

				GCTTAAAGGACGCTGAAGATTAGGAGAAGGTTACCAGTAGCT
66	chr22	42509371	42509471	ACACATTCAAGACCCCAATTCTTCACCGTGTAGATATATTCAAGGAATGGTTCCCCAA ATAAGTTCAGATCTTCTTCAAGTAAAGTATTTCATGACCAATA

[72] The sequences shown in Table 1 are sequences that can be used as invariant controls for each of the non-sex chromosomes. Of the nucleic acid sequences shown above in Table 1, SEQ ID NOs: 2, 5, 7, 12, 13, 17, 19, 24, 25, 28, 32, 36, 38, 40, 44, 46, 50, 52, 56, 58, 62 and 66 are the preferred sequence for each corresponding chromosome. Of these sequences, SEQ ID NOs: 2, 5, 13, 19, 28, 46, 50, 56, 58 and 66 are particularly preferred for use as invariant controls for use in sample input normalization.

[73] Nanoreporters can be used to detect any of the sequences of SEQ ID NOs: 1-66. Nanoreporters can also be used to detect fragments of these sequences. Fragments can be between 50 and 90 nucleotides in length. Fragments can also be 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 nucleotides in length. The target specific regions of the nanoreporters can specifically hybridize to any of the sequences of SEQ ID NOs:1-66, any fragments thereof or any complement thereof.

[74] The invention also provides methods of detecting the copy number of multiple genomic sequences simultaneously. Multiple probes made according to the nCounter® system of the invention can be used to detect multiple genomic targets in a multiplexed format. The signal generated by the presence of a number of copies of these targets can then be compared to a standard or reference sample with a known copy number. As explained above, a control or multiple controls are used to normalize sample DNA input between different assays.

[75] The basis of the nCounter® Analysis system is the unique code assigned to each gene to be assayed (International Patent Application No. PCT/US2008/059959 and Geiss *et al.* Nature Biotechnology. 2008. 26(3): 317-325; the contents of which are each incorporated herein by reference in their entireties). The code is composed of a number of positions (visualized as “spots”) and a number of colors. Colors are chosen to minimize spectral overlap during imaging. The number of positions are chosen with respect to a combination of factors that include, but are not limited to, the length of the DNA backbone, the minimum spot size that can be resolved under current imaging conditions, flexibility in code selection for modestly-sized gene sets (*i.e.* <1000 genes) and the number of potential codes for future versions of the system (for instance, in a

system with 7 positions, and 4 colors, the maximal number of specific labels is 4^7 , or 16,384 labels, if all possible combinations of codes are used).

[76] Specific capture and reporter probes are synthesized in 96-well plates using a semi-automated process. Briefly, the reporter probes are pooled. Gene-specific probes are ligated to reporter molecule backbones and the ligated backbones were annealed to a unique pool of dye-coupled RNA or DNA segments corresponding to a single code. Reporter probes are then purified using a common 5'-repeat sequence at the end of each backbone to remove excess probe oligonucleotides and dye-coupled RNA or DNA segments. Capture probes were made by ligating a second sequence-specific oligonucleotide for each gene to a universal sequence containing biotin. After ligation, the capture probes were also pooled and affinity-purified using the universal sequence to remove the excess unligated gene-specific oligonucleotides. Reporter and capture probes were combined into a single "library" and used as a single reagent in subsequent hybridizations.

[77] The expression levels of all DNA:reporter molecule:capture probe duplexes are measured in a single multiplexed hybridization reaction. The sample is combined with the probe library, and hybridization occurs in solution. After hybridization, the tripartite hybridized complexes are purified in a two-step procedure using magnetic beads linked to oligonucleotides complementary to universal sequences present on the capture and reporter probes. This dual purification process allows the hybridization reaction to be driven to completion with a large excess of gene-specific probes, as they were ultimately removed, and, thus, do not interfere with binding and imaging of the sample. All post hybridization steps are handled robotically on a custom liquid-handling robot (Prep Station, NanoString Technologies).

[78] Purified reactions are deposited by the Prep Station into individual flow cells of a sample cartridge, bound to a streptavidin-coated surface via the capture probe, electrophoresed to elongate the reporter probes, and immobilized. After processing, the sample cartridge is transferred to a fully automated imaging and data collection device (Digital Analyzer, NanoString Technologies). The expression level of a gene is measured by imaging each sample in, for instance, 4 colors and counting the number of times the code for that gene is detected. For each sample, over 600 fields-of-view (FOV) are imaged (1376 X 1024 pixels) representing approximately 10 mm^2 of the binding surface.

Typical imaging density is 100-200 counted reporters per field of view depending on the degree of multiplexing, the amount of RNA, and overall gene expression levels.

However, the system is capable of operating at densities 5- to 10-fold higher. The Digital Analyzer can accommodate up to 6 cartridges at once and current scan times for 600 FOV are 4 hours per sample cartridge. Unattended, the system can process 72 samples in 24-hours per instrument.

[79] Image processing and code counting is performed. To minimize false positives, a reporter must meet stringent criteria concerning the number, size, brightness and spacing of the spots to ensure that the code is interpreted correctly. Reporters that do not meet all of these criteria are discarded. Using these criteria, approximately 40% of the detected molecules are typically counted. No parity schemes or error correction are employed in the current system. Data is output in simple spreadsheet format listing the number of counts per DNA, or genomic DNA fragment, per sample.

