with corresponding $B_n$ primers to produce single stranded polynucleotides having structure 208 (i.e., having the reflex sequence on the 5' terminus). As shown, the $B_n$ primer for region 4 will include a sequence specific primer site that primes



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at the 3'-most primer site noted for region 4 (where "3'-most" refers to the template strand, which in Figure 3 is the top strand). This polynucleotide is copied back to produce polynucleotide 210 having reversed polarity (e.g., copied using a primer that hybridizes to the 454A' domain). Polynucleotide 210 has structure similar to polynucleotide 100 shown at the top of Figure 1. Step 4 depicts the result of the intramolecular priming between the reflex sequence and its complement followed by extension to produce the MID' and 454A' structures at the 3' end (polynucleotide 212). In the embodiments shown in Figure 3, polynucleotide 212 is treated with T7 exonuclease to remove double stranded DNA from the 5' end (as indicated above, this step is optional). The polynucleotide formed for region 4 is shown as 216 with polynucleotides for the other regions also shown (214).

It is noted here that the formation of each of the polynucleotides 214 may be accomplished either in separate reactions (i.e., structure with region 1 in proximity to the adapter domains is in a first sample, the structure with region 2 in proximity to the adapter region is in a second sample, etc.) or in one or more combined sample.

In step 6 the polynucleotides 214 are copied to reverse polarity to form polynucleotides 218. In step 7, each of these products are then primed with the second primer of the specific primer pair (see $A_n$ primers as shown in Figure 1B) each having a second Roche 454 primer site (454B) attached at the 5' end, and extended to form products 220. Steps 6 and 7 may be combined (e.g., in a single PCR or other amplification reaction).

In summary, Figure 3 shows how the reflex process can be employed to produce five daughter fragments 220 of similar length (e.g., ~500 bp) each of which contain DNA sequences that differ in their distance from the reflex sequence in the starting structure 202 while maintaining the original MID.

Figure 4 shows another exemplary use of the reflex process as described herein. In the embodiment shown in Figure 4, a target sequence (i.e., containing region of interest "E") is enriched from a pool of adapter-attached fragments. In certain embodiments, the fragments are randomly sheared, selected for a certain size range (e.g., DNA having a length from 100 to 5000 base pairs), and tagged with adapters (e.g., asymmetric adapters, e.g., as described in US Patent Application Ser. No. 12/432,080, filed on April 29, 2009). The asymmetric adaptor employed in Figure 4 contains a sequencing primer site (454A, as used in the Roche 454 sequencing platform), an MID, an X sequence, and an internal stem region (ISR), which denotes the region of complementarity for the asymmetric adapter that is adjacent to the adapter attachment site (see, e.g., the description in US Application Ser. No. 12/432,080, filed on April 29, 2009, incorporated herein by reference in its entirety). The X



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sequence can be any sequence that can serve as a binding site for a polynucleotide containing the complement of the X sequence (similar to a primer site). As described below, the X sequence allows for the annealing of an oligonucleotide having a 5' overhang that can serve as a template for extension of the 3' end of the adaptor oligonucleotide. The sequencing direction of the sequencing primer site (454A primer site in structure 401 of Figure 4) is oriented such that amplification of the adapter ligated fragment using the sequencing primer site proceeds away from the ligated genomic insert. This has the effect of making the initial asymmetric adapter ligated library 'inert' to amplification using this primer, e.g., in a PCR reaction.

To extract a region of interest (the "E" region), the library is mixed with an oligonucleotide (403) containing a 3' X' sequence and a target specific priming sequence (the 1' sequence) under hybridization/annealing conditions. The target specific sequence 1' is designed to flank one side of the region of interest (the 1' sequence adjacent to E in the genomic insert; note that only the E-containing polynucleotide fragment is shown in Figure 4), much like a PCR primer. After annealing primer 403, the hybridized complex is extended, whereby all of the adaptor tagged fragments will obtain the complement of the target specific sequence (i.e., the 1 sequence) on the 3' end (see structure 405; arrows denote the direction of extension).

Extended products 405 are then denatured and the 1/1' regions allowed to hybridize intramolecularly in a reflex process priming event, after which nucleic acid extension is performed to form structure 407 (extension is from the 1 priming site; shown with an arrow). This reflex reaction creates a product (407) that, unlike its parent structure (405), has a sequencing primer site (454A) that is oriented such the extension using this primer sequence proceeds towards the region of interest. Thus, in the absence of a priming and extension reflex reaction, extension with a sequencing primer will not generate a product containing the region of interest (the E region). In other words, only E-region containing target polynucleotides will have a 454A sequence that can amplify genomic material (structure 407).

After completing the reflex process (using 1/1' as the reflex sequences), a PCR amplification reaction is performed to amplify the region of interest (with associated adapter domains). However, before performing the PCR reaction, the fragment sample is "inactivated" from further extension using terminal transferase and ddNTPs. This inactivation prevents non-target adaptor tagged molecules from performing primer extension from the 3' primer 1 site. Once inactivated, a PCR reaction is performed using a sequencing



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primer (i.e., 454A primer 409) and a second primer that primes and extends from the opposite side of the region of interest (i.e., primer 411, which includes a 5' 454B sequencing primer site and a 3' "2" region that primes on the opposite end of E from the 1 region). Only fragments that have undergone the reflex process and contain the E region will be suitable templates for the PCR reaction and produce the desired product (413).

Thus, the process exemplified in Figure 4 allows for the movement of an adapter domain (e.g., containing functional elements and/or MID) into proximity to a desired region of interest.

The reflex process described herein can be used to perform powerful linkage analysis by combining it with nucleic acid counting methods. Any convenient method for tagging and /or counting individual nucleic acid molecules with unique tags may be employed (see, e.g., U.S. Patent 7,537,897, issued on May 26, 2009; U.S. Patent 7,217,522, issued on May 15, 2007; U.S. Patent Application 11/377,462, filed on March 16, 2006; and U.S. Patent Application 12/432,080, filed on April 29, 2009; each of which is incorporated by reference herein in their). All of this can be conducted in parallel thus saving on the cost of labor, time and materials.

In one exemplary embodiment, a large collection of sequences is tagged with MID such that each polynucleotide molecule in the sample has a unique MID. In other words, each polynucleotide in the sample (e.g., each individual double stranded or single stranded polynucleotide) is tagged with a MID that is different from every other MID on every other polynucleotide in the sample. In general, to accomplish such molecular tagging the number of distinct MID tags to be used should be many times greater than the actual number of molecules to be analyzed. This will result in the majority of individual nucleic acid molecules being labeled with a unique ID tag (see, e.g., Brenner et al., Proc. Natl. Acad. Sci. USA. 2000 97(4):1665-70). Any sequences that then result from the reflex process on that particular molecule (e.g., as described above) will thus be labeled with the same unique MID tag and thus inherently linked. Note that once all molecules in a sample are individually tagged, they can be manipulated and amplified as much as needed for processing so long as the MID tag is maintained in the products generated.

For example, we might want to sequence one thousand viral genomes (or a specific genomic region) or one thousand copies of a gene present in somatic cells. After tagging each polynucleotide in the sample with a sequencing primer site, MID and reflex sequence (as shown in the figures and described above), we use the reflex process to break each polynucleotide into lengths appropriate to the sequencing procedure being used, transferring



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the sequencing primer site and MID to each fragment (as described above). Obtaining sequence information from all of the reflex-processed samples can be used to determine the sequence of each individual polynucleotide in the starting sample, using the MID sequence to defining linkage relationships between sequences from different regions in the polynucleotide being sequenced. Using a sequencing platform with longer read lengths can minimize the number of primers to be used (and reflex fragments generated).

The advantages noted above are shown in Figure 5. This figure shows a comparison of methods for identifying nucleic acid polymorphisms in homologous nucleic acids in a sample (e.g., the same region derived from a chromosomal pair of a diploid cell or viral genomes/transcripts). The top schematic shows two nucleic acid molecules in a sample (1 and 2) having a different assortment of polymorphisms in polymorphic sites A, B and C (A1, B1, C1 and C2). Standard sequencing methods using fragmentation (left side) can identify the polymorphisms in these nucleic acids but do not retain linkage information. Employing the reflex process described herein to identify polymorphisms (right side) maintains linkage information. It is noted that not all domain structures and steps are shown in the reflex process for simplicity.

Kits and Systems

Also provided by the subject invention are kits and systems for practicing the subject methods, as described above, such vectors configured to add reflex sequences to nucleic acid inserts of interest and regents for performing any steps in the cloning or reflex process described herein (e.g., restriction enzymes, nucleotides, polymerases, primers, exonucleases, etc.). The various components of the kits may be present in separate containers or certain compatible components may be precombined into a single container, as desired.

The subject systems and kits may also include one or more other reagents for preparing or processing a nucleic acid sample according to the subject methods. The reagents may include one or more matrices, solvents, sample preparation reagents, buffers, desalting reagents, enzymatic reagents, denaturing reagents, where calibration standards such as positive and negative controls may be provided as well. As such, the kits may include one or more containers such as vials or bottles, with each container containing a separate component for carrying out a sample processing or preparing step and/or for carrying out one or more steps of a nucleic acid variant isolation assay according to the present invention.

In addition to above-mentioned components, the subject kits typically further include instructions for using the components of the kit to practice the subject methods, e.g., to prepare nucleic acid samples for perform the reflex process according to aspects of the



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subject methods. The instructions for practicing the subject methods are generally recorded on a suitable recording medium. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e., associated with the packaging or sub-packaging) etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g. via the internet, are provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions is recorded on a suitable substrate.

In addition to the subject database, programming and instructions, the kits may also include one or more control samples and reagents, e.g., two or more control samples for use in testing the kit.

Utility

The reflex process described herein provides significant advantages in numerous applications, a few of which are noted below (as well as described above).

For example, as described above, certain aspects of the reflex process define the particular sections of sequence to be analyzed by a primer pair, as in PCR (e.g., the two oligos shown as $A_n$-$B_n$ in Figure 1B). This results in higher sequence specificity as compared to other extraction methods (e.g., using probes on a microarray) that only use a single oligo sequence. The separation of the probes defines a length that can be relatively uniform (hence making subsequent handling including amplification more uniform) and can also be tailored to the particular sequencing platform being employed.

Further, as described above, aspects of the present invention can be used to analyze homologous genomic locations in a multiplexed sample (i.e., a sample having polynucleotides from different genomic samples) in which the polynucleotides are tagged with the MID. This is possible because the reflex process, which operates intramolecularly, maintains the MID thus linking any particular fragment to the sample from which it originates.

Finally, as the reflex processes described herein function intramolecularly, one can determine the genetic linkage between different regions on the same large fragment that are too far apart to be sequenced in one sequence read. Such a determination of linkage may be of great value in plant or animal genetics (e.g., to decide if a particular set of variations are



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linked together on the same stretch of chromosome) or in viral studies (e.g., to determine if particular variations are linked together on the same stretch of a viral genome/transcripts, e.g., HIV, hepatitis virus, etc.).

## EXAMPLES

Example I

Figures 6 and 7 provide experimental data and validation of the reflex process described herein using synthetic polynucleotide substrates.

METHODS

Substrate:

The 100 base oligonucleotide substrate (as shown diagrammatically in Figure 6A) was synthesized with internal fluorescein-dT positioned between the REFLEX and REFLEX' sequences. This label provides convenient and sensitive method of detection of oligonucleotide species using polyacrylamide gel electrophoresis.

Extension reactions:

Reactions were prepared which contained 1 μM of the 100 base oligonucleotide substrate, 200 μM dNTPs, presence or absence of 1 μM competitor oligonucleotide, 0.5 μl of each DNA polymerase ("DNAP"): Vent (NEB, 2 units/μl), Taq (Qiagen HotStarTaq 5 units/μl) and Herculase (Stratagene), and made up to 50 μl with the appropriate commercial buffers for each polymerase and $dH_20$. For Taq titrations 0.5 μl, 1 μl, 2 μl, and 3 μl enzyme was used in the same 50 μl volume. Reactions were heated in a Biometra thermocycler to 95 °C for 15 minutes (Taq) or 5 minutes (Herculase, Vent), followed by 55 °C or 50 °C for 30 seconds, and a final incubation at 72 °C for 10 minutes.

T7 exonuclease digestions:

Reactions were prepared with 10 μl extension reactions above, 0.5 μl T7 exonuclease (NEB, 10 units/μl), and made up to 50 μl using NEB Buffer 4 and $dH_20$. Reactions were incubated at 25 °C for 30 minutes.

Gel Electrophoresis analysis:

An 8% denaturing polyacrylamide gel was used to analyze reaction species. 0.4 μl of extension reactions, and 2 μl of digestion reactions were loaded and ran at 800V for ~1.5 hours. Gels were analyzed for fluorescein using an Amersham/General Electric Typhoon imager.



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RESULTS

Figure 6A shows the structure of each stage of reflex sequence processing with the expected nucleic acid size shown on the left. The initial single stranded nucleic acid having a sequencing primer site (the Roche 454 sequencing primer A site; listed as 454A); an MID; a reflex sequence; the insert; and a complement of the reflex sequence is 100 nucleotides in length. After self-annealing and extension, the product is expected to be 130 nucleotides in length. After removal of the double stranded region from the 5' end, the nucleic acid is expected to be 82 bases in length.

Figure 6B shows the results of three experiments using three different nucleic acid polymerases (Vent, Herculase and Taq, indicated at the top of the lanes). The temperature at which the annealing was carried out is shown at the top of each lane (either 50°C or 55°C). The sizes of the three nucleic acids as noted above are indicated on the left and right side of the gel.

As shown in figure 6B, extension appears to be most efficient under the conditions used with Herculase (Herculase is a mixture of two enzymes: modified Pfu DNAP and Archaemax (dUTPase)). Most (or all) of the initial 100 base pair nucleic acid are converted to the 130 base pair product (see lanes 6 and 7). However, after T7 exonuclease digestion the 3'-5' exonuclease activity of Herculase results in partial digestion of the desired 82 base product (note bands at and below the 82 base pairs in lanes 8 and 9).

Taq, which lacks 3'-5' exonuclease activity, shows a stronger band at the expected size of the final product after T7 exonuclease digestion (see lane 13).

Figure 7 shows the effect on the reflex process of increasing amounts of Taq polymerase as well as the use of a reflex sequence competitor (schematically shown in Figure 7A).

As shown in lanes 2 to 5, increased Taq concentration improves extension to ~90% conversion of the starting nucleic acid (see lane 5). Lanes 7 to 8 show that T7 exonuclease digestion does not leave a perfect 82 base product. This may be due to collapse of dsDNA when T7 exonuclease has nearly completed its digestion from the 5' end in the double stranded region of the fold-back structure. It is noted that in many embodiments, the removal of a few additional bases from the 5' end of the polynucleotide will not interfere with subsequent analyses, as nucleotide bases at the 5' end are often removed during subsequent steps.

As shown in Lanes 11-14, addition of a competitor (which can interfere with annealing of the reflex sequences to form the fold-back structure) results in only a small



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decrease (~5-10%) of fully extended product. Thus, as expected, the intramolecular reaction is heavily favored. Although not shown, we have observed that the competitor oligonucleotide also gets extended by the same amount (~5-10%).

The concentration of the competitor, the concentration of the reflex substrate, and the overall genetic complexity, will all likely affect specific results. The experiments shown in Figures 6 and 7 demonstrate that the core parts of the reflex processes as described herein is functional and can be implemented.

Example II

Figure 8 shows the reflex workflow (diagram at left) and exemplary results of the workflow (gel at right) for a specific region of interest (ROI). The starting material is a double stranded nucleic acid molecule (700) that contains a 454A primer site, an MID, a reflex site, and a polynucleotide of interest having three ROIs (2, 3 and 4) at different locations therein. This starting material was subjected to reflex processes (as described in above) specific for ROI 2 as shown in the diagram at the left of the figure, both with and without the use of a T7 exonuclease step (the T7 exonuclease step is shown in the diagram is indicated as "Optional").

Completion of all steps shown in the reflex process should result in a double stranded polynucleotide of 488 base pairs (702) with or without the T7 exonuclease step.

As shown in the gel on the right of Figure 8, the 488 base pair product was produced in reflex processes with and without the T7 exonuclease step.

Figure 9 shows an exemplary protocol for a reflex process based on the results discussed above. The diagram shows specific reflex process steps with indications on the right as to where purification of reaction products is employed (e.g., using Agencourt SPRI beads to remove primer oligos). One reason for performing such purification steps is to reduce the potential for generating side products in a reaction (e.g., undesirable amplicons). While Figure 9 indicates three purification steps, fewer or additional purification steps may be employed depending on the desires of the user. It is noted that the steps of reversing polarity, reflex priming and extension, and "stretch out" (or denaturation) / second reversing polarity step can be performed without intervening purification steps.

The protocol shown in Figure 9 includes the following steps:

annealing a first primer containing a 5' reflex sequence (or reflex tail, as noted in the figure) specific for the 3' primer site for the R' region to the starting polynucleotide and extending (the primer anneals to the top strand at the primer site at the right of R in



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polynucleotide 902, indicated with a *; this step represents the first denature, anneal and extend process indicated on the right);

after purification, adding a 454A primer and performing three cycles of denaturing, annealing and extending: the first cycle results in the copy-back from the 454A primer to reverse the polarity of the strand just synthesized; the second cycle breaks apart the double stranded structure produced, allows the reflex structure to form and then extend; the third cycle results in another copy-back using the same 454A primer originally added;

after purification, adding a second primer specific for the second primer site for the R' region having a 5' 454B tail (this primer anneals to the primer site 3' of the R' region in polynucleotide 904, indicated with a *) and denaturing, annealing and extending resulting in a polynucleotide product having 454A and 454B sites surrounding the MID, the reflex sequence, and R'. Note that the first primer specific for the R' region and the second primer specific for the R' region define its boundaries, as described above and depicted in Figure 1B);

after another purification, adding 454A and 454B primers and performing a PCR amplification reaction.

Example III

As described above, a reflex sequence can be an "artificial" sequence added to a polynucleotide as part of an adapter or can be based on a sequence present in the polynucleotide of interest being analyzed, e.g., a genomic sequence (or "non-artificial").

The data shown in prior Examples used "artificial" reflex sites. In this Example, the reflex site is a genomic sequence present in the polynucleotide being analyzed.

The starting material is a double stranded DNA containing a 454A site, an MID and a polynucleotide to be analyzed. The 454A and MID were added by adapter ligation to parent polynucleotide fragments followed by enrichment of the polynucleotide to be analyzed by a hybridization-based pull-out reaction and subsequent secondary PCR amplification (see Route 1 in Figure 13). Thus, the reflex site employed in this example is a sequence normally present at the 5' end of the subject polynucleotide (a genomic sequence). The polynucleotide being analyzed includes a region of interest distal to the 454A and MID sequences that is 354 base pairs in length.

This starting double stranded nucleic acid is 755 base pairs in length. Based on the length of each of the relevant domains in this starting nucleic acid, the reflex process should result in a product of 461 base pairs.