Therapeutic Applications

[80] Compositions and methods of the invention are used to detect gene or chromosome copy number in subjects who are at risk of developing an illness or disorder. Moreover, the compositions and methods of the invention are used to detect gene or chromosome copy number in subjects who have been diagnosed with an illness or disorder, and who are in need of a diagnosis or prognosis. The compositions and methods described herein are used to monitor disease progression (onset of a genetic disease or degeneration of telomeres as a consequence of aging or increased cell proliferation due to cancer) or responses to genetic therapy. Furthermore, the compositions and methods provided herein are used to screen individuals for their personal risk of developing a disorder as well as their risk of passing a disorder onto future children. Embryonic cells are tested using the compositions and methods of the invention for the presence or absence of disorders.

[81] The invention can be used to determine the risk of developing a particular biological condition, a particular disease, such as a cancer, a genetic disorder, a developmental disorder, a degenerative disorder, a neurological disorder, a stem cell disorder, or other biological condition. Furthermore, the present invention can be used to monitor the progression of a disease or responses to genetic therapy. Specifically, the invention can be used to detect, to monitor progression of, or monitor therapeutic

regimens for diseases of the heart, kidney, ureter, bladder, urethra, liver, prostate, heart, blood vessels, bone marrow, skeletal muscle, smooth muscle, various specific regions of the brain (including, but not limited to the amygdala, caudate nucleus, cerebellum, corpus callosum, fetal, hypothalamus, thalamus), spinal cord, peripheral nerves, retina, nose, trachea, lungs, mouth, salivary gland, esophagus, stomach, small intestines, large intestines, hypothalamus, pituitary, thyroid, pancreas, adrenal glands, ovaries, oviducts, uterus, placenta, vagina, mammary glands, testes, seminal vesicles, penis, lymph nodes, thymus, and spleen. The present invention can be used to detect, to monitor progression of, or monitor therapeutic regimens for a particular disease, such as a cancer, a genetic disorder, a developmental disorder, a degenerative disorder, a neurological disorder, a stem cell disorder, or other biological condition.

[82] Critically, the methods of the invention can determine the individual contributions of multiple genes to the same condition or disorder using one multiplexed reaction. Specifically, the methods of the invention can not only identify which genes are involved in a particular disorder, disease, or syndrome, but also by which mechanism, *e.g.* sequence duplication, mutation, deletion, or translocation. As such, the invention provides superior properties over all known methods of genetic screening because the methods provided elucidate the genes involved in complex multigene disorders such as Autism or Down Syndrome, which, unlike Huntington's Disease, require the participation of multiple genes. Most importantly, the methods of the invention do not require the skilled artisan to have identified or predetermined which genes may contribute to a particular disorder, disease, or syndrome prior to using these methods. If the skilled artisan applies gene specific probes that are specific for all known genes, then the abnormally increased or decreased genomic DNA copy numbers present in a sample taken from a subject having a particular disorder, disease, or syndrome will be apparent when compared to the genomic DNA copy numbers of a normal subject.

[83] In certain embodiments of these methods, the term "normal subjects" is meant to describe a person who has not been diagnosed with the disorder, disease, or syndrome under examination. Alternatively, a "normal subject" is a person of similar age, weight, gender, ethnicity and physical health who has not been diagnosed with the particular disorder, disease, or syndrome under examination. In other aspects, a "normal subject" is a person who has not been diagnosed with any genetic disorder, disease, or syndrome,

and furthermore, may be of similar age, weight, gender, ethnicity and physical health to the test subject. In another aspect, a normal subject is a predetermined numerical reference based upon, for example, national or international averages or standards.

[84] The methods of the invention encompass a variety of subjects. Subjects are plants or animals. Animals are mammals. In certain embodiments, the mammal is a human, non-human primate, mouse, rat, dog, cat, horse, or cow, but is not limited to these examples. Mammals other than humans are advantageously used as subjects that represent animal models of a particular disorder. The preferred subject is human.

[85] The methods of the invention also encompass screening of subjects for pathology at various points in their lives. In certain embodiments, the detection is performed prenatally, neonatally, postnatally, at infancy, childhood, puberty, early adulthood, adulthood, and during old age. The pre-natal subject may be tested at about 1, 2, 3, 4, 5, 6, 7, 8 or 9 months prior to their expected birth date. Other subjects may be tested at the age of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, and 99 years of age or older.

Cancer

[86] Compositions and methods of the invention are used to identify cells and subjects at risk of developing or those cells and subjects who may have a predisposition for developing cancer. Moreover, the compositions and methods of the invention are used to differentiate cancer cell type, cancer subtype, tumor grade, or cancer stage for the purpose of diagnosing or prognosing a subject at risk of developing cancer or a subject who has developed cancer. The compositions and methods of the invention are further used to monitor to progression of a tumor, cancer, or a treatment regime. Additionally, the compositions and methods of the invention are used to screen individuals for any genetic predisposition to developing cancer.

[87] The term “cancer” includes solid tumors, as well as, hematologic tumors and/or malignancies. A “precancer cell” or “precancerous cell” is a cell manifesting a cell proliferative disorder that is a precancer or a precancerous condition. A “cancer cell” or “cancerous cell” is a cell manifesting a cell proliferative disorder that is a cancer. Any

reproducible means of measurement may be used to identify cancer cells or precancerous cells. Cancer cells or precancerous cells can be identified by histological typing or grading of a tissue sample (*e.g.*, a biopsy sample). Cancer cells or precancerous cells can be identified through the use of appropriate molecular markers.

[88] The compositions and methods of the invention are used to further determine cancer severity, as it is characterized by stage, tumor grade, and expression of factors that degrade the extracellular matrix, induce vascularization, inhibit cell adhesion and enable metastasis.