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Figure 10 shows the starting material for the reflex process (left panel) and the resultant product generated using the reflex process (right panel; reflex process was performed as described in Example II, without using a T7 exonuclease step). A size ladder is included in the left hand lane of each gel to allow estimation of the size of the test material. This figure shows that the 755 base pair starting nucleic acid was processed to the expected 461 base pair product, thus confirming that a "non-artificial" reflex site is effective in moving an adapter domain from one location to another in a polynucleotide of interest in a sequence specific manner.

Example IV

Figure 11 shows a schematic of an experiment in which the reflex process is performed on a single large initial template (a "parent" fragment) to generate 5 different products ("daughter" products) each having a different region of interest (i.e., daughter products are produced having either region 1, 2, 3, 4 or 5). The schematic in Figure 11 shows the starting fragment (11,060 base pairs) and resulting products (each 488 base pairs) generated from each of the different region of interest-specific reflex reactions (reflex reactions are performed as described above). The panel (gel) on the bottom of Figure 11 shows the larger starting fragment (Lane 1) and the resulting daughter products for each region-specific reflex reaction (lanes 2 to 6, with the region of interest noted in each in the box), where the starting and daughter fragments have the expected lengths. Sequencing of the products confirmed the identity of the region of interest in each of the reflex products shown in the gel. These results demonstrate that multiple different reflex products can be generated from a single, asymmetrically tagged parent fragment while maintaining the adapter domains (e.g., the primer sites and MID).

Example V

Figure 12 details experiments performed to determine the prevalence of intramolecular rearrangement (as desired in the reflex process) vs. intermolecular rearrangement. Intermolecular rearrangement is undesirable because it can lead to the transfer of an MID from one fragment to another (also called MID switching). MID switching can occur if a reflex sequence in a first fragment hybridizes to its complement in a second fragment during the reflex process, leading to appending the MID from the second fragment to the first fragment. Thus, intermolecular rearrangement, or MID switching, should be minimized to prevent the transfer of an MID from one fragment in the sample to another, which could lead to a misrepresentation of the source of a fragment.



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To measure the prevalence of MID switching under different reflex conditions, fragments having different sizes were generated that included two different MIDs, as shown in the top panel of Figure 12. The common sequence on these fragments serves as the priming site for the first extension reaction to add the second reflex sequence (see, e.g., step 2 of Figure 3). Three exemplary fragments are shown in Figure 12 for each different fragment size (i.e., 800 base pairs with an MIDB and MIDA combination; 1900 base pairs with MIDC and MIDA combination; and 3000 base pairs with MIDD and MIDA combination). For each MID family (A, B, C and D), there are 10 different members (i.e., MIDA had 10 different members, MIDB has 10 different members, etc.). A set of 10 dual MID fragments for each different size fragment (i.e., 800, 1900 and 3000 base pairs) were generated, where the MID pairs (i.e., MIDA/MIDB, MIDA/MIDC, and MIDA/MIDD) were designated as 1/1, 2/2, 3/3, 4/4, 5/5, 6/6, 7/7, 8/8, 9/9, and 10/10. All 10 fragments of the same size were then mixed together and a reflex protocol was performed.

Due to the domain structure of the fragments, a successful reflex process results in the two MIDs for each fragment being moved to within close enough proximity to be sequenced in a single read using the Roche 454 sequencing platform (see the reflex products shown in the schematic of Figure 12). The reflex reactions for each fragment size were performed at four different fragment concentrations to determine the effect of this parameter, as well as fragment length, in the prevalence of MID switching. The reflex products from each reaction performed were subjected to 454 sequencing to determine the identity of both MIDs on each fragment, and thereby the proportion of MID switching that occurred.

The panel on the bottom left of Figure 12 shows the rate of MID switching (Y axis, shown in % incorrect (or switched) MID pair) for each different length fragment at each different concentration (X axis; 300, 30, 3 and 0.3 nM). As shown in this panel, the MID switch rate decreases with lower concentrations, as would be expected, because intermolecular, as opposed to intramolecular, binding events are concentration dependent (i.e., lower concentrations lead to reduced intermolecular hybridization/binding). In addition, the MID switch rate decreases slightly with length. This is somewhat unexpected as the ends of longer DNA fragments are effectively at a lower concentration with respect to one another. The reasons for why we do not see this is probably because the production of reflex priming intermediates continues during the final PCR, which means that reflex priming reactions are happening continuously which contributes to MID switching. It is probably the case that the shorter reflex products are able to undergo a higher rate of 'background' reflexing, and therefore increase the overall MID switch rate a little.



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These results demonstrate that MID switching can be minimized (e.g., to below 2%, below 1% or even to nearly undetectable levels) by altering certain parameters of the reaction, e.g., by reducing fragment concentration and/or fragment length.

The panel on the bottom right of Figure 12 shows the frequency of MID switching in the reflex process for the 800 base pair fragments (i.e., MIDA/MIDB containing fragments). In this figure, the area of each circle is proportional to the number of reads containing the corresponding MIDA and MIDB species (e.g., MIDA1/MIDB1; MIDA1/MIDB2; etc.). Thus, a circle representing 200 reads will be 40 times larger in terms of area than a circle representing 5 reads.

As noted above, the MIDA/MIDB combinations having the same number (shown on the X and Y axis, respectively) represent the MIDA/MIDB combinations present in the sample prior to the reflex process being performed (i.e., MIDA/MIDB combinations 1/1, 2/2, 3/3, 4/4, 5/5, 6/6, 7/7, 8/8, 9/9, and 10/10 were present in the starting sample). All other MIDA/MIDB combinations identified by Roche 454 sequencing were the result of MID switching.

This figure shows that the MID switching that occurs during the reflex process is random, i.e., that MID switching is not skewed based on the identity of the MIDs in the reaction).

Exemplary Reflex Protocols

Figure 13 shows a diagram of exemplary protocols for performing the reflex process on pools of nucleic acids, for example, pools of nucleic acids from different individuals, each of which are labeled with a unique MID. In Route 3, a pooled and tagged extended library is subjected directly to a reflex process. In Route 2, the pooled library is enriched by target-specific hybridization followed by performing the reflex process. In Route 1 employs enrichment by PCR amplification. As shown in Figure 13, PCR enrichment can be performed directly on the pooled tagged extended library or in a secondary PCR reaction after a hybridization-based enrichment step has been performed (as in Route 2) to generate an amplicon substrate that is suitable for the reflex process. Additional routes for preparing a polynucleotide sample for performing a reflex process can be implemented (e.g., having additional amplification, purification, and/or enrichment steps), which will generally be dependent on the desires of the user.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes



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and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Accordingly, 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.



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## CLAIMS

That which is claimed is:

1. A method of moving a domain in a nucleic acid, the method comprising:

a) annealing a reflex sequence in a polynucleotide strand in a sample with a complement of the reflex sequence present in the polynucleotide strand, wherein the polynucleotide strand comprises the following in a 5' to 3' orientation:

a first domain;

the reflex sequence;

a polynucleotide of interest; and

the complement of the reflex sequence, wherein the complement of the reflex sequence is present at the 3' end of the polynucleotide strand; and

b) extending from the 3' end of the complement of the reflex sequence through the first domain to produce a double stranded region;

whereby a complement of the first domain is present at the 3' end of the extended polynucleotide strand, thereby moving the first domain in the polynucleotide strand.

2. The method of claim 1, wherein the first domain comprises a multiplex identifier (MID).

3. The method of claim 1, wherein the first domain comprises a primer site.

4. The method of claim 1, wherein the reflex sequence is from 10 to 50 nucleotides in length.

5. The method of claim 1, wherein the reflex sequence comprises an RNA polymerase site.

6. The method of claim 1, the method further comprising removing the first domain and the reflex sequence from the 5' end of the double stranded region.

7. The method of claim 6, wherein the removing step comprises treating the nucleic acid of step b with T7 exonuclease.

8. The method of claim 1, wherein the first domain is present in an adapter region attached to the polynucleotide of interest.



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9. The method of claim 8, wherein the reflex sequence is present in the adapter region.

10. The method of claim 8, wherein the reflex sequence is a sequence present within the 5' region of the polynucleotide of interest.

11. The method of claim 1, wherein the sample is a multiplexed sample, wherein the first domain in each of the polynucleotide strands in the multiplexed sample comprises a MID corresponding to its parental sample.

12. The method of claim 1, wherein the sample comprises multiple polynucleotide strands, and wherein each polynucleotide strand in the sample comprises a unique MID in the first domain.

13. The method of claim 1, wherein the polynucleotide strand is produced by:

annealing a nucleic acid synthesis primer to a parent polynucleotide strand, wherein the parent polynucleotide strand comprises the following in a 5' to 3' orientation:

the first domain;

the reflex sequence; and

a second domain comprising the polynucleotide of interest;

wherein the nucleic acid synthesis primer comprises:

a 3' priming domain that is complementary to a site adjacent to and 3' of the polynucleotide of interest in the second domain; and

a 5' reflex sequence;

extending the nucleic acid synthesis primer to produce an extension product; and

replicating the resultant extension product with a second nucleic acid synthesis primer that anneals at the 3' end of the complement of the first domain, thereby producing the polynucleotide strand.

14. The method of claim 13, wherein the length of the second domain is from 30 bases to 30 kilobases.

15. The method of claim 13, wherein the parent polynucleotide strand is enriched prior to the annealing step based on its sequence.



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16. The method of claim 1, further comprising the steps of:

c) replicating the polynucleotide strand of step b with a first nucleic acid synthesis primer that anneals at the 3' end of the complement of the first domain to produce a first extension product;

d) annealing a second nucleic acid synthesis primer to the first extension product, wherein the second nucleic acid synthesis primer comprises a 3' priming domain that is complementary to a site within the polynucleotide of interest in the first extension product; and

e) extending the second synthesis primer to produce a second extension product.

17. The method of claim 16, wherein the second synthesis primer comprises a 5' domain that is not complementary to the polynucleotide of interest in the first extension product.

18. The method of claim 17, wherein the first domain comprises a first primer site and the 5' domain of the second synthesis primer comprises a second primer site.

19. The method of claim 18, wherein the length of the polynucleotide of interest in the second extension product is from 50 to 10,000 nucleotides.

20. A polynucleotide strand comprising the following in a 5' to 3' orientation:

a first domain;

a reflex sequence;

a polynucleotide of interest; and

a complement of the reflex sequence, wherein the complement of the reflex sequence is present at the 3' end of the polynucleotide strand.



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## ABSTRACT OF THE DISCLOSURE

Aspects of the present invention are drawn to processes for moving a region of interest in a polynucleotide from a first position to a second position with regard to a domain within the polynucleotide, also referred to as a "reflex method". In certain embodiments, the reflex method results in moving a region of interest into functional proximity to specific domain elements present in the polynucleotide (e.g., primer sites and/or MID). Compositions, kits and systems that find use in carrying out the reflex processes described herein are also provided.



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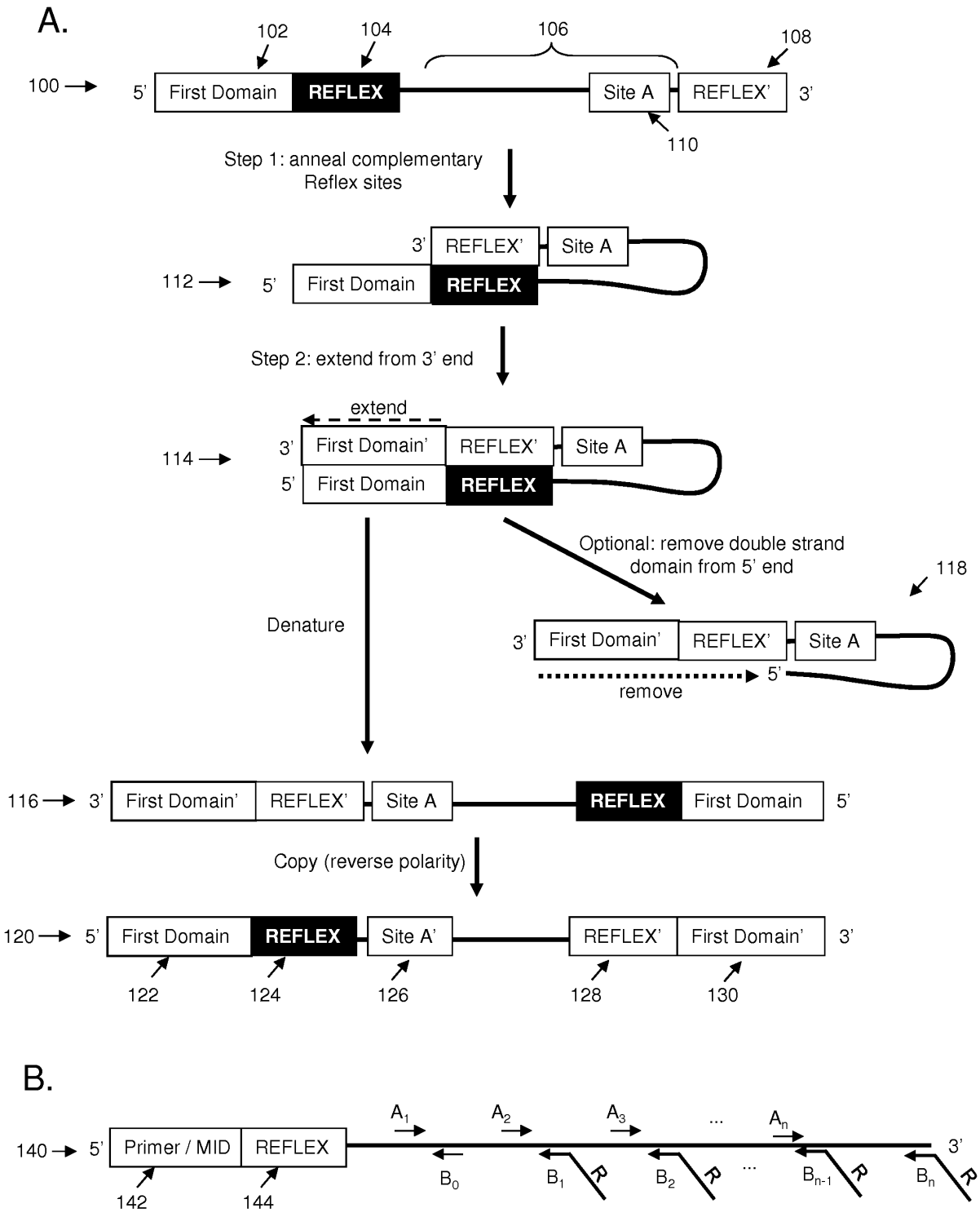

A.
102
104
106
108
100
5'
First Domain
REFLEX
Site A
REFLEX'
3'
110
Step 1: anneal complementary Reflex sites
3'
REFLEX'
Site A
112
5'
First Domain
REFLEX
Step 2: extend from 3' end
extend
114
3'
First Domain'
REFLEX'
Site A
5'
First Domain
REFLEX
Optional: remove double strand domain from 5' end
118
Denature
3'
First Domain'
REFLEX'
Site A
5'
remove
116
3'
First Domain'
REFLEX'
Site A
REFLEX
First Domain
5'
Copy (reverse polarity)
120
5'
First Domain
REFLEX
Site A'
REFLEX'
First Domain'
3'
122
124
126
128
130
B.
140
5'
Primer / MID
REFLEX
142
144
A1
A2
A3
...
An
3'
B0
B1
B2
Bn-1
Bn
R

**Fig. 1**

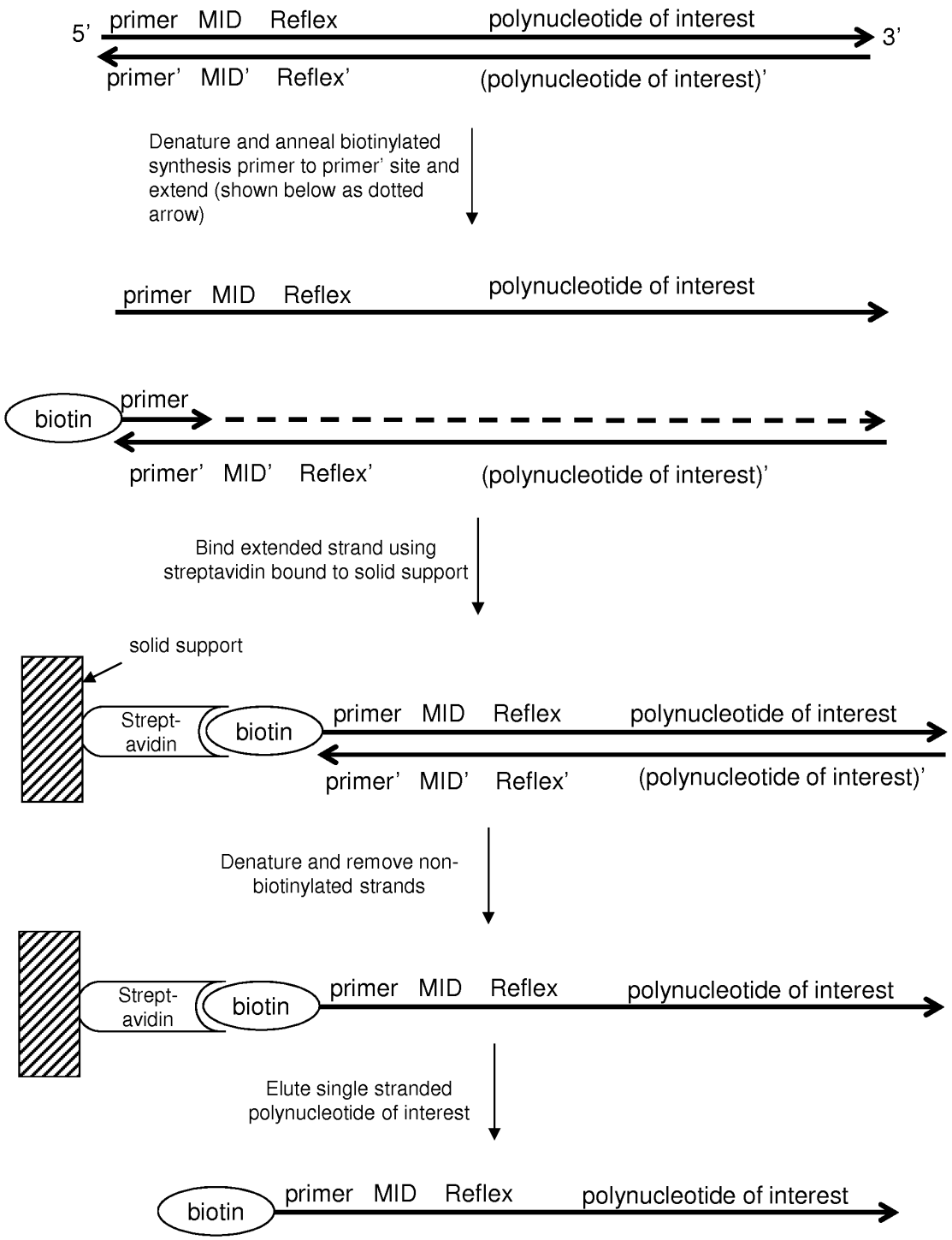
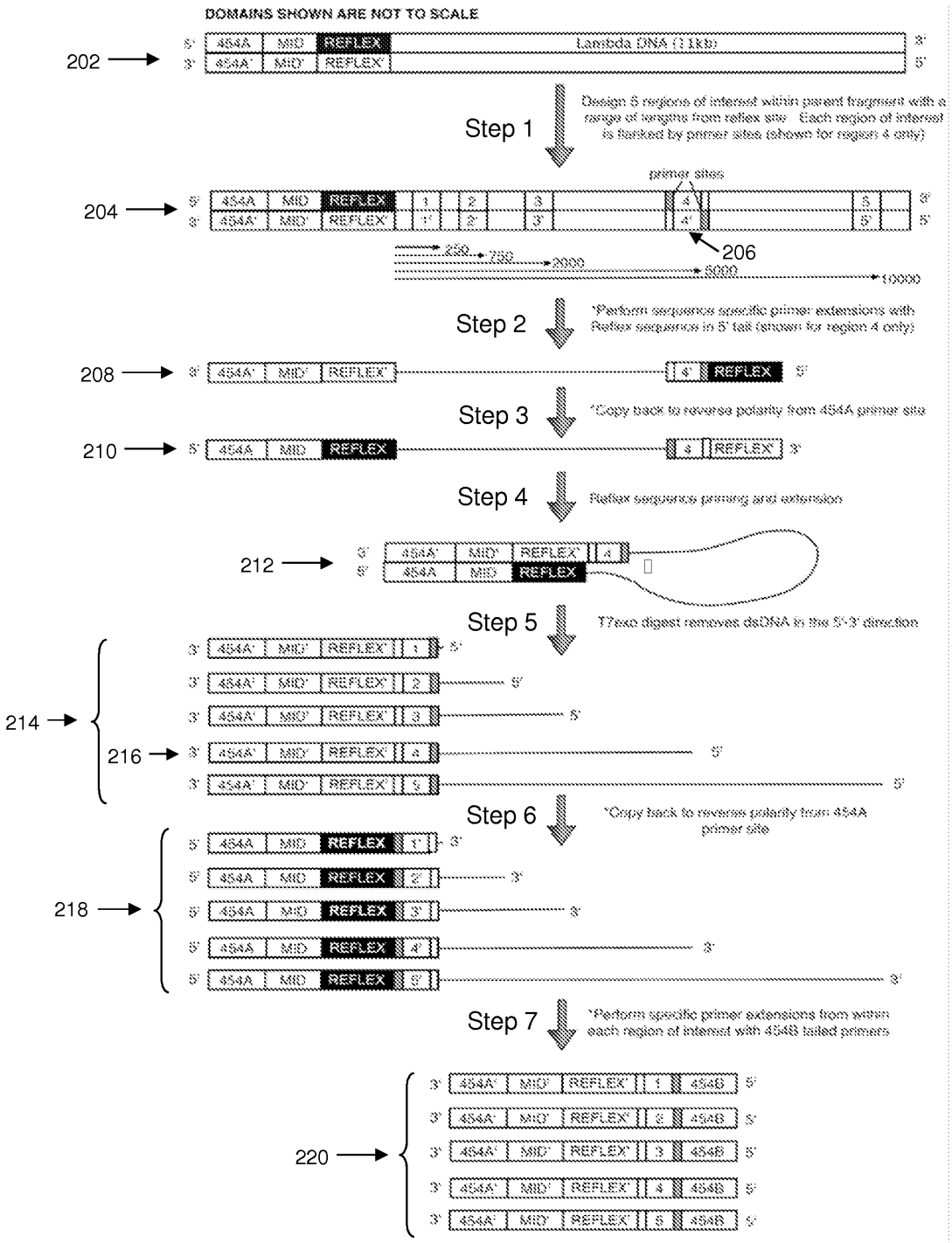

5'
primer MID Reflex
polynucleotide of interest
3'
primer' MID' Reflex'
(polynucleotide of interest)'
Denature and anneal biotinylated synthesis primer to primer' site and extend (shown below as dotted arrow)
primer MID Reflex
polynucleotide of interest
biotin
primer
primer' MID' Reflex'
(polynucleotide of interest)'
Bind extended strand using streptavidin bound to solid support
solid support
Strept-avidin
biotin
primer MID Reflex
polynucleotide of interest
primer' MID' Reflex'
(polynucleotide of interest)'
Denature and remove non-biotinylated strands
Strept-avidin
biotin
primer MID Reflex
polynucleotide of interest
Elute single stranded polynucleotide of interest
biotin
primer MID Reflex
polynucleotide of interest

**Fig. 2**




Primer extension reactions with * may be performed such that isolation of single strand species is facilitated (e.g., using primers with binding moieties and/or multiple cycles of extension)

**Fig. 3**

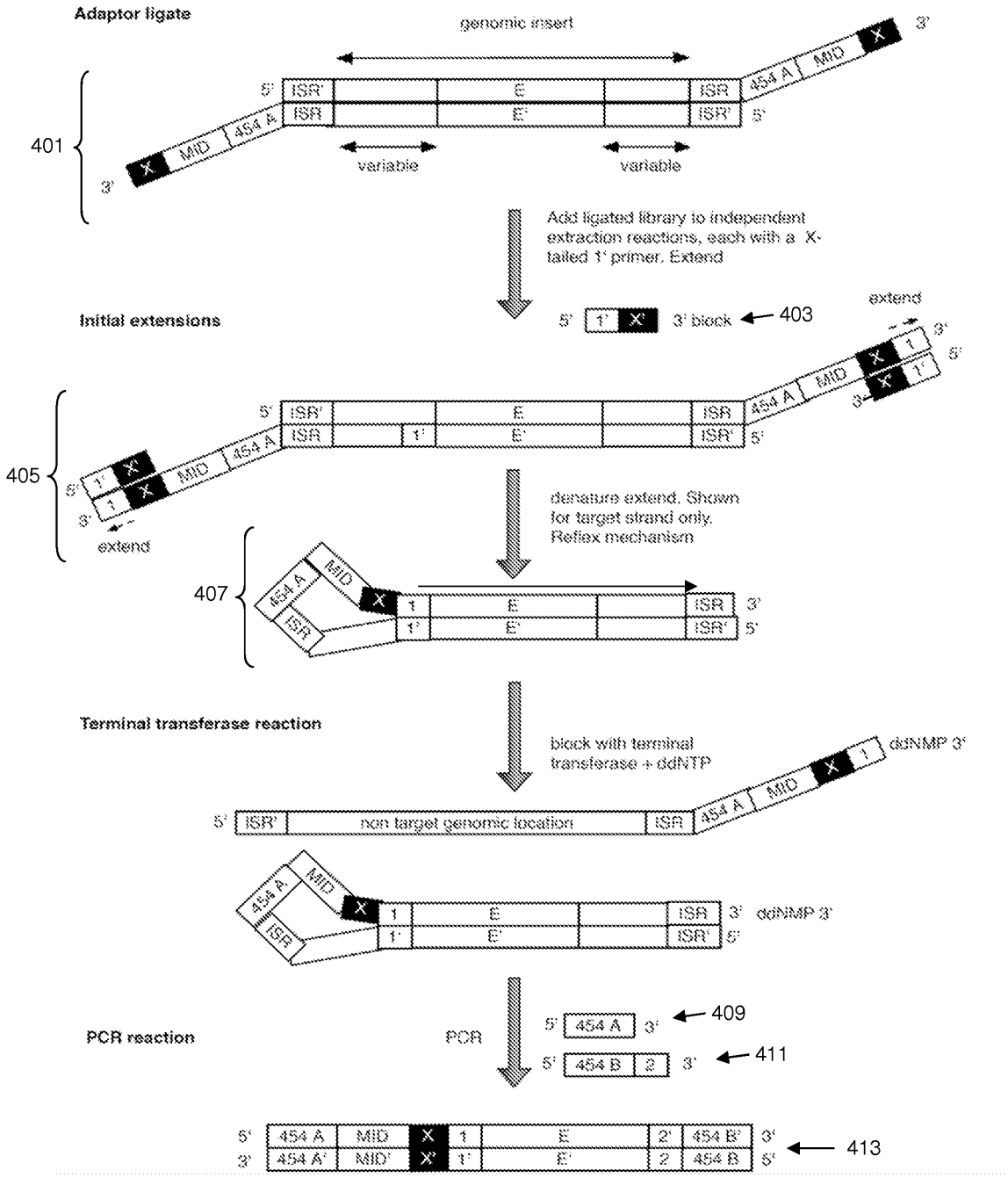

Adaptor ligate
genomic insert
401
5'
3'
ISR'
ISR
E
E'
454 A
MID
X
variable
variable
Add ligated library to independent extraction reactions, each with a X-tailed 1' primer. Extend
Initial extensions
5' 1' X' 3' block
403
extend
405
1'
1
extend
denature extend. Shown for target strand only. Reflex mechanism
407
Terminal transferase reaction
block with terminal transferase + ddNTP
ddNMP 3'
non target genomic location
PCR reaction
PCR
454 A
454 B
2
409
411
454 A'
MID'
X'
454 B'
413

**Fig. 4**

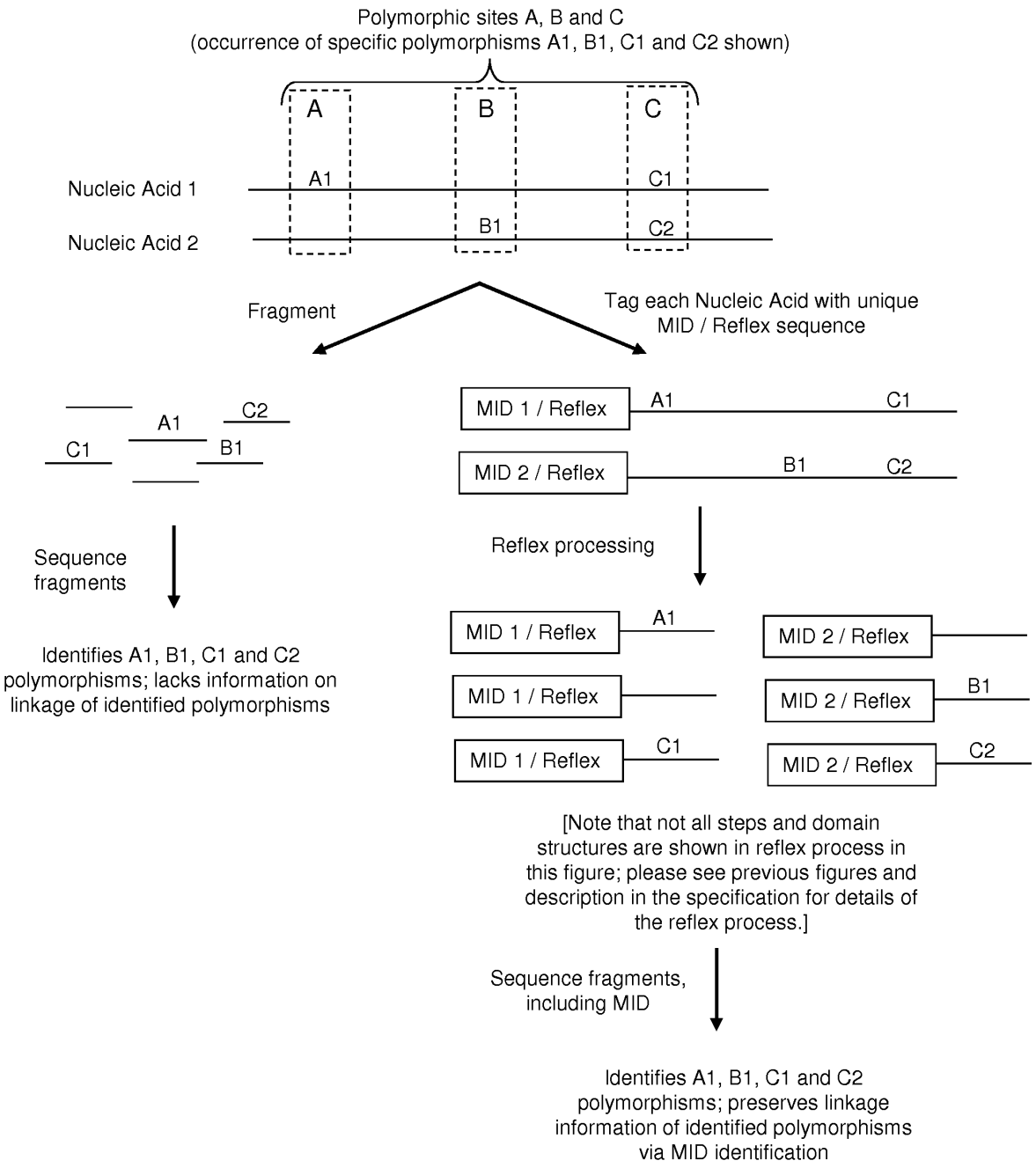
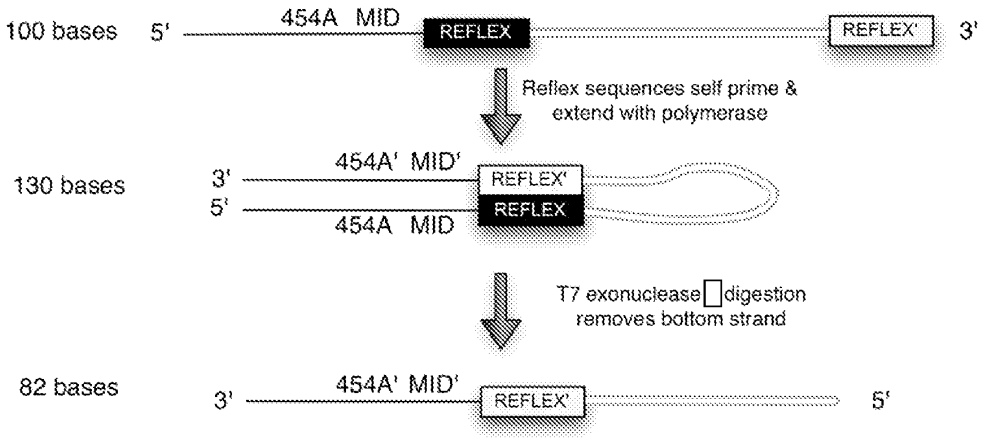
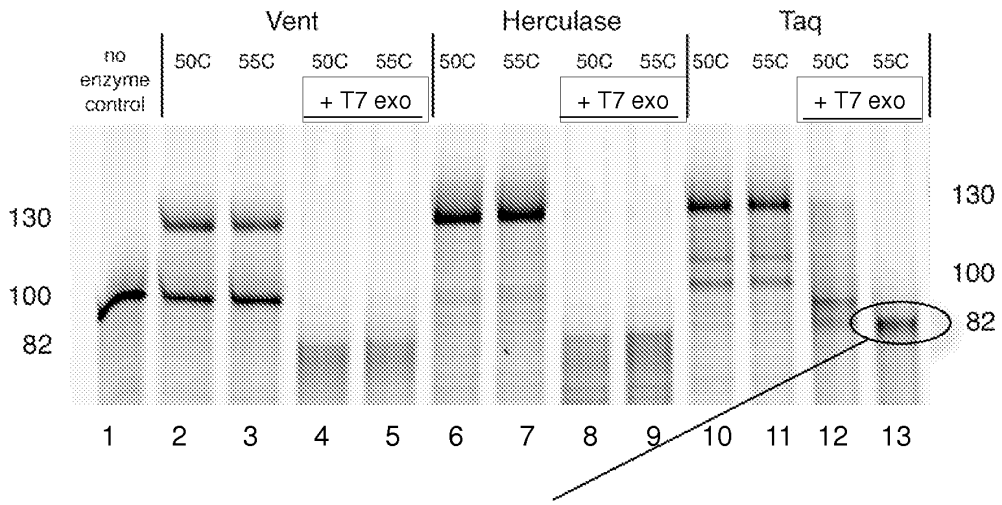

Polymorphic sites A, B and C
(occurrence of specific polymorphisms A1, B1, C1 and C2 shown)
A
B
C
Nucleic Acid 1
A1
C1
Nucleic Acid 2
B1
C2
Fragment
Tag each Nucleic Acid with unique MID / Reflex sequence
C2
A1
C1
B1
MID 1 / Reflex
A1
C1
MID 2 / Reflex
B1
C2
Sequence fragments
Reflex processing
Identifies A1, B1, C1 and C2 polymorphisms; lacks information on linkage of identified polymorphisms
MID 1 / Reflex
A1
MID 2 / Reflex
MID 1 / Reflex
MID 2 / Reflex
B1
MID 1 / Reflex
C1
MID 2 / Reflex
C2
[Note that not all steps and domain structures are shown in reflex process in this figure; please see previous figures and description in the specification for details of the reflex process.]
Sequence fragments, including MID
Identifies A1, B1, C1 and C2 polymorphisms; preserves linkage information of identified polymorphisms via MID identification

**Fig. 5**

A.




B.




Extension is best with Herculase, but 3'-5' exonuclease activity results in partial digestion of the desired 82 base product. Taq, which lacks 3'-5' exonuclease activity, shows a stronger band at the expected size of the final product.

**Fig. 6**

A.

5'
454A MID
REFLEX
REFLEX'
3'
+ Competitor
5'
REFLEX'
3'

B.