[89] Exemplary cancers include, but are not limited to, adrenocortical carcinoma, AIDS-related cancers, AIDS-related lymphoma, anal cancer, anorectal cancer, cancer of the anal canal, appendix cancer, childhood cerebellar astrocytoma, childhood cerebral astrocytoma, basal cell carcinoma, skin cancer (non-melanoma), biliary cancer, extrahepatic bile duct cancer, intrahepatic bile duct cancer, bladder cancer, urinary bladder cancer, bone and joint cancer, osteosarcoma and malignant fibrous histiocytoma, brain cancer, brain tumor, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, visual pathway and hypothalamic glioma, breast cancer, bronchial adenomas/carcinoids, carcinoid tumor, gastrointestinal, nervous system cancer, nervous system lymphoma, central nervous system cancer, central nervous system lymphoma, cervical cancer, childhood cancers, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, lymphoid neoplasm, mycosis fungoides, Sezary Syndrome, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), germ cell tumor, ovarian germ cell tumor, gestational trophoblastic tumor glioma, head and neck cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, ocular cancer, islet cell tumors (endocrine pancreas), Kaposi Sarcoma, kidney cancer, renal cancer, kidney cancer, laryngeal cancer, acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, lip and oral cavity cancer, liver cancer, lung cancer, non-small cell lung cancer,

small cell lung cancer, AIDS-related lymphoma, non-Hodgkin lymphoma, primary central nervous system lymphoma, Waldenström macroglobulinemia, medulloblastoma, melanoma, intraocular (eye) melanoma, merkel cell carcinoma, mesothelioma malignant, mesothelioma, metastatic squamous neck cancer, mouth cancer, cancer of the tongue, multiple endocrine neoplasia syndrome, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/ myeloproliferative diseases, chronic myelogenous leukemia, acute myeloid leukemia, multiple myeloma, chronic myeloproliferative disorders, nasopharyngeal cancer, neuroblastoma, oral cancer, oral cavity cancer, oropharyngeal cancer, ovarian cancer, ovarian epithelial cancer, ovarian low malignant potential tumor, pancreatic cancer, islet cell pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, prostate cancer, rectal cancer, renal pelvis and ureter, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, ewing family of sarcoma tumors, Kaposi Sarcoma, soft tissue sarcoma, uterine cancer, uterine sarcoma, skin cancer (non-melanoma), skin cancer (melanoma), merkel cell skin carcinoma, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, testicular cancer, throat cancer, thymoma, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter and other urinary organs, gestational trophoblastic tumor, urethral cancer, endometrial uterine cancer, uterine sarcoma, uterine corpus cancer, vaginal cancer, vulvar cancer, and Wilm's Tumor.

Developmental and Degenerative Disorders

[90] Compositions and methods of the invention are used to identify cells and subjects at risk of developing a developmental or degenerative disorder or those cells and subjects who may have a predisposition for developing a developmental or degenerative disorder. Moreover, the compositions and methods of the invention are used to differentiate developmental disorders, degenerative disorders, or developmental from degenerative disorders for the purpose of diagnosing or prognosing a subject at risk of presenting or a subject who has been diagnosed with a developmental or degenerative disorder. The compositions and methods of the invention are further used to monitor to progression of

a developmental disorder, a degenerative disorder, or a treatment regime. Additionally, the compositions and methods of the invention are used to screen individuals for any genetic predisposition for presenting a developmental or degenerative disorder himself/herself, or for producing a child having a developmental or degenerative disorder.

[91] The term “developmental disorder” includes any disorder that initially presents in an individual during gestation or early postnatal development. Early postnatal development encompasses a period of time from birth to age 18. Although developmental disorders are often considered synonymous with mental disabilities that cause mental, emotional, or cognitive deficits, the term “developmental disorder” is meant to encompass any disorder that presents in either a fetus or a child aged 18 years or less, regardless of the specific signs or symptoms associated with the disorder. Moreover, developmental disorders are typically characterized by an inadequate or malfunctioning development of biological or psychological process. Developmental disorders are also characterized by behavioral traits, family history, brain morphology, or genetic/biomarkers that are present during development and predict or indicate the individual’s risk of developing the disease in adulthood (*e.g.* Huntington’s Disease, Amyotrophic lateral sclerosis or ALS, and Schizophrenia).

[92] A specific developmental disorder selectively affects one area of development, sparing essentially all other areas of development. Specific developmental disorders affect primarily hearing, vision, speech, or metabolism. However, a pervasive developmental disorder involves delays in the development of many basic skills, most notably the ability to socialize with others, because these conditions affect the child’s ability to communicate and to use imagination. Pervasive developmental disorders include, but are not limited to, autism and autism spectrum disorders, Asperger’s syndrome, childhood disintegrative disorder, Rett’s Syndrome, attention-deficit disorder (ADD), and unspecified but pervasive disorders.