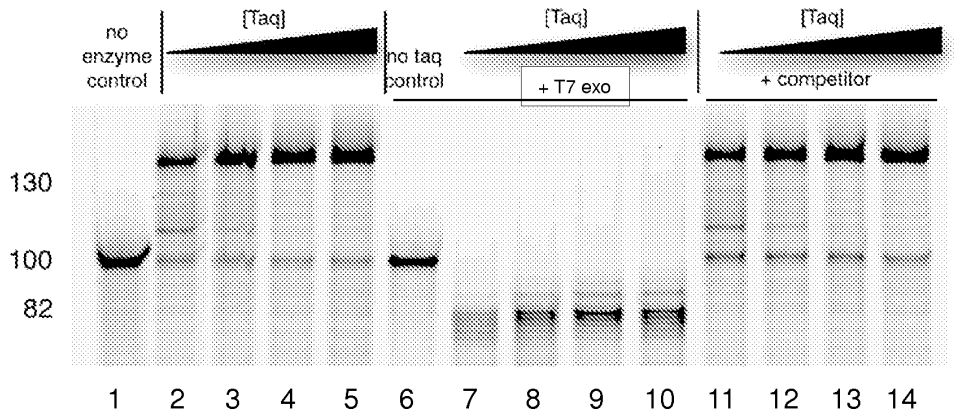
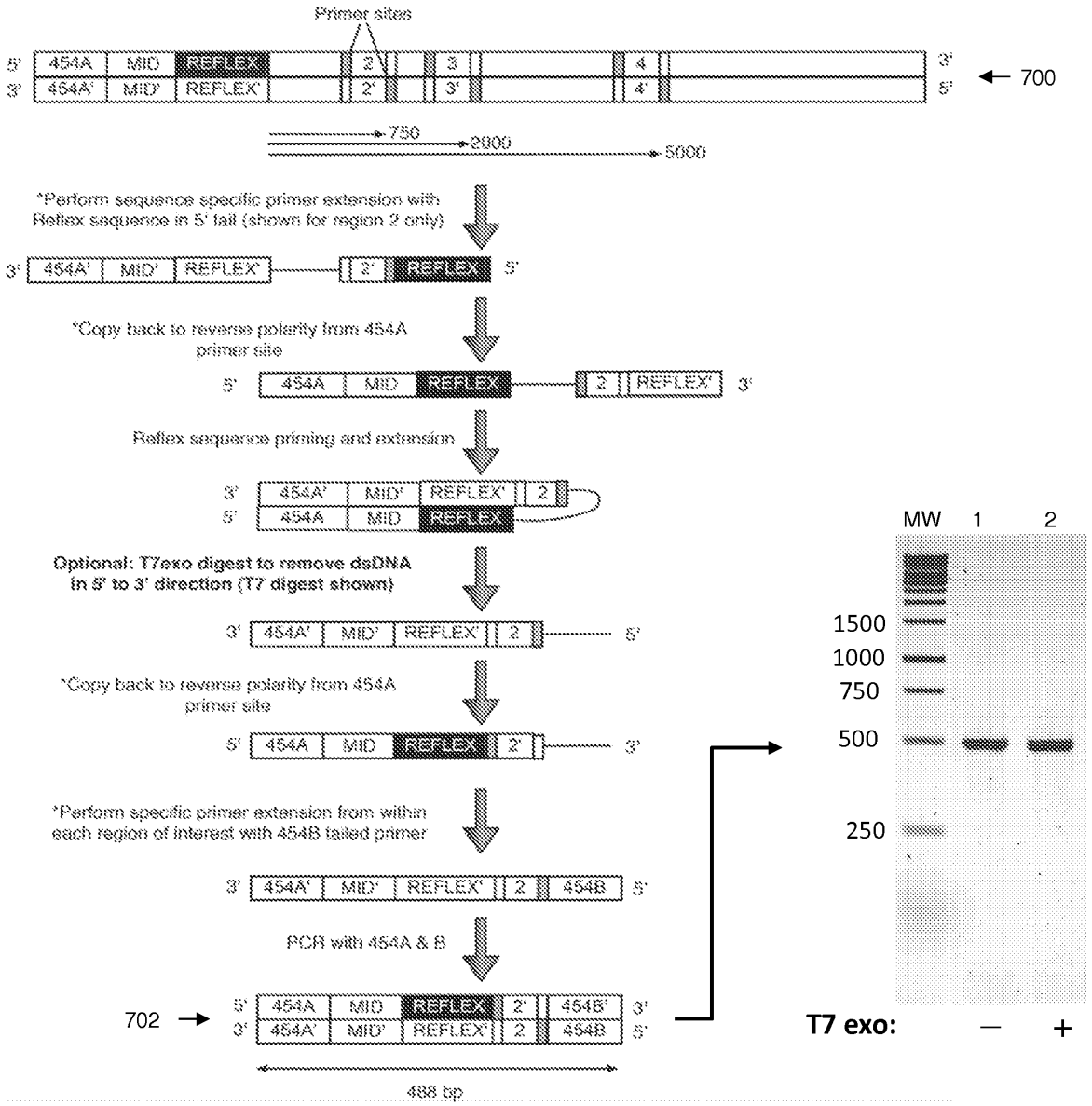

no enzyme control
[Taq]
no taq control
[Taq]
+ T7 exo
[Taq]
+ competitor
130
100
82
1 2 3 4 5 6 7 8 9 10 11 12 13 14

**Fig. 7**




Primer extension reactions with * may be performed such that isolation of single strand species is facilitated (e.g., using primers with binding moieties and/or multiple cycles of extension)

**Fig. 8**

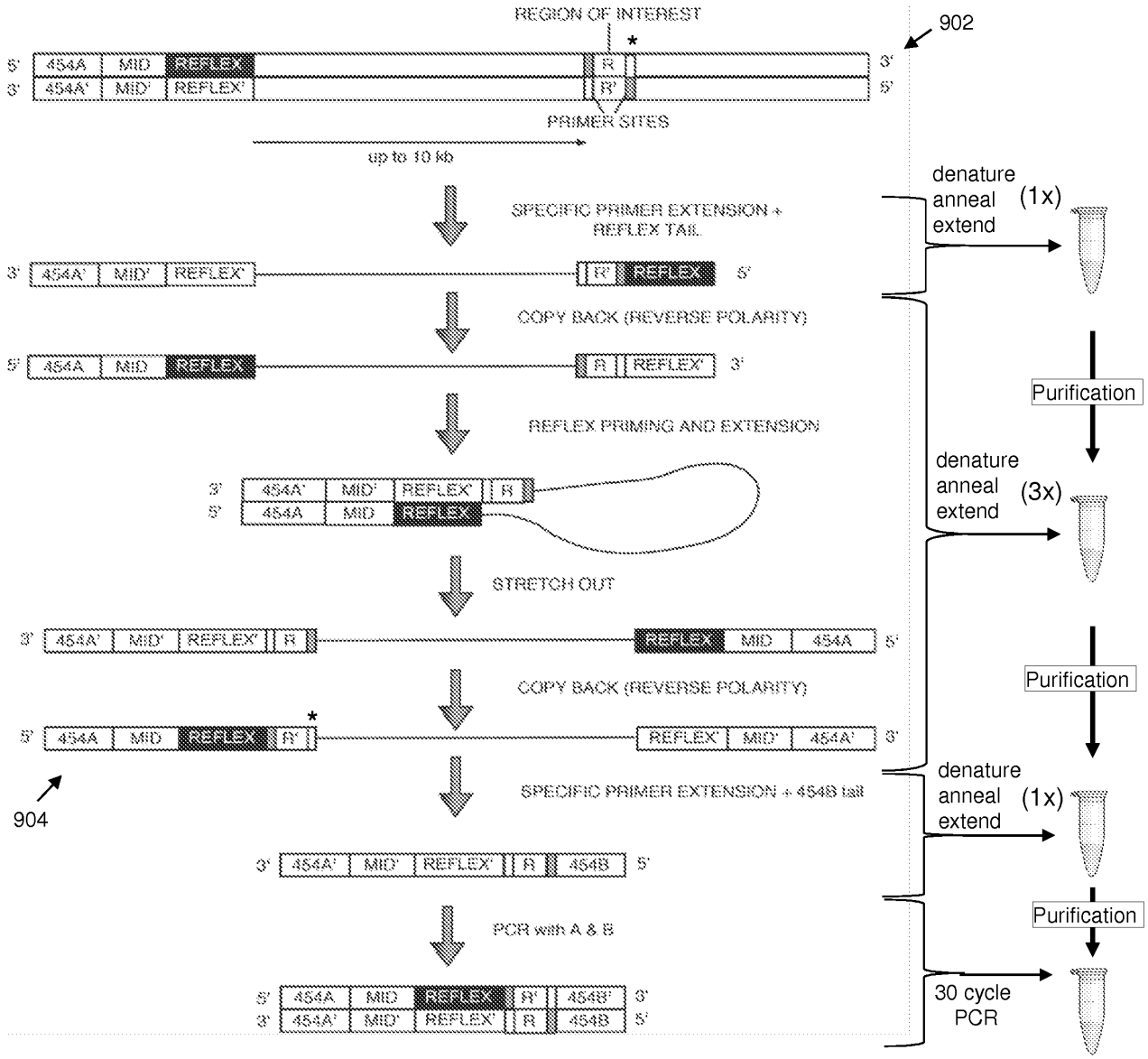

REGION OF INTEREST
902
5' 454A MID REFLEX R 3'
3' 454A' MID' REFLEX' R' 5'
PRIMER SITES
up to 10 kb
SPECIFIC PRIMER EXTENSION + REFLEX TAIL
3' 454A' MID' REFLEX' R' REFLEX 5'
COPY BACK (REVERSE POLARITY)
5' 454A MID REFLEX R REFLEX' 3'
REFLEX PRIMING AND EXTENSION
3' 454A' MID' REFLEX' R
5' 454A MID REFLEX
STRETCH OUT
3' 454A' MID' REFLEX' R REFLEX MID 454A 5'
COPY BACK (REVERSE POLARITY)
5' 454A MID REFLEX R' REFLEX' MID' 454A' 3'
904
SPECIFIC PRIMER EXTENSION + 454B tail
3' 454A' MID' REFLEX' R 454B 5'
PCR with A & B
5' 454A MID REFLEX R' 454B' 3'
3' 454A' MID' REFLEX' R 454B 5'
denature
anneal
extend
(1x)
Purification
denature
anneal
extend
(3x)
Purification
denature
anneal
extend
(1x)
Purification
30 cycle
PCR

**Fig. 9**

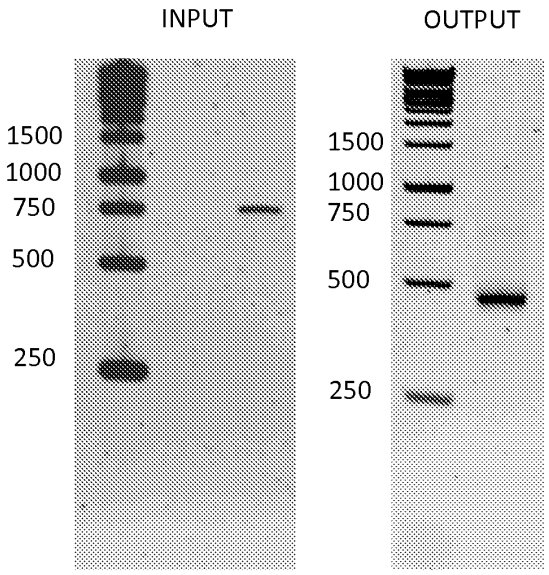
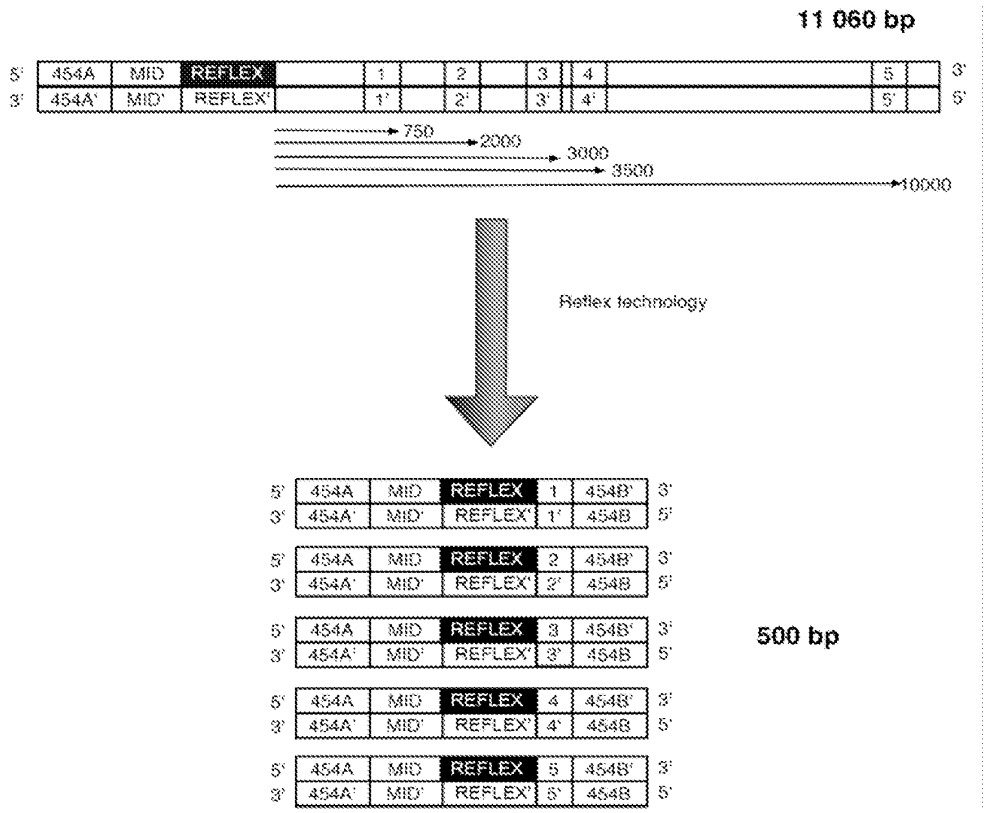



**Fig. 10**


11 060 bp
5' 454A MID REFLEX 1 2 3 4 5 3'
3' 454A' MID' REFLEX' 1' 2' 3' 4' 5' 5'
750
2000
3000
3500
10000
Reflex technology
5' 454A MID REFLEX 1 454B' 3'
3' 454A' MID' REFLEX' 1' 454B 5'
5' 454A MID REFLEX 2 454B' 3'
3' 454A' MID' REFLEX' 2' 454B 5'
5' 454A MID REFLEX 3 454B' 3'
3' 454A' MID' REFLEX' 3' 454B 5'
5' 454A MID REFLEX 4 454B' 3'
3' 454A' MID' REFLEX' 4' 454B 5'
5' 454A MID REFLEX 5 454B' 3'
3' 454A' MID' REFLEX' 5' 454B 5'
500 bp

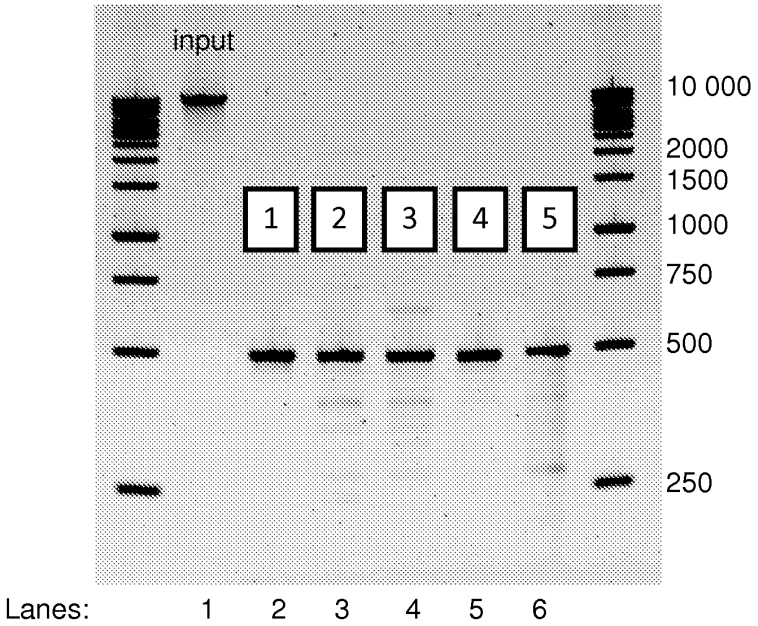
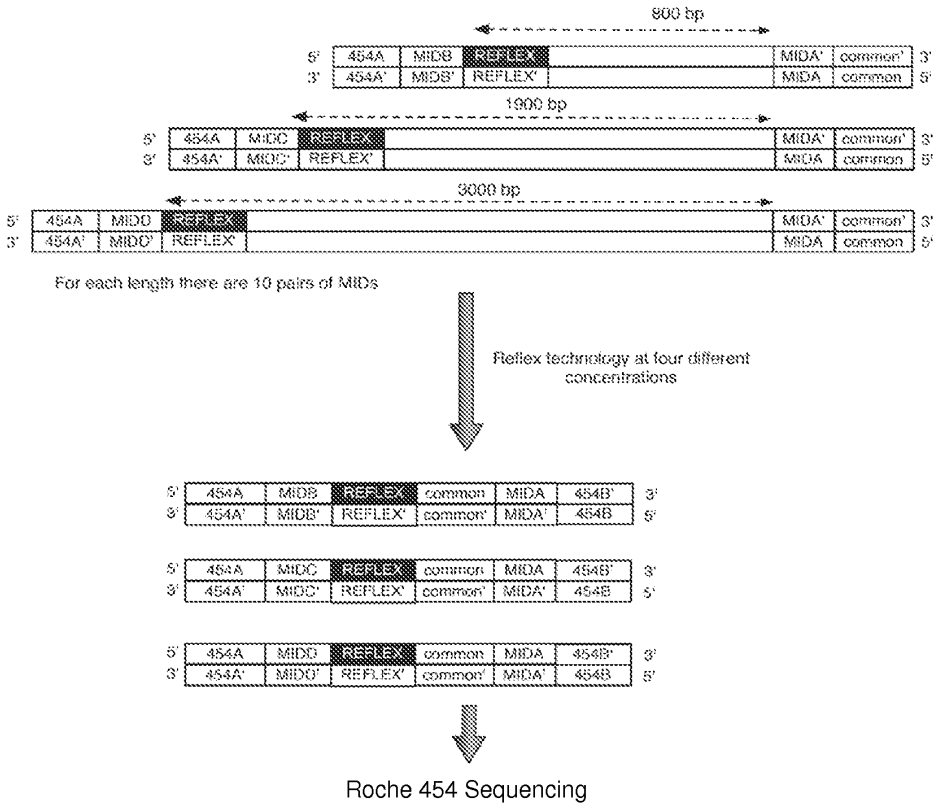
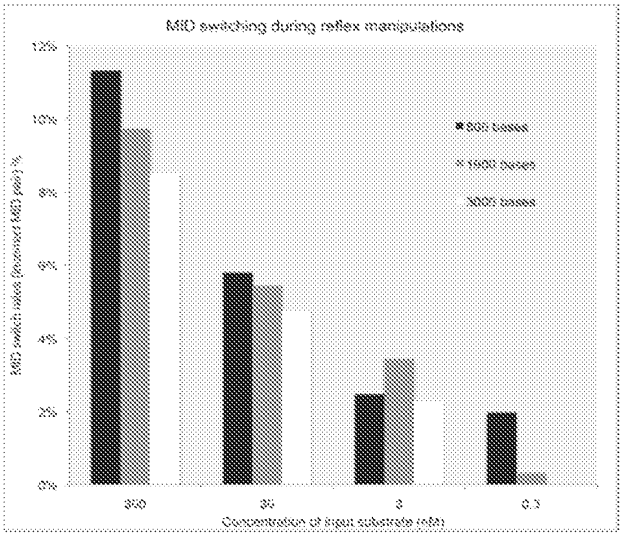

input
1
2
3
4
5
10 000
2000
1500
1000
750
500
250
Lanes: 1 2 3 4 5 6

**Fig. 11**


800 bp
5' 454A MIDB REFLEX MIDA' common' 3'
3' 454A' MIDB' REFLEX' MIDA common 5'
1900 bp
5' 454A MIDC REFLEX MIDA' common' 3'
3' 454A' MIDC' REFLEX' MIDA common 5'
3000 bp
5' 454A MIDD REFLEX MIDA' common' 3'
3' 454A' MIDD' REFLEX' MIDA common 5'
For each length there are 10 pairs of MIDs
Reflex technology at four different concentrations
5' 454A MIDB REFLEX common MIDA 454B' 3'
3' 454A' MIDB' REFLEX' common' MIDA' 454B 5'
5' 454A MIDC REFLEX common MIDA 454B' 3'
3' 454A' MIDC' REFLEX' common' MIDA' 454B 5'
5' 454A MIDD REFLEX common MIDA 454B' 3'
3' 454A' MIDD' REFLEX' common' MIDA' 454B 5'
Roche 454 Sequencing