[93] Exemplary developmental disorders also include, but are not limited to, Autism spectrum disorders (ASD), Angelman Syndrome, central auditory processing disorder (CAPD), cerebral palsy, Down Syndrome, expressive language disorder, IsoDendric 15 (abbreviated idic(15)), Lanau-Kleffner Syndrome, neural tube defects, phenylketonuria (PKU), Prader-Willi Syndrome, seizure disorders, epilepsy, Tourette Syndrome,

Williams Syndrome, hearing loss, deafness, blindness, vision impairment, jaundice / kernicterus, cluttering (speech disfluency), agnosias (visual, auditory, and somatosensory), anorexia nervosa disorder, acute stress disorder, adjustment disorder, bipolar disorder, body dysmorphic disorder, breathing-related sleep disorders, asthma, brief psychotic episode, bulimia nervosa, schizophrenia, Huntington's Disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), chronic motor or vocal tic disorder, circadian rhythm sleep disorder, conduct disorder, communication/language disorders, Cornelia de Lange Syndrome, fatal familial insomnia (FFI), Fahr's Syndrome (or idiopathic basal ganglia calcification), migraine, neoplasm (benign and malignant), Lupus erythematosus, autoimmune disorders, diabetes (type I), Wilson's Disease, Bell's Palsy, congenital heart disease, microcephaly, neonatal encephalitis, hydrocephalus, Parkinson's Disease, narcolepsy, muscular dystrophy, Guillain-Barre Syndrome, neurofibromatosis, Von Hippel-Lindau Disease, dyslexia, familial hypercholesterolemia, polycystic kidney disease, hereditary spherocytosis, hereditary breast and ovarian syndrome, marfan syndrome, sickle cell anemia, sickle cell disease, cystic fibrosis, mucopolysaccharidoses, glycogen storage diseases, galactosemia, hemophilia, Androgenetic alopecia, Lebner's hereditary optic neuropathy, autoimmune disease, cleft palate, obesity, Gauchers Disease, Rett Syndrome, ataxia telangiectasia, long QT Syndrome, Alport Syndrome, male pattern baldness, SRY sex determination, achondroplasia, Cockayne syndrome, DiGeorge syndrome, fragile X syndrome, severe combined immunodeficiency, Waardenburg syndrome, Werner syndrome, Zellweger syndrome, adrenoleukodystrophy, glucose galactose malabsorption, hereditary hemochromatosis, Lesch-Nyhan syndrome, maple syrup urine disease, Menkes syndrome, Neimann-Pick syndrome, porphyria, Refsum disease, Tangier disease, Tay-Sachs disease, diastrophic dysplasia, Ellis-van Creveld Syndrome (chondroectodermal dysplasia), paroxysmal nocturnal hemoglobinuria, thalassemia, Crohn's disease, Best disease, glaucoma, retinoblastoma, congenital adrenal hyperplasia, autoimmune polyglandular syndrome, multiple endocrine neoplasia, familial Mediterranean fever, immunodeficiency with hyper- IgM, Charcot-Marie-Tooth syndrome, fibrodysplasia ossificans progressive, myotonic dystrophy, essential tremor, Friedrich's Ataxia, spinal muscular atrophy, spinocerebellar ataxia, tuberous sclerosis, alpha-1-antitrypsin deficiency, and Pendred Syndrome.

[94] The term “degenerative disorder” includes any disorder that initially presents in an adult individual. The term adult encompasses a period of time from age 18 to death. Although degenerative disorders are often considered synonymous with mental disabilities that cause mental, emotional, or cognitive deficits, the term “degenerative disorder” is meant to encompass any disorder that presents in an adult aged 18 years or older, regardless of the specific signs or symptoms associated with the disorder. Moreover, degenerative disorders are typically characterized by the deregulation or malfunction of an ordinarily operable biological or psychological process. Degenerative disorders can result from genetic predisposition, environmental factors, or exposure to pathogens such as a virus or prion.

[95] Exemplary degenerative disorders include, but are not limited to, Alzheimer’s Disease, dementia, senility, agnosias (visual, auditory, and somatosensory), acute stress disorder, adjustment disorder, bipolar disorder, body dysmorphic disorder, breathing-related sleep disorders (sleep apnea), brief psychotic episode, bulimia nervosa, schizophrenia, Huntington’s Disease (HD), Parkinson’s Disease, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Capgras (delusion) Syndrome, chronic fatigue syndrome, circadian rhythm sleep disorder, conduct disorder, communication/language disorders, Creutzfeldt-Jakob Disease (CJD), kuru, Gerstmann–Sträussler–Scheinker syndrome (GSS), fatal familial insomnia (FFI), cyclothymic disorder, acquired immune deficiency syndrome (AIDS), depression, addiction, Cushing’s Syndrome (also called hyperadrenocorticism or hypercorticism), neoplasm (benign and malignant), stroke, diabetes (Type II), aneurysm, cardiovascular disease (including heart disease), Meniere’s Disease, deafness, blindness, multiple system atrophy, Neiman Pick Disease, arteriosclerosis, progressive supranuclear palsy, cancer, Tay-Sachs Disease, keratoconus, macular degeneration, inflammatory bowel disease (IBD), prostatitis, male pattern baldness, obesity, paroxysmal nocturnal hemoglobinuria, thalassemia, Crohn’s disease, Best disease, glaucoma, Gyrate atrophy of the choroid and retina, Charcot-Marie-Tooth syndrome, fibrodysplasia ossificans progressive, myotonic dystrophy, osteoarthritis, osteoporosis, arthritis, and rheumatoid arthritis.

Neurological Disorders

[96] Compositions and methods of the invention are used to identify cells and subjects at risk of developing a neurological disorder or those cells and subjects who may have a

predisposition for developing a neurological disorder. Moreover, the compositions and methods of the invention are used to differentiate neurological disorders for the purpose of diagnosing or prognosing a subject at risk of presenting or a subject who has been diagnosed with a neurological disorder. The compositions and methods of the invention are further used to monitor to progression of a neurological disorder or a treatment regime. Additionally, the compositions and methods of the invention are used to screen individuals for any genetic predisposition for presenting a neurological disorder himself/herself, or for producing a child having a neurological disorder.