MID switching during reflex manipulations
12%
10%
8%
6%
4%
2%
0%
800 bases
1900 bases
3000 bases
300
30
3
0.3
Concentration of ligat substrate (nM)

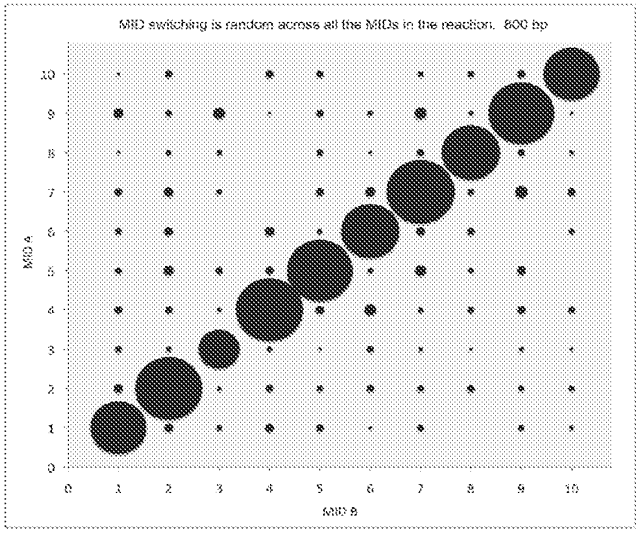

MID switching is random across all the MIDs in the reaction. 800 bp
MID A
MID B
0 1 2 3 4 5 6 7 8 9 10

**Fig. 12**

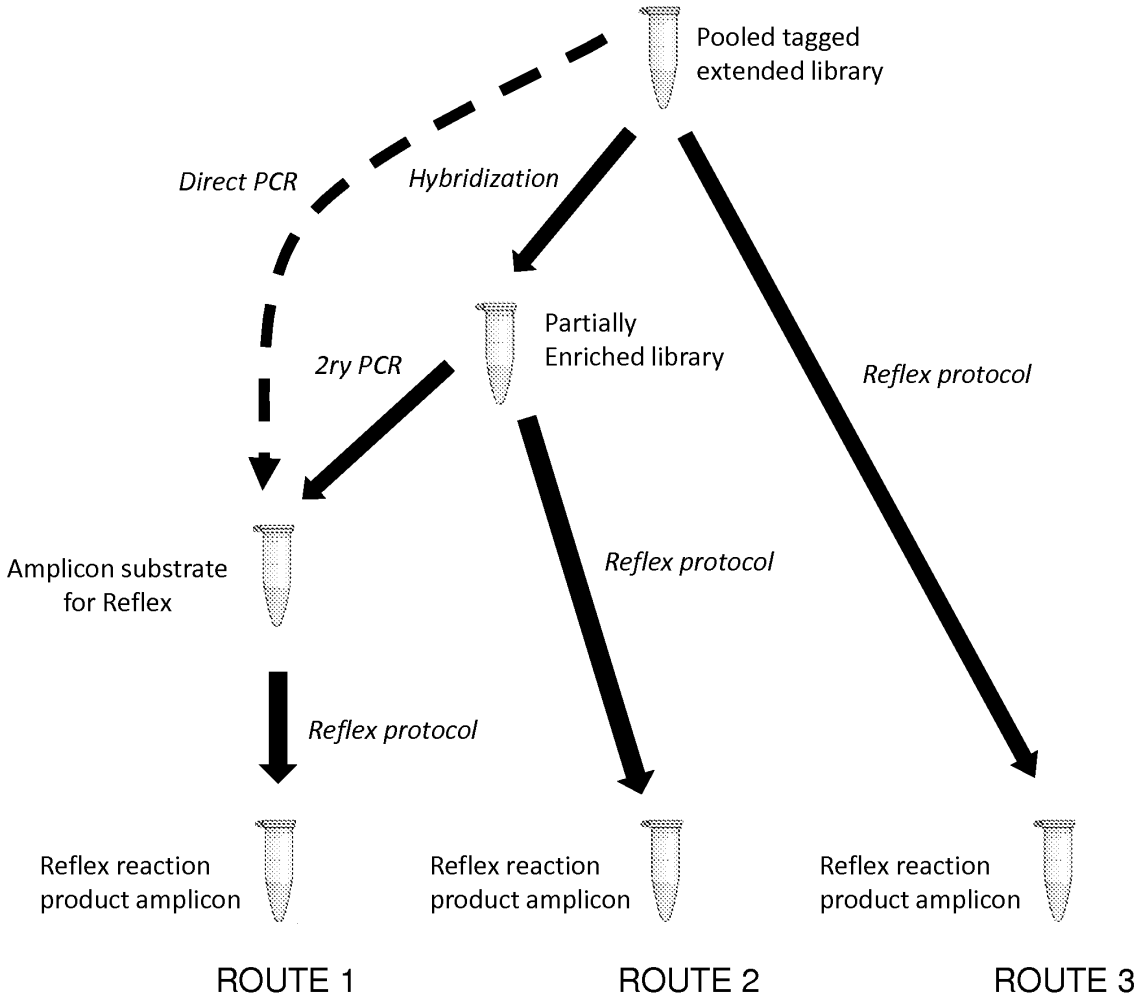

Pooled tagged extended library
Direct PCR
Hybridization
Partially Enriched library
2ry PCR
Reflex protocol
Amplicon substrate for Reflex
Reflex protocol
Reflex protocol
Reflex reaction product amplicon
Reflex reaction product amplicon
Reflex reaction product amplicon
ROUTE 1
ROUTE 2
ROUTE 3

**Fig. 13**

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | CGLC-020CON4 |
|---|---|---|
| | Application Number | |
| Title of Invention | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement | |

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

## Secrecy Order 37 CFR 5.2

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

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|---|---|---|---|

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| **City** | Ely | **State/Province** | |
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**Legal Name**

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|---|---|---|---|

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|---|---|---|---|
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| **Address 2** | GT Abington | | |
| **City** | Great Shelford | **State/Province** | |
| **Postal Code** | CB1 6A3 | **Country** i | GB |

**Inventor 3** Remove

**Legal Name**

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | CGLC-020CON4 |
|---|---|---|
| | Application Number | |
| Title of Invention | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement | |

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | ROBERT | | OSBORNE | |

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

| City | Great Chesterford | Country of Residence i | GB |
|---|---|---|---|

**Mailing Address of Inventor:**

| | | | |
|---|---|---|---|
| **Address 1** | 38 Pilgrim Close | | |
| **Address 2** | | | |
| **City** | Great Chesterford | **State/Province** | |
| **Postal Code** | CB10 1QG | **Country** i | GB |

**Inventor 4** Remove

**Legal Name**

| Prefix | Given Name | Middle Name | Family Name | Suffix |
|---|---|---|---|---|
| | ANDREW | | SLATTER | |

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

| City | London | Country of Residence i | GB |
|---|---|---|---|

**Mailing Address of Inventor:**

| | | | |
|---|---|---|---|
| **Address 1** | 65a Huddleston Road | | |
| **Address 2** | | | |
| **City** | London | **State/Province** | |
| **Postal Code** | N7 0AE | **Country** i | GB |

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

## Correspondence Information:

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

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

| | | | |
|---|---|---|---|
| **Customer Number** | 93726 | | |
| **Email Address** | docket@bozpat.com | Add Email | Remove Email |

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | CGLC-020CON4 |
|---|---|---|
| | Application Number | |
| Title of Invention | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement | |

## Application Information:

| | | | |
|---|---|---|---|
| **Title of the Invention** | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement | | |
| **Attorney Docket Number** | CGLC-020CON4 | **Small Entity Status Claimed** ☒ | |
| **Application Type** | Nonprovisional | | |
| **Subject Matter** | Utility | | |
| **Total Number of Drawing Sheets (if any)** | 13 | **Suggested Figure for Publication (if any)** | |

## Filing By Reference :

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

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

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

## Publication Information:

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

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

## Representative Information:

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

| | | | |
|---|---|---|---|
| Please Select One: | ◉ Customer Number | ○ US Patent Practitioner | ○ Limited Recognition (37 CFR 11.9) |
| Customer Number | 93726 | | |

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| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | CGLC-020CON4 |
|---|---|---|
| | Application Number | |
| Title of Invention | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement | |

## Domestic Benefit/National Stage Information:

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

| Prior Application Status | Pending | | | | Remove |
|---|---|---|---|---|---|
| Application Number | Continuity Type | | Prior Application Number | Filing Date (YYYY-MM-DD) | |
| | Continuation of | | 14021790 | 2013-09-09 | |
| Prior Application Status | Patented | | | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 14021790 | Continuation of | 13859450 | 2013-04-09 | 8563274 | 2013-10-22 |
| Prior Application Status | Abandoned | | | | Remove |
| Application Number | Continuity Type | | Prior Application Number | Filing Date (YYYY-MM-DD) | |
| 13859450 | Continuation of | | 13622872 | 2012-09-19 | |
| Prior Application Status | Patented | | | | Remove |
| Application Number | Continuity Type | Prior Application Number | Filing Date (YYYY-MM-DD) | Patent Number | Issue Date (YYYY-MM-DD) |
| 13622872 | Continuation of | 13387343 | 2012-02-15 | 8298767 | 2012-10-30 |
| Prior Application Status | Expired | | | | Remove |
| Application Number | Continuity Type | | Prior Application Number | Filing Date (YYYY-MM-DD) | |
| 13387343 | a 371 of international | | IB2010002243 | 2010-08-13 | |
| Prior Application Status | Expired | | | | Remove |
| Application Number | Continuity Type | | Prior Application Number | Filing Date (YYYY-MM-DD) | |
| IB2010002243 | Claims benefit of provisional | | 61288792 | 2009-12-21 | |
| Prior Application Status | Expired | | | | Remove |
| Application Number | Continuity Type | | Prior Application Number | Filing Date (YYYY-MM-DD) | |
| IB2010002243 | Claims benefit of provisional | | 61235595 | 2009-08-20 | |

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

## Foreign Priority Information:

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

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Application Data Sheet 37 CFR 1.76 | Attorney Docket Number | CGLC-020CON4 |
|---|---|---|
| | Application Number | |
| Title of Invention | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement | |

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

Remove

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

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

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

## Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

## Applicant Information:

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

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | CGLC-020CON4 |
|---|---|---|
| | Application Number | |
| Title of Invention | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement | |

**Applicant 1** Remove

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

Clear

◉ Assignee ◯ Legal Representative under 35 U.S.C. 117 ◯ Joint Inventor

◯ Person to whom the inventor is obligated to assign. ◯ Person who shows sufficient proprietary interest

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

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

| | | | |
|---|---|---|---|
| Organization Name | Population Genetics Technologies LTD | | |
| **Mailing Address Information:** | | | |
| **Address 1** | Babraham Research Campus | | |
| Address 2 | | | |
| **City** | Cambridge | **State/Province** | |
| **Country** i | GB | Postal Code | CB22 3AT |
| Phone Number | | Fax Number | |
| Email Address | | | |

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

## Assignee Information including Non-Applicant Assignee Information:

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

**Assignee 1**

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

Remove

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



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00062

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| **Application Data Sheet 37 CFR 1.76** | Attorney Docket Number | CGLC-020CON4 |
|---|---|---|
| | Application Number | |
| Title of Invention | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement | |

| Prefix | **Given Name** | Middle Name | **Family Name** | Suffix |
|---|---|---|---|---|
| | | | | |

**Mailing Address Information For Assignee including Non-Applicant Assignee:**

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

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

## Signature:

Remove

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

| **Signature** | /James S. Keddie,Reg. No. 48,920/ | | | Date (YYYY-MM-DD) | 2014-02-04 |
|---|---|---|---|---|---|
| First Name | James S. | Last Name | Keddie | Registration Number | 48920 |

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

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

# Privacy Act Statement

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

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

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

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

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

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

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

| | |
|---|---|
| **EFS ID:** | 18112419 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement |
| **First Named Inventor/Applicant Name:** | Sydney Brenner |
| **Customer Number:** | 93726 |
| **Filer:** | James Samuel Keddie |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | CGLC-020CON4 |
| **Receipt Date:** | 04-FEB-2014 |
| **Filing Date:** | |
| **Time Stamp:** | 18:24:14 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | CGLC-020-CON4_Appln_fr_parent.pdf | 311265<br>44421a6d090cfc457a239c6340976cd1f97e879a | yes | 43 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Specification | 1 | 39 |
| | Claims | 40 | 42 |
| | Abstract | 43 | 43 |

| | | | | | |
|---|---|---|---|---|---|
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Drawings-only black and white line drawings | CGLC-020CON4-Figures.pdf | 1552139<br>b2007392d68c5bb579ae40e91ee5d9afdcce4289 | no | 13 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Application Data Sheet | CGLC-020CON4-ADS.pdf | 1562147<br>1bb6bc4036f39af83f120b32627dccf0182b03a4 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 3425551 | | |

**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.**

# SCORE Placeholder Sheet for IFW Content

Application Number: 14172694 Document Date: 02/04/2014

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Form Revision Date: September 30, 2013

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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 |
|---|---|---|---|---|---|---|
| 14/172,694 | 02/04/2014 | 1636 | 0.00 | CGLC-020CON4 | 20 | 2 |

**CONFIRMATION NO. 2029**

**FILING RECEIPT**

*OC000000066733957*

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

Date Mailed: 02/25/2014

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**

**Inventor(s)**

SYDNEY BRENNER, Ely, UNITED KINGDOM;
GI MIKAWA, Great Shelford, UNITED KINGDOM;
ROBERT OSBORNE, Great Chesterford, UNITED KINGDOM;
ANDREW SLATTER, London, UNITED KINGDOM;

**Applicant(s)**

Population Genetics Technologies LTD, CAMBRIDGE, UNITED KINGDOM

**Assignment For Published Patent Application**

Population Genetics Technologies LTD, CAMBRIDGE, UNITED KINGDOM

**Power of Attorney:** None

**Domestic Priority data as claimed by applicant**

This application is a CON of 14/021,790 09/09/2013
which is a CON of 13/859,450 04/09/2013 PAT 8563274
which is a CON of 13/622,872 09/19/2012 ABN
which is a CON of 13/387,343 02/15/2012 PAT 8298767
which is a 371 of PCT/IB2010/002243 08/13/2010
which claims benefit of 61/288,792 12/21/2009
and claims benefit of 61/235,595 08/20/2009

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

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

**If Required, Foreign Filing License Granted:** 02/20/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/172,694**

**Projected Publication Date:** To Be Determined - pending completion of Missing Parts

**Non-Publication Request:** No

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

Compositions and Methods for Intramolecular Nucleic Acid Rearrangement

**Preliminary Class**

435

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

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

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

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

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## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

**GRANTED**

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

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

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IPR2023-00876
Page 00071

# PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number
14/172,694

## 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 | 70 | | N/A | |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | 300 | | N/A | |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | 360 | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 20 minus 20 = | * | x 40 = | 0.00 | OR | | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 2 minus 3 = | * | x 210 = | 0.00 | | | |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | 0.00 | | | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | 0.00 | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | 730 | | 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 = | |
| AMENDMENT A | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| AMENDMENT A | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| AMENDMENT A | 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 = | |
| AMENDMENT B | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| AMENDMENT B | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| AMENDMENT B | 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".
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| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | CGLC-020CON4 |

**CONFIRMATION NO. 2029**

**FORMALITIES LETTER**

*OC000000066733958*

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

Date Mailed: 02/25/2014

# NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

**FILED UNDER 37 CFR 1.53(b)**

***Filing Date Granted***

**Items Required To Avoid Abandonment:**

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

**SUMMARY OF FEES DUE:**

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **70** basic filing fee.
- $ **70** surcharge.
- $ **300** search fee.
- $ **360** examination fee.
- $( **0.00**) previous unapplied payment amount.
- $ **800** TOTAL FEE BALANCE DUE.

**Items Required To Avoid Processing Delays:**

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's

oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  SYDNEY BRENNER
  GI MIKAWA
  ROBERT OSBORNE
  ANDREW SLATTER

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

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Alexandria VA 22313-1450

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/fberhane/

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PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | | |
|---|---|---|
| | Application Number | 14172694 |
| | Filing Date | 2014-02-04 |
| | First Named Inventor | BRENNER, Sydney |
| | Art Unit | 1636 |
| | Examiner Name | |
| | Attorney Docket Number | CGLC-020CON4 |

| **U.S.PATENTS** | | | | | | Remove |
|---|---|---|---|---|---|---|
| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
| | 1 | 6723513 | | 2004-04-20 | LEXOW, Preben | |
| | 2 | 7544473 | | 2009-06-09 | BRENNER, Sydney | |
| | 3 | 7700325 | | 2010-04-20 | CANTOR, et al. | |
| | 4 | 8101346 | | 2012-01-24 | TAKAHAMA, Shinichiro | |
| | 5 | 8298767 | | 2012-10-30 | BRENNER, et al. | |
| | 6 | 8318460 | | 2012-11-27 | CANTOR, et al. | |
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| | Examiner Name | |
| | Attorney Docket Number | CGLC-020CON4 |

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|---|---|---|---|---|---|---|
| | 1 | 20040224331 | | 2004-11-11 | CANTOR, et al. | |
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| | Attorney Docket Number | CGLC-020CON4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 12 | 20120316074 | | 2012-12-13 | SAXONOV, Serge | |
| | 13 | 20130059310 | | 2013-03-07 | BRENNER, et al. | |

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|---|---|---|---|---|---|---|---|---|
| | 1 | EP1841879 | EP | | 2007-10-10 | COMPASS GENETICS, LLC. | | ☐ |
| | 2 | EP1672064 | EP | | 2006-06-21 | RIKEN | | ☐ |
| | 3 | WO200190418 | WO | | 2001-11-29 | THE REGENTS OF THE UNIVERSITY OF CALIFORNIA | | ☐ |
| | 4 | WO2004061083 | WO | | 2004-07-22 | AMGEN INC | | ☐ |
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|---|---|---|---|
| | 1 | BOULANGER, et al, "Massively parallel haplotyping on microscopic beads for the high-throughput phase analysis of single molecules", PLoS One, Vol 7:1-10, 2012. | ☐ |
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| | Examiner Name | |
| | Attorney Docket Number | CGLC-020CON4 |

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| | 19 | TURNER, et al, "High-throughput haplotype determination over long distances by haplotype fusion PCR and ligation haplotyping", Nat Protoc., 4:1771-83, 2009. | ☐ |
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| | 24 | YAN, et al, "Rapid one-step construction of hairpin RNA", Biochem Biophys Res Commun., 4:464-8, 2009. | ☐ |

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**EXAMINER SIGNATURE**

| Examiner Signature | | Date Considered | |
|---|---|---|---|

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

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

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | Application Number | 14172694 |
|---|---|---|
| | Filing Date | 2014-02-04 |
| | First Named Inventor | BRENNER, Sydney |
| | Art Unit | 1636 |
| | Examiner Name | |
| | Attorney Docket Number | CGLC-020CON4 |

**CERTIFICATION STATEMENT**

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

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

**OR**

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

☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

**SIGNATURE**

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

| Signature | /James S. Keddie, Reg. No. 48,920/ | Date (YYYY-MM-DD) | 2014-04-02 |
|---|---|---|---|
| Name/Print | James S. Keddie | Registration Number | 48920 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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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:

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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.