[97] The term “neurological disorder” includes any disorder that initially presents within the nervous system of an individual. Neurological disorders present with a variety of signs and symptoms including, but not limited to, psychological, mood, or behavioral changes; loss or decreased acuity of one or more senses (vision, hearing, touch); increased pain or burning sensations; lack of coordination or balance; loss of memory; loss of control over voluntary or involuntary movement; speech or balance; visual or auditory hallucinations; seizures; headaches; decreased movement; and ultimately, coma or death. Neurological disorders can result from genetic predisposition for developing the neurological disorder, one or more environmental factors that induce a the disorder to enhance the individual’s genetic predisposition, or exposure of an individual to infectious agents such as a virus, a bacteria, a fungus, or a prion that induces the disorder or enhances the individual’s genetic predisposition.

[98] Exemplary neurological disorders include, but are not limited to, autism spectrum disorders (ASD), Angelman Syndrome, bipolar disorder, attention-deficit disorder (ADD), central auditory processing disorder (CAPD), cerebral palsy, Down Syndrome, expressive language disorder, IsoDendric 15 (abbreviated idic(15)), Lanau-Kleffner Syndrome, neural tube defects, seizure disorders, epilepsy, Tourette Syndrome, traumatic brain injury (TBI), childhood disintegrative disorder, agnosias (visual, auditory, and somatosensory), anorexia nervosa disorder, acute stress disorder, adjustment disorder, bipolar disorder, body dysmorphic disorder, breathing-related sleep disorders, brief psychotic episode, bulimia nervosa, schizophrenia, Huntington’s Disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Capgras (delusion) Syndrome, chronic motor or vocal tic disorder, circadian rhythm sleep disorder, cluttering (speech disfluency), conduct disorder, communication/language disorders, Creutzfeldt-Jakob

Disease (CJD), kuru, Gerstmann–Sträussler–Scheinker syndrome (GSS), fatal familial insomnia (FFI), depression, addiction, Fahr’s Syndrome (or idiopathic basal ganglia calcification), migraine, neoplasm (benign and malignant), aphasia, paralysis, Bell’s Palsy, cerebrovascular disease, encephalitis, hydrocephalus, microcephaly, Parkinson’s Disease, trigeminal neuralgia, narcolepsy, muscular dystrophy, Guillain-Barre Syndrome, neurofibromatosis, dyslexia, Rett Syndrome, Fragile X syndrome, adrenoleukodystrophy, ataxia telangiectasia, Cockayne syndrome, deafness, Duchenne muscular dystrophy, Gaucher disease, Lesch-Nyhan syndrome, maple syrup urine disease, Menkes syndrome, phenylketonuria, Prader-Willi syndrome, spinal muscular atrophy, spinocerebellar ataxia, tuberous sclerosis, Neimann-Pick syndrome, Refsum disease, Tay-Sachs disease, Charcot-Marie-Tooth syndrome, fibrodysplasia ossificans progressive, myotonic dystrophy, and Meniere’s Disease.

Stem Cell Disorders

[99] Compositions and methods of the invention are used to identify cells and subjects at risk of developing a “stem cell” disorder or those cells and subjects who may have a predisposition for developing a stem cell disorder. Moreover, the compositions and methods of the invention are used to differentiate stem cell disorders for the purpose of diagnosing or prognosing a subject at risk of presenting or a subject who has been diagnosed with a stem cell disorder. The compositions and methods of the invention are further used to monitor to progression of a stem cell disorder or a treatment regime. Additionally, the compositions and methods of the invention are used to screen individuals for any genetic predisposition for presenting a stem cell disorder himself/herself, or for producing a child having a stem cell disorder.

[100] The term “stem cell disorder” includes any disorder that initially presents within a totipotent (or omnipotent), pluripotent, multipotent, oligopotent, or unipotent stem cell of an individual. Alternatively, or in addition, a stem cell disorder includes any disorder which can be treated or prevented by administering a composition including a stem cell to the individual. Stem cells are characterized by their ability to produce daughter cells, one of which will differentiate and the other of which will remain an undifferentiated stem cell. The potency of a stem cell relates to differentiation potential of the daughter cell that becomes committed to a particular cell fate. Specifically, the terms totipotent stem cell or omnipotent stem cell describe stem cells that can give rise to both embryonic

stem cells or, alternatively, the stem cell can generate every type of cell in the human body. Pluripotent stem cells have a more restricted potential than totipotent stem cells, however, these stem cells can generate cells derived from any of the three germ layers (ectoderm, mesoderm, or endoderm). Multipotent stem cells have a more restricted potential than pluripotent stem cells, however, these stem cells can generate cells within a related lineage. Multipotent stem cells are often considered adult stem cells because they are found in, for instance, the adult brain (neural stem cells that give rise to neurons and all types of glia) and bones (bone marrow stem cells that give rise to all types of blood cells). Oligopotent stem cells have a more restricted potential than multipotent stem cells, however, these stem cells can generate a few related types of cells. For example, the corneal epithelium contains oligopotent stem cells that produce only corneal and conjunctival cells. Unipotent cells are the most restricted cell type because they can only reproduce their own cell type, however, they do maintain the ability to self-renew. Muscle stem cells are nonlimiting examples of unipotent stem cells.

[101] Exemplary stem cell disorders include, but are not limited to, autism spectrum disorders (ASD), neural tube defects, seizure disorders, epilepsy, hearing loss, deafness, blindness, vision impairment, jaundice / kernicterus, cluttering (speech disfluency), agnosias (visual, auditory, and somatosensory), Huntington's Disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), chronic motor or vocal tic disorder, circadian rhythm sleep disorder, Alzheimer's Disease, dementia, senility, diabetes, Parkinson's Disease, muscular dystrophy, Guillain-Barre Syndrome, sickle cell anemia or sickle cell disease, ataxia telangiectasia, Cockayne syndrome, DiGeorge syndrome, severe combined immunodeficiency, porphyria, paroxysmal nocturnal hemoglobinuria, thalassemia, familial Mediterranean fever, immunodeficiency with hyper- IgM, Charcot-Marie-Tooth syndrome, fibrodysplasia ossificans progressive, myotonic dystrophy, spinal muscular atrophy, spinocerebellar ataxia, and Gauchers Disease.

[102]

Nanoreporters and nCounter® System overview

[103] The basis of the nCounter® Analysis system is the unique code assigned to each nucleic acid target to be assayed (International Patent Application No. PCT/US2008/059959 and Geiss *et al.* Nature Biotechnology. 2008. 26(3): 317-325; the contents of which are each incorporated herein by reference in their entireties). The code

is composed of an ordered series of colored fluorescent spots which create a unique barcode for each target to be assayed. A pair of probes is designed for each DNA or RNA target, a biotinylated capture probe and a reporter probe carrying the fluorescent barcode. This system is also referred to, herein, as the nanoreporter code system.

[104] Specific reporter and capture probes are synthesized for each target. Briefly, sequence-specific DNA oligonucleotide probes are attached to code-specific reporter molecules. Capture probes are made by ligating a second sequence-specific DNA oligonucleotide for each target to a universal oligonucleotide containing biotin. Reporter and capture probes are all pooled into a single hybridization mixture, the “probe library”.

[105] The relative abundance of each target is measured in a single multiplexed hybridization reaction. The sample is combined with the probe library, and hybridization occurs in solution. After hybridization, the tripartite hybridized complexes are purified in a two-step procedure using magnetic beads linked to oligonucleotides complementary to universal sequences present on the capture and reporter probes. This dual purification process allows the hybridization reaction to be driven to completion with a large excess of target-specific probes, as they are ultimately removed, and, thus, do not interfere with binding and imaging of the sample. All post hybridization steps are handled robotically on a custom liquid-handling robot (Prep Station, NanoString Technologies).

[106] Purified reactions are deposited by the Prep Station into individual flow cells of a sample cartridge, bound to a streptavidin-coated surface via the capture probe, electrophoresed to elongate the reporter probes, and immobilized. After processing, the sample cartridge is transferred to a fully automated imaging and data collection device (Digital Analyzer, NanoString Technologies). The expression level of a target is measured by imaging each sample and counting the number of times the code for that target is detected. For each sample, typically 600 fields-of-view (FOV) are imaged (1376 X 1024 pixels) representing approximately 10 mm² of the binding surface. Typical imaging density is 100-1200 counted reporters per field of view depending on the degree of multiplexing, the amount of sample input, and overall target abundance. Data is output in simple spreadsheet format listing the number of counts per target, per sample.

[107] Many nanoreporters, referred to as singular nanoreporters, are composed of one molecular entity. However, to increase the specificity of a nanoreporter and/or to improve the kinetics of its binding to a target molecule, a preferred nanoreporter is a dual

nanoreporter composed of two molecular entities, each containing a different target-specific sequence that binds to a different region of the same target molecule. In a dual nanoreporter, at least one of the two nanoreporter probes is labeled. This labeled nanoreporter probe is referred to herein as a "reporter probe". The other nanoreporter probe is not necessarily labeled. Such unlabeled components of dual nanoreporters are referred to herein as "capture probes" and often have affinity tags attached, such as biotin, which are useful to immobilize and/or stretch the complex containing the dual nanoreporter and the target molecule to allow visualization and/or imaging of the complex. When both probes are labeled or both have affinity tags, the probe with more label monomer attachment regions is referred to as the reporter probe and the other probe in the pair is referred to as a capture probe.

[108] For both single and dual nanoreporters, a fully assembled and labeled nanoreporter probe comprises two main portions, a target-specific sequence that is capable of binding to a target molecule, and a labeled portion which provides a "code" of signals associated with the target-specific sequence. Upon binding of the nanoreporter probe to the target molecule, the code identifies the target molecule to which the nanoreporter is bound.

[109] Nanoreporters are modular structures. In some embodiments, the nanoreporter comprises a plurality of different detectable molecules. In some embodiments, a labeled nanoreporter, is a molecular entity containing certain basic elements: (i) a plurality of unique label attachment regions attached in a particular, unique linear combination, and (ii) complementary polynucleotide sequences attached to the label attachment regions of the backbone. In some embodiments, the labeled nanoreporter comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more unique label attachment regions attached in a particular, unique linear combination, and complementary polynucleotide sequences attached to the label attachment regions of the backbone. In some embodiments, the labeled nanoreporter comprises 6 or more unique label attachment regions attached in a particular, unique linear combination, and complementary polynucleotide sequences attached to the label attachment regions of the backbone. A nanoreporter probe further comprises a target-specific sequence, also attached to the backbone.

[110] The term label attachment region includes a region of defined polynucleotide sequence within a given backbone that may serve as an individual attachment point for a

detectable molecule. In some embodiments, the label attachment regions comprise designed sequences.

[111] In some embodiments, the label nanoreporter also comprises a backbone containing a constant region. The term constant region includes tandemly-repeated sequences of about 10 to about 25 nucleotides that are covalently attached to a nanoreporter. The constant region can be attached at either the 5' region or the 3' region of a nanoreporter, and may be utilized for capture and immobilization of a nanoreporter for imaging or detection, such as by attaching to a solid substrate a sequence that is complementary to the constant region. In certain aspects, the constant region contains 2, 3, 4, 5, 6, 7, 8, 9, 10, or more tandemly-repeated sequences, wherein the repeat sequences each comprise about 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more nucleotides, including about 12-18, 13-17, or about 14-16 nucleotides.