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

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

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 Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 18644558 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Customer Number:** | 93726 |
| **Filer:** | James Samuel Keddie |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | CGLC-020CON4 |
| **Receipt Date:** | 02-APR-2014 |
| **Filing Date:** | 04-FEB-2014 |
| **Time Stamp:** | 13:46:39 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal Letter | CGLC-020CON4-IDS_Transmittal.pdf | 47318<br>4734fb0448c43d3816ef1cec52c8434766495e92 | no | 2 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Information Disclosure Statement (IDS) Form (SB08) | CGLC-020CON4-IDS-1449.pdf | 615207<br>358e443c2268e1827100ca9e328f73f33c7f583e | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 662525 | |

**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.**

**Electronically Filed**

| **INFORMATION DISCLOSURE STATEMENT**<br><br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | Attorney Docket | CGLC-020CON4 |
|---|---|---|
| | First Named | Brenner, Sydney |
| | Application Number | 14/172,694 |
| | Confirmation No. | 2029 |
| | Filing Date | February 4, 2014 |
| | Group Art Unit | 1636 |
| | Examiner Name | |
| | Title: "*Compositions and Methods for Intramolecular Nucleic Acid Rearrangement*" | |

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO-SB/08A and a copy of each document is also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO-SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO-SB/08A, indicating the document cited therein have been considered and made of record herein.

**All of the references identified herein were disclosed in parent application serial number 14/021,790, filed 9/9/2013 and as such, copies thereof are not included pursuant to the provisions of 37 CFR § 1.98(d).**

**Statements**

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d):** Each item of information contained in the information disclosure statement filed herewith was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office and was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(l):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

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

---

**Fees**

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number CGLC-020CON4.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS, LLP

Date: April 2, 2014

By: /James S. Keddie, Reg. No.48,920/
James S. Keddie, Reg. No.48,920

BOZICEVIC, FIELD & FRANCIS, LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. 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(c).

I hereby appoint:

■ Practitioners associated with Customer Number: 93726

**OR**

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

| Name | Registration Number | Name | Registration Number |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

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

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

■ The address associated with Customer Number: 93726

**OR**

☐

| | | | |
|---|---|---|---|
| Firm or Individual Name | | | |
| Address | | | |
| City | | State | Zip |
| Country | | | |
| Telephone | | Email | |

Assignee Name and Address: Population Genetics Technologies Ltd
Babraham Research Campus
Cambridge, United Kingdom CB22 3AT

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

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

| | | | |
|---|---|---|---|
| Signature | Mel Kronick | Date | 09/25/2012 |
| Name | Mel Kronick, Ph.D. | Telephone | (650) 269-0445 |
| Title | Director | | |

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 3 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.

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 19223039 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Customer Number:** | 93726 |
| **Filer:** | James Samuel Keddie |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | CGLC-020CON4 |
| **Receipt Date:** | 05-JUN-2014 |
| **Filing Date:** | 04-FEB-2014 |
| **Time Stamp:** | 19:27:11 |
| **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 | Assignee showing of ownership per 37 CFR 3.73. | CGLC-020CON4-373c_Statement.pdf | 30655<br>d82ba27639b1f91365824082650b69f97717171f | no | 2 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Power of Attorney | CGLC-Population_Genetics_Technologies_Ltd.pdf | 1460141<br>c50fabd5174a8857ee4641a8f4ff9010e5dc50d8 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 1490796 | |

**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.**

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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# STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: **Population Genetics Technologies Ltd**

Application No./Patent No.: **14/172,694** Filed/Issue Date: **February 4, 2014**

Titled: **Compositions and Methods for Intramolecular Nucleic Acid Rearrangement**

**Population Genetics Technologies LTD**, a **Corporation**
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

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

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

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

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

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

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

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

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

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

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

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel **032865**, Frame **0340**, or for which a copy thereof is attached.

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

1. From: _____ 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.



This collection of information is required by 37 CFR 3.73(b). 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. 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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## STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

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

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

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

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

| | |
|---|---|
| **/James S. Keddie, Reg. No. 48,920/** | **June 5, 2014** |
| Signature | Date |
| **James S. Keddie** | **48,920** |
| Printed or Typed Name | Title or Registration Number |

**SUBMITTED ELECTRONICALLY**

| **PRELIMINARY AMENDMENT Under CFR 1.115** | Attorney Docket No. | CGLC-020CON4 |
|---|---|---|
| | Confirmation No. | 2029 |
| | First Named Inventor | Brenner, Sydney |
| | Application Number | 14/172,694 |
| | Filing Date | February 4, 2014 |
| | Group Art Unit | 1636 |
| | Examiner Name | |
| Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | Title: "Compositions and Methods for Intramolecular Nucleic Acid Rearrangement" | |

Sir:

Prior to the examination of the above-referenced application on the merits, please enter the amendments below.

## IN THE SPECIFICATION

Please insert the following paragraph after the title on page one of the specification:

### CROSS REFERENCE TO RELATED APPLICATIONS

This application is continuation of 14/021,790, filed September 9, 2013, which is a continuation of 13/859,450, filed April 9, 2013, which is a continuation of 13/622,872, filed September 19, 2012, which is a continuation of 13/387,343, filed February 15, 2012, which is a §371 National Phase Application of PCT/IB2010/002243, filed August 13, 2010, which claims priority to US Provisional Application No. 61/235,595, filed August 20, 2009 and US Provisional Application No. 61/288,792, filed December 21, 2009; all of which are herein incorporated by reference.



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00093

## AMENDMENTS TO THE CLAIMS

Please amend the claims as shown below. A complete listing of the claims in this case, including their current status identifier, is shown below.

1. (Currently Amended) A method of **sample analysis**, ~~moving a domain in a nucleic acid, the method~~ comprising:

a) annealing a reflex sequence in a polynucleotide strand in a sample with a complement of the reflex sequence present in the polynucleotide strand, wherein the polynucleotide strand comprises the following in a 5' to 3' orientation:

a first domain;

the reflex sequence;

a polynucleotide of interest **having a desired site that is distal to the first domain**; and

the complement of the reflex sequence, wherein the complement of the reflex sequence is present at the 3' end of the polynucleotide strand; ~~and~~

b) extending from the 3' end of the complement of the reflex sequence through the first domain to produce a double stranded region~~;~~ **comprising** ~~whereby~~ a complement of the first domain ~~is present~~ at the 3' end of the extended polynucleotide strand, thereby moving the first domain ~~in the polynucleotide strand~~ **into proximity with the desired site; and**

**c) amplifying the desired site from the polynucleotide strand of step b) using a first nucleic acid synthesis primer that anneals at the 3' end of the complement of the first domain and a second nucleic acid synthesis primer that comprises a 3' priming domain that is complementary to a site within the polynucleotide of interest.**

2. (Original) The method of claim 1, wherein the first domain comprises a multiplex identifier (MID).

3. (Original) The method of claim 1, wherein the first domain comprises a primer site.



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00094

4. (Original) The method of claim 1, wherein the reflex sequence is from 10 to 50 nucleotides in length.

5. (Currently Amended) The method of claim 1, wherein the **first domain** ~~reflex sequence~~ comprises an RNA polymerase site.

6. (Original) The method of claim 1, the method further comprising removing the first domain and the reflex sequence from the 5' end of the double stranded region.

7. (Original) The method of claim 6, wherein the removing step comprises treating the nucleic acid of step b with T7 exonuclease.

8. (Original) The method of claim 1, wherein the first domain is present in an adapter region attached to the polynucleotide of interest.

9. (Original) The method of claim 8, wherein the reflex sequence is present in the adapter region.

10. (Original) The method of claim 8, wherein the reflex sequence is a sequence present within the 5' region of the polynucleotide of interest.

11. (Currently Amended) The method of claim 1, wherein the sample is a multiplexed sample, wherein the first domain in each of the polynucleotide strands in the multiplexed sample comprises a MID **that identifies the sample from which the polynucleotide strand is derived** ~~corresponding to its parental sample~~.

12. (Original) The method of claim 1, wherein the sample comprises multiple polynucleotide strands, and wherein each polynucleotide strand in the sample comprises a unique MID in the first domain.

13. (Original) The method of claim 1, wherein the polynucleotide strand is produced by:

annealing a nucleic acid synthesis primer to a parent polynucleotide strand, wherein the parent polynucleotide strand comprises the following in a 5' to 3' orientation:

the first domain;

the reflex sequence; and

a second domain comprising the polynucleotide of interest;

wherein the nucleic acid synthesis primer comprises:

a 3' priming domain that is complementary to a site adjacent to and 3' of the polynucleotide of interest in the second domain; and

a 5' reflex sequence;

extending the nucleic acid synthesis primer to produce an extension product; and

replicating the resultant extension product with a second nucleic acid synthesis primer that anneals at the 3' end of the complement of the first domain, thereby producing the polynucleotide strand.

14. (Original) The method of claim 13, wherein the length of the second domain is from 30 bases to 30 kilobases.

15. (Original) The method of claim 13, wherein the parent polynucleotide strand is enriched prior to the annealing step based on its sequence.

16. (Cancelled)

17. (Currently Amended) The method of **claim 1** ~~claim 16~~, wherein the second synthesis primer comprises a 5' domain that is not complementary to the polynucleotide of interest in the first extension product.

18. (Original) The method of claim 17, wherein the first domain comprises a first primer site and the 5' domain of the second synthesis primer comprises a second primer site.



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00096

19. (Original) The method of claim 18, wherein the length of the polynucleotide of interest in the second extension product is from 50 to 10,000 nucleotides.

20. (Cancelled)

21. (New) The method of claim 1, further comprising sequencing the desired site.



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00097

## REMARKS UNDER 37 CFR § 1.115

**Formal Matters**

Claims 1-15, 17-19 and 21 are pending.

Claims 16 and 20 have been canceled without prejudice. Claims 1, 5, 11 and 17 are amended. Claim 21 is new. Claim 16 has been incorporated into claim 1, with further support shown in Fig. 3. Further support for the amendments and new claim is found at, for example: the section bridging pages 30 and 31; the paragraph bridging pages 30 and 31; page 20, lines 18-19; the sentence bridging pages 17 and 18; page 24 lines 20-23; page 20 line 16-17; the sentence bridging pages 7 and 8; page 21, lines 22-26; page 24, lines 20-24, claims 2 and 3; the paragraph bridging pages 7 and 8; page 21 lines 22-26; page 13 lines 13-15; page 25, lines 5-7 and page 21, lines 22-26. No new matter has been added.

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CGLC-020CON4.

Respectfully submitted,

Date: June 6, 2014

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie, Ph.D.
Registration No. 48,920

BOZICEVIC FIELD & FRANCIS LLP
1900 University Ave., Suite 200
East Palo Alto, California 94303
(650) 327-3400 main
(650) 327-3231 fax
docket@bozpat.com



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00098

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 14172694 |
| **Filing Date:** | 04-Feb-2014 |
| **Title of Invention:** | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Filer:** | James Samuel Keddie |
| **Attorney Docket Number:** | CGLC-020CON4 |

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 | 70 | 70 |
| Utility Search Fee | 2111 | 1 | 300 | 300 |
| Utility Examination Fee | 2311 | 1 | 360 | 360 |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| Late Filing Fee for Oath or Declaration | 2051 | 1 | 70 | 70 |
| **Petition:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |
| Extension - 2 months with $0 paid | 2252 | 1 | 300 | 300 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **1100** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 19233310 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Customer Number:** | 93726 |
| **Filer:** | James Samuel Keddie |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | CGLC-020CON4 |
| **Receipt Date:** | 06-JUN-2014 |
| **Filing Date:** | 04-FEB-2014 |
| **Time Stamp:** | 14:48:04 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Credit Card |
| Payment was successfully received in RAM | $1100 |
| RAM confirmation Number | 1204 |
| Deposit Account | |
| Authorized User | |

## File Listing:

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

| | | | | | |
|---|---|---|---|---|---|
| 1 | Oath or Declaration filed | CGLC-020CON4_AIA_Dec_fr_parent_Signed.pdf | 2461258<br>c5458e8147cf98ab4b8fa8e1ec42323e59c70de8 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | | CGLC-020CON4_Prelim_Amend.pdf | 36289<br>6880ebcd62fe8f3a46e84b3ba635093dd921728a | yes | 7 |
| | **Multipart Description/PDF files in .zip description** | | | | |
| | **Document Description** | | **Start** | **End** | |
| | Preliminary Amendment | | 1 | 1 | |
| | Specification | | 2 | 2 | |
| | Claims | | 3 | 6 | |
| | Applicant Arguments/Remarks Made in an Amendment | | 7 | 7 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Fee Worksheet (SB06) | fee-info.pdf | 38581<br>bdd0a8b6980aab60ff7b8aed87add31d9eb14d4b | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 2536128 | | |

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**<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.**

PTO/AIA/01 (06-12)
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# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

**Title of Invention**: Compositions and Methods for Intramolecular Nucleic Acid Rearrangement

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 13622872 filed on September 19, 2012.

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

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

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

## WARNING:

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

LEGAL NAME OF INVENTOR

Inventor: Sydney Brenner Date (Optional) :

Signature: Sydney Brenner

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

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

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LEGAL NAME OF INVENTOR

Inventor: Gi Mikawa Date (Optional): 5-Nov-2012

Signature: Gi Mikawa

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

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

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LEGAL NAME OF INVENTOR

Inventor: Robert Osborne Date (Optional): 5/11/12

Signature: Robert Osborne

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

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LEGAL NAME OF INVENTOR

Inventor: Andrew Slatter Date (Optional): 5th November 2012

Signature: Andrew Slatter

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

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| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>14/172,694 | Filing Date<br>02/04/2014 | ☐ 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

| 06/06/2014 | (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)) | * 19 | Minus | ** 20 | = 0 | X $40 = | 0 |
| Independent (37 CFR 1.16(h)) | * 1 | Minus | ***3 | = 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
/DORIS ISAAC/

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 14/172,694 | 02/04/2014 | 1636 | 800 | CGLC-020CON4 | 19 | 1 |

**CONFIRMATION NO. 2029**

**UPDATED FILING RECEIPT**

*OC000000068944020*

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

Date Mailed: 06/12/2014

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**

**Inventor(s)**

SYDNEY BRENNER, Ely, UNITED KINGDOM;
GI MIKAWA, Great Shelford, UNITED KINGDOM;
ROBERT OSBORNE, Great Chesterford, UNITED KINGDOM;
ANDREW SLATTER, London, UNITED KINGDOM;

**Applicant(s)**

Population Genetics Technologies LTD, CAMBRIDGE, UNITED KINGDOM

**Assignment For Published Patent Application**

Population Genetics Technologies LTD, CAMBRIDGE, UNITED KINGDOM

**Power of Attorney:** The patent practitioners associated with Customer Number 93726

**Domestic Priority data as claimed by applicant**

This application is a CON of 14/021,790 09/09/2013 PAT 8679756
which is a CON of 13/859,450 04/09/2013 PAT 8563274
which is a CON of 13/622,872 09/19/2012 ABN
which is a CON of 13/387,343 02/15/2012 PAT 8298767
which is a 371 of PCT/IB2010/002243 08/13/2010
which claims benefit of 61/288,792 12/21/2009
and claims benefit of 61/235,595 08/20/2009

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

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

**If Required, Foreign Filing License Granted:** 02/20/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/172,694**

**Projected Publication Date:** 09/18/2014

**Non-Publication Request:** No

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

Compositions and Methods for Intramolecular Nucleic Acid Rearrangement

**Preliminary Class**

435

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

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00109

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

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## Title 37, Code of Federal Regulations, 5.11 & 5.15

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IPR2023-00876
Page 00110

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10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00111

| PATENT APPLICATION FEE DETERMINATION RECORD<br>Substitute for Form PTO-875 | Application or Docket Number<br>14/172,694 |
|---|---|

## 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 | 70 | | N/A | |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | 300 | | N/A | |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | 360 | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 19 minus 20 = | * | x 40 = | 0.00 | OR | | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 1 minus 3 = | * | x 210 = | 0.00 | | | |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | 0.00 | | | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | 0.00 | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | 730 | | 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 = | |
| AMENDMENT A | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| AMENDMENT A | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| AMENDMENT A | 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 = | |
| AMENDMENT B | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| AMENDMENT B | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| AMENDMENT B | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
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www.uspto.gov

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | CGLC-020CON4 |

**CONFIRMATION NO. 2029**

**POA ACCEPTANCE LETTER**

*OC000000068943981*

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

Date Mailed: 06/12/2014

## NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/05/2014.

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.

/nton/

---

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | CGLC-020CON4 |

**CONFIRMATION NO. 2029**

**PUBLICATION NOTICE**

*OC000000070835954*

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

**Title:**Compositions and Methods for Intramolecular Nucleic Acid Rearrangement

**Publication No.**US-2014-0272985-A1
**Publication Date:**09/18/2014

## NOTICE OF PUBLICATION OF APPLICATION

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

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

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

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

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

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

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

| | |
|---|---|
| Electronic Petition Request | **TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT** |
| Application Number | 14172694 |
| Filing Date | 04-Feb-2014 |
| First Named Inventor | SYDNEY BRENNER |
| Attorney Docket Number | CGLC-020CON4 |
| Title of Invention | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement |

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

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

| Owner | Percent Interest |
|---|---|
| Population Genetics Technologies Ltd | 100% |

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

8298767

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

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

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

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

Applicant claims the following fee status:

◉ Small Entity

○ Micro Entity

○ Regular Undiscounted

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

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 48920

○ A sole inventor

○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

○ A joint inventor; all of whom are signing this request

| | |
|---|---|
| Signature | /James S. Keddie, Reg. No. 48,920/ |
| Name | James S. Keddie |

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

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 14172694 |
| **Filing Date:** | 04-Feb-2014 |
| **Title of Invention:** | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Filer:** | James Samuel Keddie |
| **Attorney Docket Number:** | CGLC-020CON4 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| Statutory or Terminal Disclaimer | 1814 | 1 | 160 | 160 |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |

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

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

Application No.: 14172694

Filing Date: 04-Feb-2014

Applicant/Patent under Reexamination: BRENNER et al.