[112] The nanoreporters described herein can comprise synthetic, designed sequences. In some embodiments, the sequences contain a fairly regularly-spaced pattern of a nucleotide (*e.g.* adenine) residue in the backbone. In some embodiments, a specific nucleotide is spaced at least an average of 8, 9, 10, 12, 15, 16, 20, 30, or 50 bases apart. In some embodiments, a nucleotide is spaced at least an average of 8 to 16 bases apart. In some embodiments, a nucleotide is spaced at least an average of 8 bases apart. This allows for a regularly spaced complementary nucleotide in the complementary polynucleotide sequence having attached thereto a detectable molecule. For example, in some embodiments, when the nanoreporter sequences contain a fairly regularly-spaced pattern of adenine residues in the backbone, whose complement is a regularly-spaced pattern of uridine (U) residues in complementary RNA segments, the *in vitro* transcription of the segments can be done using an aminoallyl-modified uridine base, which allows the covalent amine coupling of dye molecules at regular intervals along the segment. In some embodiments, the sequences contain about the same number or percentage of a nucleotide (*e.g.* adenine) that is spaced at least an average of 8, 9, 10, 12, 15, 16, 20, 30, or 50 bases apart in the sequences. This allows for similar number or percentages in the complementary polynucleotide sequence having attached thereto a detectable molecule. Thus, in some embodiments, the sequences contain a nucleotide that is not regularly-spaced but that is spaced at least an average of 8, 9, 10, 12, 15, 16,

20, 30, or 50 bases apart. In some embodiments, 20%, 30%, 50%, 60%, 70%, 80%, 90% or 100% of the complementary nucleotide is coupled to a detectable molecule. For instance, in some embodiments, when the nanoreporter sequences contain a similar percentage of adenine residues in the backbone and the in vitro transcription of the complementary segments is done using an aminoallyl-modified uridine base, 20%, 30%, 50%, 60%, 70%, 80%, 90% or 100% of the aminoallyl-modified uridine base can be coupled to a detectable molecule. Alternatively, the ratio of aminoallyl-modified uridine bases and uridine bases can be changed during the in vitro transcription process to achieve the desired number of sites which can be attached to a detectable molecule. For example, in vitro transcription process can take place in the presence of a mixture with a ratio of 1/1 of uridine to aminoallyl-modified uridine bases, when some or all the aminoallyl-modified uridine bases can be coupled to a detectable molecule.

[113] In some embodiments, the nanoreporters described herein have a fairly consistent melting temperature (T_m). Without intending to be limited to any theory, the T_m of the nanoreporters described herein provides for strong bonds between the nanoreporter backbone and the complementary polynucleotide sequence having attached thereto a detectable molecule, therefore, preventing dissociation during synthesis and hybridization procedures. In addition, the consistent T_m among a population of nanoreporters allows for the synthesis and hybridization procedures to be tightly optimized, as the optimal conditions are the same for all spots and positions. In some embodiments, the sequences of the nanoreporters have a 50% guanine/cytosine (G/C), with no more than three G's in a row. Thus, in some embodiments, the disclosure provides a population of nanoreporters in which the T_m among the nanoreporters in the population is fairly consistent. In some embodiments, the disclosure provides a population of nanoreporters in which the T_m of the complementary polynucleotide sequences when hybridized to its label attachment regions is about 80° C, 85° C, 90° C, 100° C or higher. In some embodiments, the disclosure provides a population of nanoreporters in which the T_m of the complementary polynucleotide sequences when hybridized to its label attachment regions is about 80° C or higher.

[114] In some embodiments, the nanoreporters described herein have minimal or no secondary structures, such as any stable intra-molecular base-pairing interaction (*e.g.* hairpins). Without intending to be limited to any theory, the minimal secondary structure

in the nanoreporters provides for better hybridization between the nanoreporter backbone and the polynucleotide sequence having attached thereto a detectable molecule. In addition, the minimal secondary structure in the nanoreporters provides for better detection of the detectable molecules in the nanoreporters. In some embodiments, the nanoreporters described herein have no significant intra-molecular pairing under annealing conditions of 75° C, 1 X SSPE. Secondary structures can be predicted by programs known in the art such as MFOLD. In some embodiments, the nanoreporters described herein contain less than 1% of inverted repeats in each strand, wherein the inverted repeats are 9 bases or greater. In some embodiments, the nanoreporters described herein contain no inverted repeats in each strand. In some embodiments, the nanoreporters do not contain any inverted repeat of 9 nucleotides or greater across a sequence that is 1100 base pairs in length. In some embodiments, the nanoreporters do not contain any inverted repeat of 7 nucleotides or greater across any 100 base pair region. In some embodiments, the nanoreporters described herein contain less than 1% of inverted repeats in each strand, wherein the inverted repeats are 9 nucleotides or greater across a sequence that 1100 base pairs in length. In some embodiments, the nanoreporters described herein contain less than 1% of inverted repeats in each strand, wherein the inverted repeats are 7 nucleotides or greater across any 100 base pair region. In some embodiments, the nanoreporters described herein contain a skewed strand specific content such that one strand is CT-rich and the other is GA-rich.