Electronic Terminal Disclaimer filed on March 25, 2015

☒ APPROVED

**This patent is subject to a terminal disclaimer**

☐ DISAPPROVED

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

U.S. Patent and Trademark Office

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 21878380 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Customer Number:** | 93726 |
| **Filer:** | James Samuel Keddie |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | CGLC-020CON4 |
| **Receipt Date:** | 25-MAR-2015 |
| **Filing Date:** | 04-FEB-2014 |
| **Time Stamp:** | 18:55:32 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Credit Card |
| Payment was successfully received in RAM | $160 |
| RAM confirmation Number | 4579 |
| Deposit Account | |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Electronic Terminal Disclaimer-Filed | eTerminal-Disclaimer.pdf | 33358<br>3d270e8e54b179852c50bf8c6dc1c93bafd1ab48 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 30462<br>155d613aac7cf42429d3c4aaf0ffca9713cf7c91 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 63820 | | |

**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.**

| FILED ELECTRONICALLY | | |
|---|---|---|
| **Interview Summary** | Attorney Docket No. | CGLC-020CON4 |
| | Confirmation No. | 2029 |
| | First Named Inventor | Brenner, Sydney |
| Address to:<br>Mail Stop<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | Application Number | 14/172,694 |
| | Filing Date | February 4, 2014 |
| | Group Art Unit | 1634 |
| | Examiner Name | BHAT,Narayan Kameshwar |
| | *Title: "Compositions and Methods for Intramolecular Nucleic Acid Rearrangement"* | |

Dear Sirs:

The accompanying Terminal Disclaimer is filed in response to a request made by Examiner Narayan Kameshwar Bhat to the undersigned on March 25, 2015.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number CGLC-020CON4.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: March 25, 2015

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie
Registration No. 48,920

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 21878604 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | Compositions and Methods for Intramolecular Nucleic Acid Rearrangement |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Customer Number:** | 93726 |
| **Filer:** | James Samuel Keddie |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | CGLC-020CON4 |
| **Receipt Date:** | 25-MAR-2015 |
| **Filing Date:** | 04-FEB-2014 |
| **Time Stamp:** | 18:56:53 |
| **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 | Applicant summary of interview with examiner | CGLC-020CON4-Interview_Summary.pdf | 28479<br>e1db34acb240b1b63cce265dce8eeb1b697c7712 | no | 1 |

**Warnings:**

**Information:**

| Total Files Size (in bytes): | 28479 |
|---|---|

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**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

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

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

# NOTICE OF ALLOWANCE AND FEE(S) DUE

93726 7590 04/14/2015
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

| EXAMINER |
|---|
| BHAT, NARAYAN KAMESHWAR |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 04/14/2015

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | CGLC-020CON4 | 2029 |

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

| 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 | 07/14/2015 |

**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.**



PTOL-85 (Rev. 02/11)

10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00125

## 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)

93726 7590 04/14/2015
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

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. |
|---|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | CGLC-020CON4 | 2029 |

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

| 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 | 07/14/2015 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| BHAT, NARAYAN KAMESHWAR | 1634 | 435-006100 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "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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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | CGLC-020CON4 | 2029 |

93726 7590 04/14/2015
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

| EXAMINER |
|---|
| BHAT, NARAYAN KAMESHWAR |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 04/14/2015

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

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

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

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



PTOL-85 (Rev. 02/11)

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## 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. 14/172,694 | Applicant(s) BRENNER ET AL. | |
|---|---|---|---|
| | Examiner NARAYAN BHAT | 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 *2/4/2014*.
   ☐ 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 *1-13,15,17,18 and 21*. 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 *3/24/15* .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☒ Other *IMIS-3/25/15*.

/NARAYAN BHAT/
Primary Examiner, Art Unit 1634



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## NOTICE OF ALLOWANCE

1. The present application is being examined under the pre-AIA first to invent provisions. This office action is in response to the papers filed on December 4, 2014. Instant application is a continuation of 14/021,790, filed 09/09/2013 now U.S. Patent 8,679,756, is a continuation of 13/859,450, filed 04/09/2013, now U.S. Patent 8,563,274, which is a continuation of 13/622,872, filed 09/19/2012, now abandoned, is a continuation of 13/387,343, filed 02/15/2012, now U.S. Patent 8,298,767, which is a national stage entry of PCT/IB2010/002243, claiming the priority from provisional application 61288792 (filed 12/21/2009) and 61235595 (filed 08/20/2009). The method steps of instant pending claims comprise the allowed limitation of '767 patent, which are non-obvious improvements over the arts of the record and the ones cited in the IDS of April 2, 2014.

### *Interview Summary*

2. For compact prosecution, the examiner contacted the representative Mr. Keddie on March 24, 2015 to inform that the method steps of instant pending claims comprising the limitations of allowed '767 patent including the limitation of polynucleotide that is from 100 bases to 30 kilo bases in length are allowable pending (i) filing a terminal disclaimer (TD) over claims of '767 patent and (ii) amending the abstract to replace the term "MID" with "multiplex identifier". During the interview the representative informed that the suggested amendments need the approval from the applicant and will get back within a day with the further course of action. The TD was filed on March 25, 2015 and

approved by the office on the same day. The representative authorized to enter the suggested amendments electronically on March 25, 2015. The electronic communications between the representative and the examiner are made of record.

### *Drawings*

3. The drawings of February 4, 2014 are acceptable.

### *Specification*

4. As discussed in the interview summary section, amendment to the abstract by replacing the term “MID” with “multiplex identifier” does not introduce any new matter because it only lists the full version of the “MID” as recited in the instant specification.

### *Information Disclosure Statement*

5. The information disclosure statement (IDS) submitted on April 2, 2014 is being considered by the examiner. All the references cited therein have been considered by the examiner.

The method steps of instant pending claims comprise the allowed limitation of ‘767 patent, which are non-obvious improvements over the arts of the record and the ones cited in the IDS of April 2, 2014.

***Claim Status and Remarks regarding ODP***

6. In the claim listing of June 6, 2014, claims 1-15, 17-19 and 21 are pending in this application. Claims 1, 5, 11 and 17 are amended. Claims 16 and 20 are cancelled. The claim amendments do not introduce any new matter.

As discussed in the interview summary section, upon entry of amended claims via examiner's amendments, claims 1-13, 15, 17, 18 and 21 are pending in this application. Claim 1 is further amended. Claims 14, 16, 19 and 20 are canceled. The claim amendments do not introduce any new matter.

Claims 1-13, 15, 17, 18 and 21 are allowable because they comprise all steps of allowed '767 patent except for the further features of the first domain but includes additional amplification step. It is in the examiner's opinion the steps of amended claim 1 are non-obvious improvements over the arts of the record because the spatial organization of different structural features of the polynucleotide comprising the reflex sequence allowing to move a region of interest in a polynucleotide from a first position to a second position with regard to a domain within the polynucleotide.

The potential ODP rejection of instant claims 1-13, 15, 17, 18 and 21 over claims 1-18 of '767 patent has been overcome by filing the TD and its approval by the office on March 25, 2015.

It is in the examiner's opinion, the scope of '756 and '274 patent from other CON applications are different from the instant allowed claims. Therefore the TDs are not requested with regard to '756 and '274 patents.

**EXAMINER'S AMENDMENT**

7. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given electronically by applicant's representative Mr. Kiddie on March 25, 2015.

Please replace the term "MID" in line 5 of the abstract of February 4, 2014 with the phrase "multiplex identifier".

In the claim listing of June 6, 2014, please cancel claims 14 and 19.

In the claim listing of June 6, 2014, in claim 1 please insert the phrase "that is from 100 bases to 30 kilo bases in length and" in line 8 after the phrase "a polynucleotide of interest".

8. Claims 1-13, 15, 17, 18 and 21 have been renumbered 1-17.

***Conclusion***

9. Claims 1-13, 15, 17, 18 and 21 are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571)-272-0731. 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.

/Narayan K. Bhat/

Primary Examiner, Art Unit 1634

| Examiner-Initiated Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 14/172,694 | BRENNER ET AL. | |
| | Examiner | Art Unit | |
| | NARAYAN BHAT | 1634 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *Examiner: Bhat*. (3)_____.

(2) *Representative: Mr. Keddie* . (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*.

Identification of prior art discussed: *US 8,298,767*.

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...)

*For compact prosecution, the examiner contacted the representative Mr. Keddie on March 24, 2015 to inform that the method steps of instant pending claims comprising the limitations of allowed '767 patent including the limitation of polynucleotide that is from 100 bases to 30 kilo bases in length are allowable pending (i) filing a terminal disclaimer (TD) over claims of '767 patent and (ii) amending the abstract to replace the term "MID" with "multiplex identifier". During the interview the representative informed that the suggested amendments need the approval from the applicant and will get back within a day with the further course of action. The TD was filed on March 25, 2015 and approved by the office on the same day. The representative authorized to enter the suggested amendments electronically on March 25, 2015. The electronic communications between the representative and the examiner are made of record* .

**Applicant recordation instructions**: It is not necessary for applicant to provide a separate record of the substance of 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

| /NARAYAN BHAT/<br>Primary Examiner, Art Unit 1634 | |
|---|---|



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PubMed brenner s AND polynucleotide

Summary 50 per page Sort by Most Recent

Results: 22

1. Bifidobacterium adolescentis protects from the development of nonalcoholic steatohepatitis in a mouse model.
Reichold A, Brenner SA, Spruss A, Förster-Fromme K, Bergheim I, Bischoff SC.
J Nutr Biochem. 2014 Feb;25(2):118-25. doi: 10.1016/j.jnutbio.2013.09.011. Epub 2013 Nov 6.
PMID: 24445036

2. Reflex: intramolecular barcoding of long-range PCR products for sequencing multiple pooled DNAs.
Casbon JA, Slatter AF, Musgrave-Brown E, Osborne RJ, Lichtenstein CP, **Brenner S**.
Nucleic Acids Res. 2013 May 1;41(10):e112. doi: 10.1093/nar/gkt228. Epub 2013 Apr 10.
PMID: 23580546 Free PMC Article

3. Evolution and functional characterisation of melanopsins in a deep-sea chimaera (elephant shark, Callorhinchus milii).
Davies WI, Tay BH, Zheng L, Danks JA, **Brenner S**, Foster RG, Collin SP, Hankins MW, Venkatesh B, Hunt DM.
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Soergel DA, Dey N, Knight R, Brenner SE.
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5. Aptamer selection by high-throughput sequencing and informatic analysis.
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Kulkarni RP, Tohari S, Ho A, **Brenner S**, Venkatesh B.
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PMID: 20395217 Free PMC Article

8. Notch signaling enhances osteogenic differentiation while inhibiting adipogenesis in primary human bone marrow stromal cells.



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9. Genetic basis of tetrodotoxin resistance in pufferfishes.
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J Biol Chem. 2003 Feb 21;278(8):5597-604. Epub 2002 Dec 18.
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11. Molecular cloning of the novel human G protein-coupled receptor (GPCR) gene mapped on chromosome 9.
Yamaguchi F, Tokuda M, Hatase O, **Brenner S**.
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12. Surface display of proteins on bacteriophage lambda heads.
Mikawa YG, Maruyama IN, **Brenner S**.
J Mol Biol. 1996 Sep 13;262(1):21-30.
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Proc Natl Acad Sci U S A. 1996 Aug 6;93(16):8485-9.
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14. Isolation, characterization and evolution of nine pufferfish (Fugu rubripes) actin genes.
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J Mol Biol. 1996 Jun 21;259(4):655-65.
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Yan H, Yang J, Marasco J, Yamaguchi K, **Brenner S**, Collins F, Karbon W.
Proc Natl Acad Sci U S A. 1996 May 14;93(10):4661-5.
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18. McGuigan TL, Livak KJ, **Brenner S**.
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A selective lambda phage cloning vector with automatic excision of the insert in a plasmid.
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20. nucleotide cofactor.
Zlotnick A, Mitchell RS, Brenner SL.
J Biol Chem. 1990 Oct 5;265(28):17050-4.
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recA protein-promoted ATP hydrolysis occurs throughout recA nucleoprotein filaments.
21. Brenner SL, Mitchell RS, Morrical SW, Neuendorf SK, Schutte BC, Cox MM.
J Biol Chem. 1987 Mar 25;262(9):4011-6.
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A new selective phage cloning vector, lambda 2001, with sites for XbaI, BamHI, HindIII, EcoRI, SstI
22. and XhoI.
Karn J, Matthes HW, Gait MJ, **Brenner S**.
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PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | | |
|---|---|---|
| | Application Number | 14172694 |
| | Filing Date | 2014-02-04 |
| | First Named Inventor | BRENNER, Sydney |
| | Art Unit | ~~1636~~ 1634 |
| | Examiner Name | Bhat N. |
| | Attorney Docket Number | CGLC-020CON4 |

14172694 - GAU: 1634

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|---|---|---|
| | Filing Date | 2014-02-04 |
| | First Named Inventor | BRENNER, Sydney |
| | Art Unit | ~~1636~~ 1634 |
| | Examiner Name | Bhat N. |
| | Attorney Docket Number | CGLC-020CON4 |

14172694 - GAU: 1634

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| Examiner Signature | /Narayan Bhat/ | Date Considered | 03/26/2015 |
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## Bhat, Narayan

**From:** James S. Keddie <keddie@bozpat.com>
**Sent:** Wednesday, March 25, 2015 8:07 PM
**To:** Bhat, Narayan
**Subject:** RE: 14/172,694

I filed the TD today. This case should be good to go now. Thanks.

---

**From:** James S. Keddie
**Sent:** Wednesday, March 25, 2015 1:03 PM
**To:** 'Bhat, Narayan'
**Subject:** RE: 14/172,694

This looks fine but I'm too swamped to file the TD. Here's the amendment -- please go ahead and prep the Exr's amendment and I'll file an e-TD first thing tomorrow. Thanks. James

---

**From:** Bhat, Narayan [mailto:Narayan.Bhat@USPTO.GOV]
**Sent:** Wednesday, March 25, 2015 10:54 AM
**To:** James S. Keddie
**Subject:** RE: 14/172,694

I meant "that is from 100 bases to 30 kilo bases in length".

Narayan K Bhat

Primary Examiner, AU 1634,

Remsen 3C09, TC 1600, USPTO, DOC, Alexandria, VA-22313
T: 571-272-5540
Fax: 571-273-5540

---

**From:** James S. Keddie [mailto:keddie@bozpat.com]
**Sent:** Wednesday, March 25, 2015 1:43 PM
**To:** Bhat, Narayan
**Subject:** RE: 14/172,694

Dear Exr. Bhat,

Did you mean "that is from 100 bases to 30 kilo bases in length" (i.e., "30 kb", not "3 kb")?

James

---

**From:** Bhat, Narayan [mailto:Narayan.Bhat@USPTO.GOV]
**Sent:** Tuesday, March 24, 2015 9:36 AM
**To:** James S. Keddie
**Subject:** RE: 14/172,694

Mr. Keddie,
Thank you very much for your prompt response. If you want to an interview tomorrow, that is OK with me. Please suggest the time. I have reviewed the prosecution histories of the parent application 13/387,343 resulting in the issuance of patent (US 8,298,767), instant pending claims and the specification. If following suggestions are acceptable, you can send the amended claims and the abstract and authorize to enter them via examiner's amendments. However, you need to file the TD and after its acceptance by the office, I can issue the allowance action pending minor amendments to address 112 issues or typographical error.

Amendments : Claim 1. In line 8 add the limitation of "a polynucleotide of interest that is from 100 bases to 3 kilo bases in length; having", to be in line with allowed claim limitation of '767 patent and also to overcome potential new matter rejection.
Claim 14 and 19– need to be cancelled or amended to further limit claim 1.

Abstract – replace the acronym "MID" with "multiplex identifier".
Filing of a terminal disclaimer and its approval by the office to overcome the potential ODP rejection instant pending claims over claims of '767 patent.

Narayan K Bhat

Primary Examiner, AU 1634,

Remsen 3C09, TC 1600, USPTO, DOC, Alexandria, VA-22313
T: 571-272-5540
Fax: 571-273-5540

---

**From:** James S. Keddie [mailto:keddie@bozpat.com]
**Sent:** Tuesday, March 24, 2015 11:55 AM
**To:** Bhat, Narayan
**Subject:** 14/172,694

14/172,694

Dear Exr. Bhat,

Thanks for your voicemail. My client is on a plane to the UK right now, so I will get back to you tomorrow if that is okay.

James

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|---|---|---|---|---|
| 14/172,694 | 02/04/2014<br>**RULE** | 435 | 1634 | CGLC-020CON4 |

**APPLICANTS**

Population Genetics Technologies LTD, CAMBRIDGE, UNITED KINGDOM, Assignee (with 37 CFR 1.172 Interest);

**INVENTORS**

SYDNEY BRENNER, Ely, UNITED KINGDOM;
GI MIKAWA, Great Shelford, UNITED KINGDOM;
ROBERT OSBORNE, Great Chesterford, UNITED KINGDOM;
ANDREW SLATTER, London, UNITED KINGDOM;

/NKB/

**** CONTINUING DATA ***************************

This application is a CON of 14/021,790 09/09/2013 PAT 8679756
which is a CON of 13/859,450 04/09/2013 PAT 8563274
which is a CON of 13/622,872 09/19/2012 ABN
which is a CON of 13/387,343 02/15/2012 PAT 8298767
which is a 371 of PCT/IB2010/002243 08/13/2010
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| Foreign Priority claimed ☐ Yes ☑ No<br>35 USC 119(a-d) conditions met ☐ Yes ☐ No<br>Verified and Acknowledged /NARAYAN KAMESHWAR BHAT/ Examiner's Signature | ☐ Met after Allowance<br>Initials | STATE OR COUNTRY<br>UNITED KINGDOM | SHEETS DRAWINGS<br>13 | TOTAL CLAIMS<br>19 | INDEPENDENT CLAIMS<br>1 |

**ADDRESS**

EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303
UNITED STATES

**TITLE**

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R Osborne, A Slatter - US Patent App. 13/164,153, 2011 - Google Patents
**...** In the reflex system, a complement to the **reflex sequence** is present (eg, inserted in an adapter domain) on the same strand of the **polynucleotide** as the **reflex sequence** (eg, the same strand of a double-stranded **polynucleotide** or on the same single stranded **polynucleotide ...**
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S Brenner, G Mikawa, R Osborne, A Slatter - US Patent 8,563,274, 2013 - Google Patents
**...** As described above, we obtain a single stranded **polynucleotide** having, in the 5′ to 3′ orientation, a primer site (eg, for Roche 454 sequencing), an MID, a **reflex sequence** and the **polynucleotide** to be sequenced. Numerous **...**
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| | NARAYAN BHAT | 1634 |

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

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| CPC | | | | | | |
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| **Symbol** | | | | | **Type** | **Version** |
| C12Q | | 1 | / | 686 | F | 2013-01-01 |
| C12Q | | 1 | / | 6855 | I | 2013-01-01 |
| C12Q | | 1 | / | 6806 | I | 2013-01-01 |
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| C12Q | | 2563 | / | 179 | A | 1 | 2 | 2013-01-01 |
| C12Q | | 2537 | / | 143 | A | 1 | 3 | 2013-01-01 |
| C12Q | | 2535 | / | 122 | A | 1 | 4 | 2013-01-01 |
| C12Q | | 1 | / | 6855 | I | 2 | 1 | 2013-01-01 |
| C12Q | | 2525 | / | 161 | A | 2 | 2 | 2013-01-01 |
| C12Q | | 2525 | / | 155 | A | 2 | 3 | 2013-01-01 |
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| NONE<br><br>(Assistant Examiner) | (Date) | **Total Claims Allowed:**<br>17 | |
| /NARAYAN BHAT/<br>Primary Examiner.Art Unit 1634<br><br>(Primary Examiner) | 03/29/2015<br><br>(Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>None |

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| US ORIGINAL CLASSIFICATION | | | | | | INTERNATIONAL CLASSIFICATION | | | | | | | | | |
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| CLASS | | | SUBCLASS | | | CLAIMED | | | | | NON-CLAIMED | | | | |
| 435 | | | 6.1 | | | C | 1 | 2 | Q | 1 / 68 (2006.01.01) | | | | | |
| CROSS REFERENCE(S) | | | | | | C | 1 | 2 | P | 19 / 34 (2006.01.01) | | | | | |
| | | | | | | C | 1 | 2 | M | 1 / 34 (2006.01.01) | | | | | |
| CLASS | SUBCLASS (ONE SUBCLASS PER BLOCK) | | | | | C | 0 | 7 | H | 21 / 02 (2006.01.01) | | | | | |
| 435 | 6.1 | 6.11 | 6.12 | 91.2 | 91.53 | C | 0 | 7 | H | 21 / 04 (2006.01.01) | | | | | |
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| NONE<br><br>(Assistant Examiner) | (Date) | **Total Claims Allowed:**<br>17 | |
| /NARAYAN BHAT/<br>Primary Examiner.Art Unit 1634<br><br>(Primary Examiner) | 03/29/2015<br><br>(Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>None |



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| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
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|---|---|---|---|
| NONE<br><br>(Assistant Examiner) | (Date) | **Total Claims Allowed:**<br>17 | |
| /NARAYAN BHAT/<br>Primary Examiner.Art Unit 1634<br><br>(Primary Examiner) | 03/29/2015<br><br>(Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>None |

U.S. Patent and Trademark Office Part of Paper No. 20150326

**EAST Search History**

**EAST Search History (Interference)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L19 | 736 | ((reflex or shuf$5 or moving) near3 sequence) near5 (polynucleotide or oligonucleotide or dna or nucleic) | USPAT; UPAD | OR | ON | 2015/03/26 19:24 |
| L20 | 560 | 19 and (dna or nucleic or polynucleotide) near5 ("desired site" or snp or polymorph$4 or mutation) | USPAT; UPAD | OR | ON | 2015/03/26 19:24 |
| L21 | 11 | 20 and (reflex or shuffl$3 or mov$3) near5 (complement$3 near3 sequence) | USPAT; UPAD | OR | ON | 2015/03/26 19:24 |

**3/26/2015 7:25:51 PM**
**C:\Users\nbhat1\Documents\EAST\Workspaces\14172694-3-24-15.wsp**



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00177

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 14172694 | BRENNER ET AL. |
| | **Examiner** | **Art Unit** |
| | NARAYAN BHAT | 1634 |

## CPC- SEARCHED

| Symbol | Date | Examiner |
|---|---|---|
| C12Q1/68, C12Q1/686, C07H21/02, G01N31/22 and G01N33/52. | 3/26/15 | Bhat N. |

## CPC COMBINATION SETS - SEARCHED

| Symbol | Date | Examiner |
|---|---|---|
| | | |

## US CLASSIFICATION SEARCHED

| Class | Subclass | Date | Examiner |
|---|---|---|---|
| 435 | 6.1, 6.11, 6.12, 91.2, 91.53 and 287.2 | 3/26/15 | Bhat N. |
| 536 | 23.1, 24.2, 24.3 and 24.33 | 3/26/15 | Bhat N. |
| 422 | 430 | 3/26/15 | Bhat N. |

## SEARCH NOTES

| Search Notes | Date | Examiner |
|---|---|---|
| Reviewed the arts filed in the IDS of 4/2/2014. It is noted that the said arts are the ones that are applied during the prosecution of copending applications resulting in the issuace of the patents. | 3/26/15 | Bhat N. |
| Reviewed the copending applications in PALM from the inventors and claims in eDAN for potential ODP issues. | 3/26/15 | Bhat N. |
| Reviewed the prosecution histories of the parent and copending applications resulting in the issuance of the patents. | 3/26/15 | Bhat N. |
| Reviewed the PCT and provisional applications for the support for the allowed claims. | 3/26/15 | Bhat N. |
| Updated the search for the topics in EAST, Pubmed and Google scholar. Search histories are enclosed. | 3/26/15 | Bhat N. |

## INTERFERENCE SEARCH

| US Class/ CPC Symbol | US Subclass / CPC Group | Date | Examiner |
|---|---|---|---|

| | |
|---|---|
| | /NARAYAN BHAT/<br>Primary Examiner.Art Unit 1634 |



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00178

| INTERFERENCE SEARCH | | | |
|---|---|---|---|
| **US Class/ CPC Symbol** | **US Subclass / CPC Group** | **Date** | **Examiner** |
| | Searched using key words in EAST. Search history is enclosed. | 3/26/15 | Bhat N. |

| | |
|---|---|
| | /NARAYAN BHAT/<br>Primary Examiner.Art Unit 1634 |



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00179

**EAST Search History**

**EAST Search History (Prior Art)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 10 | (reflex near3 sequence) near5 (anneal$3 or bind$3 or hybridi$6) near5 (polynucleotide or oligonucleotide or dna or nucleic) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 18:45 |
| L2 | 4 | 1 and (reflex near3 sequence) near5 (extend$3 or elongat$4) near5 ("3'" or "3 '") | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 18:45 |
| L3 | 1711 | (shuffl$3 or mov$3) near5 (domain or region or segment or section) near5 (dna or nucleic or polynucleotide) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:04 |
| L4 | 377 | 3 and (complement$3 near3 sequence) near5 "3'" | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:06 |
| L5 | 142 | 4 and (extend$3 or elongat$3) near5 "3'" | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:07 |
| L6 | 129 | 5 and (dna or nucleic or polynucleotide) near5 ("desired site" or snp or polymorph$4 or mutation) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:08 |
| L7 | 98 | 6 and amplif$6 near5 ("desired site" or snp or polymorph$4 or mutation) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:09 |
| L8 | 8 | 7 and reflex | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:09 |
| L9 | 624202 | "435"/$.ccls. or "536"/$.ccls. or "422"/$.ccls. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:12 |
| L10 | 37763 | (C12Q1/68 or C12Q1/686 or C07H21/02 or G01N31/22 or G01N33/52).cpc. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:14 |



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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00180

| | | | | | | |
|---|---|---|---|---|---|---|
| L11 | 1674 | (9 or 10) and ((reflex or shuf$5 or moving) near3 sequence) near5 (polynucleotide or oligonucleotide or dna or nucleic) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:17 |
| L12 | 1437 | 11 and (domain or segment or region or section) near5 (polynucleotide or oligonucleotide or dna or nucleic) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:19 |
| L13 | 1143 | 12 and (dna or nucleic or polynucleotide) near5 ("desired site" or snp or polymorph$4 or mutation) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:19 |
| L15 | 19 | 13 and (reflex or shuffl$3 or mov$3) near5 (complement$3 near3 sequence) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:21 |
| L16 | 2038 | ((reflex or shuf$5 or moving) near3 sequence) near5 (polynucleotide or oligonucleotide or dna or nucleic) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:23 |
| L17 | 1416 | 16 and (dna or nucleic or polynucleotide) near5 ("desired site" or snp or polymorph$4 or mutation) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:23 |
| L18 | 22 | 17 and (reflex or shuffl$3 or mov$3) near5 (complement$3 near3 sequence) | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/26 19:23 |
| S1 | 27814 | population.as. or BRENNER.in. or MIKAWA.in. or OSBORNE.in. or SLATTER.in. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/24 10:10 |
| S2 | 6 | S1 and (reflex near3 sequence).clm. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/24 10:14 |
| S3 | 3 | S2 and (reflex near3 sequence) near5 (anneal$3 or bind$3 or hybridi$6) near5 (polynucleotide or oligonucleotide or dna or nucleic).clm. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/24 10:15 |
| S4 | 19 | (reflex near3 sequence).clm. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/24 10:20 |
| S5 | 3 | S4 and (reflex near3 sequence) near5 (anneal$3 or bind$3 or hybridi$6) near5 (polynucleotide or oligonucleotide or dna or nucleic).clm. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/24 10:21 |



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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00181

| | | | | | | |
|---|---|---|---|---|---|---|
| S6 | 3 | S4 and (reflex near3 sequence) near5 (extend$3 or elongat$4) near5 ("3'" or "3 '").clm. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/24 10:22 |
| S7 | 1 | S6 and amplif$5.clm. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/24 10:26 |
| S8 | 3 | S6 and (amplif$5 or replicat$4).clm. | US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB | OR | ON | 2015/03/24 10:27 |

**3/26/2015 7:25:31 PM**
**C:\Users\nbhat1\Documents\EAST\Workspaces\14172694-3-24-15.wsp**



10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00182

FILED ELECTRONICALLY

# 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)

93726 7590 04/14/2015
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

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. |
|---|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | CGLC-020CON4 | 2029 |

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

| 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 | 07/14/2015 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| BHAT, NARAYAN KAMESHWAR | 1634 | 435-006100 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "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 James S. Keddie
2 Bozicevic, Field & Francis, LLP
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: Population Genetics Technologies LTD.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Cambridge, United Kingdom

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-3038 is attached.~~
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 50-0815 (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 /James S. Keddie, Reg. No. 48,920/ Date July 6, 2015

Typed or printed name James S. Keddie Registration No. 48,920



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

10x Genomics, Inc. Exhibit 2009
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00876
Page 00183

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 14172694 |
| **Filing Date:** | 04-Feb-2014 |
| **Title of Invention:** | COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Filer:** | James Samuel Keddie/Tiffany Turner |
| **Attorney Docket Number:** | CGLC-020CON4 |

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:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Utility Appl Issue Fee | 2501 | 1 | 480 | 480 |
| Publ. Fee- Early, Voluntary, or Normal | 1504 | 1 | 0 | 0 |
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **480** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 22827804 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Customer Number:** | 93726 |
| **Filer:** | James Samuel Keddie |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | CGLC-020CON4 |
| **Receipt Date:** | 06-JUL-2015 |
| **Filing Date:** | 04-FEB-2014 |
| **Time Stamp:** | 16:33:28 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Credit Card |
| Payment was successfully received in RAM | $480 |
| RAM confirmation Number | 3387 |
| Deposit Account | |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Issue Fee Payment (PTO-85B) | CGLC-020CON4_Issue_Fee_Transmittal.pdf | 202909<br>d252d1c866762d4619a9714b6ef396c771ecb6ec | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 32261<br>d2b385f1b94820ace205a9e0f73027229a4ca634 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 235170 | | |

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

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 14/172,694 | 08/11/2015 | 9102980 | CGLC-020CON4 | 2029 |

93726 7590 07/22/2015
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

# ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

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

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

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

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

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

Population Genetics Technologies LTD, CAMBRIDGE, UNITED KINGDOM;
SYDNEY BRENNER, Ely, UNITED KINGDOM;
GI MIKAWA, Great Shelford, UNITED KINGDOM;
ROBERT OSBORNE, Great Chesterford, UNITED KINGDOM;
ANDREW SLATTER, London, UNITED KINGDOM;

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IR103 (Rev. 10/09)

**Filed Electronically**

| **CHANGE OF CORRESPONDENCE ADDRESS** | Attorney Docket | CGLC-020CON4 |
|---|---|---|
| | First Named Inventor | Brenner, Sydney |
| | Application Number | 14/172,694 |
| | Confirmation No. | 2029 |
| | Filing Date | February 4, 2014 |
| | Group Art Unit | 1634 |
| Address to:<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | Examiner Name | BHAT, NARAYAN KAMESHWAR |
| | Title: "Compositions and Methods for Intramolecular Nucleic Acid Rearrangement" | |

Please change the Correspondence Address for the above-identified application to:

☒ **The address associated with Customer Number <u>43850</u>**

| | | | |
|---|---|---|---|
| **Firm Name** | Morgan, Lewis & Bockius LLP | | |
| **Individual Name** | | | |
| **Address** | One Market, Spear Street Tower | | |
| **City, State, Zip** | San Francisco, California 94105 | | |
| **Country** | U.S.A. | | |
| **Telephone** | (415) 442-1000 | Facsimile | (415) 442-1001 |

**SIGNATURE OF ATTORNEY/AGENT OF RECORD**

| | | | |
|---|---|---|---|
| Name/Reg. No. | James S. Keddie, 48,920 | | |
| Signature | /James S. Keddie, Reg. No. 48,920/ | Date | 07-27-2016 |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 26472418 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Customer Number:** | 93726 |
| **Filer:** | James Samuel Keddie |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | CGLC-020CON4 |
| **Receipt Date:** | 27-JUL-2016 |
| **Filing Date:** | 04-FEB-2014 |
| **Time Stamp:** | 19:27:07 |
| **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 | Change of Address | CGLC-020CON4-Change_Corresp.pdf | 20715<br>5bf3c45472c0d30f6ac89d20854e825c06792dc3 | no | 1 |

**Warnings:**

| Information: | |
|---|---|
| **Total Files Size (in bytes):** | 20715 |

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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/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
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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(c).

I hereby appoint:

■ Practitioners associated with Customer Number: 43850

**OR**

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

| Name | Registration Number | Name | Registration Number |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

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

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

■ The address associated with Customer Number: 43850

**OR**

| | | | |
|---|---|---|---|
| Firm or Individual Name | | | |
| Address | | | |
| City | | State | Zip |
| Country | | | |
| Telephone | | Email | |

Assignee Name and Address: 10X Genomics, Inc.
7068 Koll Center Parkway, Suite 401
Pleasanton, CA 94566

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

**SIGNATURE of Assignee of Record**

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

| | | | |
|---|---|---|---|
| Signature | | Date | 8/13/2015 |
| Name | Matthew Murphy | Telephone | (925) 401-7495 |
| Title | Vice President, General Counsel | | |

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 3 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.

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 28637899 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Customer Number:** | 43850 |
| **Filer:** | Gargi Talukder/s Gloss |
| **Filer Authorized By:** | Gargi Talukder |
| **Attorney Docket Number:** | 104371-5016-US04 |
| **Receipt Date:** | 15-MAR-2017 |
| **Filing Date:** | 04-FEB-2014 |
| **Time Stamp:** | 19:52:03 |
| **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 | | US04_POA.pdf | 214152<br>187c58294fd944965eb57e477e1f2cdf8389495d | yes | 2 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Assignee showing of ownership per 37 CFR 3.73 | 1 | 1 |
| | Power of Attorney | 2 | 2 |
| **Warnings:** | | | |
| **Information:** | | | |
| | **Total Files Size (in bytes):** | 214152 | |

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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/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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## STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: 10X GENOMICS, INC.

Application No./Patent No.: 9,102,980 Filed/Issue Date: August 11, 2015

Titled: COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

10X GENOMICS, INC., a corporation
(Name of Assignee) (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. [ ] the 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 039162, Frame 0347, or for which a copy therefore 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.

Gargi Talukder
Signature

3/15/17
Date

Gargi Talukder
Printed or Typed Name

Attorney of record
Title

This collection of information is required by 37 CFR 3.73(b). 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. 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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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | 104371-5016-US04 |

**CONFIRMATION NO. 2029**

**POA ACCEPTANCE LETTER**

43850
MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

*OC000000090077456*

Date Mailed: 03/23/2017

## NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/15/2017.

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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Alexandria, Virginia 22313-1450
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| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | 104371-5016-US04 |

**CONFIRMATION NO. 2029**

**POWER OF ATTORNEY NOTICE**

43850
MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

*OC000000090077373*

Date Mailed: 03/23/2017

## NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/15/2017.

- 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**.

/cvorachack/

PTO/SB/123 (04-15)
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# CHANGE OF CORRESPONDENCE ADDRESS
## *Patent*

Address to:
Mail Stop Post Issue
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

| | |
|---|---|
| Patent Number | 9,102,980 |
| Issue Date | August 11, 2015 |
| Application Number | 14/172,694 |
| Filing Date | February 4, 2014 |
| First Named Inventor | Sydney BRENNER |
| Attorney Docket Number | 104371-5016-US04 |

Please change the Correspondence Address for the above-identified patent to:

☒ The address associated with Customer Number: 156830

***OR***

☐ **Firm *or* Individual Name**

**Address**

**City** | **State** | **ZIP**

**Country**

**Telephone** | **Email**

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This form will not affect any "fee address" provided for the above-identified patent. To change a "fee address" use the "Fee Address Indication Form" (PTO/SB/47).

I am the:

☐ Patentee.

☐ 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).

☒ Attorney or agent of record. Registration Number 61,368.

| | |
|---|---|
| Signature | /Gargi Talukder/ |
| Typed or Printed Name | Gargi Talukder |
| Date | August 10, 2018 |
| Telephone | 415.442.1000 |

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 than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.33. 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 3 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: Mail Stop Post Issue, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 33437748 |
| **Application Number:** | 14172694 |
| **International Application Number:** | |
| **Confirmation Number:** | 2029 |
| **Title of Invention:** | COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT |
| **First Named Inventor/Applicant Name:** | SYDNEY BRENNER |
| **Customer Number:** | 43850 |
| **Filer:** | Gargi Talukder/Sheila Gloss |
| **Filer Authorized By:** | Gargi Talukder |
| **Attorney Docket Number:** | 104371-5016-US04 |
| **Receipt Date:** | 10-AUG-2018 |
| **Filing Date:** | 04-FEB-2014 |
| **Time Stamp:** | 17:18:38 |
| **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 | Change of Address | 104371-5016-US04_Corr.pdf | 62791<br>4b3048f48b97c1aa773db720c010ecefb09ec25f | no | 1 |

**Warnings:**

| Information: | |
|---|---|
| **Total Files Size (in bytes):** | 62791 |

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

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

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY.DOCKET NO./TITLE | REQUEST ID |
|---|---|---|---|---|
| 14/172,694 | 02/04/2014 | SYDNEY BRENNER | 104371-5016-US04 | 177471 |

## Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 11/08/2022 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:** | /Zara Doddridge/ |
| **Name:** | Zara Doddridge |
| **Registration Number:** | 59098 |