[115] The disclosure also provides unique nanoreporters. In some embodiments, the nanoreporters described herein contain less than 1% of direct repeats. In some embodiments, the nanoreporters described herein contain no direct repeats. In some embodiments, the nanoreporters do not contain any direct repeat of 9 nucleotides or greater across a sequence that 1100 base pairs in length. In some embodiments, the labeled nanoreporters do not contain any direct repeat of 7 nucleotides or greater across any 100 base pair region. In some embodiments, the nanoreporters described herein contain less than 1% of direct repeats in each strand, wherein the direct repeats are 9 nucleotides or greater across a sequence that 1100 base pairs in length. In some embodiments, the nanoreporters described herein contain less than 1% of direct repeats in each strand, wherein the direct repeats are 7 nucleotides or greater across any 100 base pair region. In some embodiments, the nanoreporters described herein contain less than

85, 80, 70, 60, 50, 40, 30, 20, 10, or 5% homology to any other sequence used in the backbones or to any sequence described in the REFSEQ public database. In some embodiments, the nanoreporters described herein contain less than 85% homology to any other sequence used in the backbones or to any sequence described in the REFSEQ public database. In some embodiments, the nanoreporters described herein contain less than 20, 16, 15, 10, 9, 7, 5, 3, 2 contiguous bases of homology to any other sequence used in the backbones or to any sequence described in the REFSEQ public database. In some embodiments, the nanoreporters described herein have no more than 15 contiguous bases of homology and no more than 85% identity across the entire length of the nanoreporter to any other sequence used in the backbones or to any sequence described in the REFSEQ public database.

[116] In some embodiments, the sequence characteristics of the nanoreporter probes described herein provide sensitive detection of a target molecule. For instance, the binding of the nanoreporter probes to target molecules which results in the identification of the target molecules can be performed by individually detecting the presence of the nanoreporter. This can be performed by individually counting the presence of one or more of the nanoreporter molecules in a sample.

[117] The complementary polynucleotide sequences attached to a nanoreporter backbone serve to attach detectable molecules, or label monomers, to the nanoreporter backbone. The complementary polynucleotide sequences may be directly labeled, for example, by covalent incorporation of one or more detectable molecules into the complementary polynucleotide sequence. Alternatively, the complementary polynucleotide sequences may be indirectly labeled, such as by incorporation of biotin or other molecule capable of a specific ligand interaction into the complementary polynucleotide sequence. In such instances, the ligand (*e.g.*, streptavidin in the case of biotin incorporation into the complementary polynucleotide sequence) may be covalently attached to the detectable molecule. Where the detectable molecules attached to a label attachment region are not directly incorporated into the complementary polynucleotide sequence, this sequence serves as a bridge between the detectable molecule and the label attachment region, and may be referred to as a bridging molecule, *e.g.*, a bridging nucleic acid.

[118] The nucleic-acid based nanoreporter and nanoreporter-target complexes

described herein comprise nucleic acids, which may be affinity-purified or immobilized using a nucleic acid, such as an oligonucleotide, that is complementary to the constant region or the nanoreporter or target nucleic acid. As noted above, in some embodiments the nanoreporters comprise at least one constant region, which may serve as an affinity tag for purification and/or for immobilization (for example to a solid surface). The constant region typically comprises two or more tandemly-repeated regions of repeat nucleotides, such as a series of 15-base repeats. In such exemplary embodiments, the nanoreporter, whether complexed to a target molecule or otherwise, can be purified or immobilized by an affinity reagent coated with a 15-base oligonucleotide which is the reverse complement of the repeat unit.

[119] Nanoreporters, or nanoreporter-target molecule complexes, can be purified in two or more affinity selection steps. For example, in a dual nanoreporter, one probe can comprise a first affinity tag and the other probe can comprise a second (different) affinity tag. The probes are mixed with target molecules, and complexes comprising the two probes of the dual nanoreporter are separated from unbound materials (*e.g.*, the target or the individual probes of the nanoreporter) by affinity purification against one or both individual affinity tags. In the first step, the mixture can be bound to an affinity reagent for the first affinity tag, so that only probes comprising the first affinity tag and the desired complexes are purified. The bound materials are released from the first affinity reagent and optionally bound to an affinity reagent for the second affinity tag, allowing the separation of complexes from probes comprising the first affinity tag. At this point only full complexes would be bound. The complexes are finally released from the affinity reagent for the second affinity tag and then preferably stretched and imaged. The affinity reagent can be any solid surface coated with a binding partner for the affinity tag, such as a column, bead (*e.g.*, latex or magnetic bead) or slide coated with the binding partner. Immobilizing and stretching nanoreporters using affinity reagents is fully described in U.S. Publication No. 2010/0161026, which is incorporated by reference herein in its entirety.

[120] The sequence of signals provided by the label monomers associated with the various label attachment regions of the backbone of a given nanoreporter allows for the unique identification of the nanoreporter. For example, when using fluorescent labels, a nanoreporter having a unique identity or unique spectral signature is associated with a

target-specific sequence that recognizes a specific target molecule or a portion thereof. When a nanoreporter is exposed to a mixture containing the target molecule under conditions that permit binding of the target-specific sequence(s) of the nanoreporter to the target molecule, the target-specific sequence(s) preferentially bind(s) to the target molecule. Detection of the nanoreporter signal, such as the spectral code of a fluorescently labeled nanoreporter, associated with the nanoreporter allows detection of the presence of the target molecule in the mixture (qualitative analysis). Counting all the label monomers associated with a given spectral code or signature allows the counting of all the molecules in the mixture associated with the target-specific sequence coupled to the nanoreporter (quantitative analysis). Nanoreporters are thus useful for the diagnosis or prognosis of different biological states (*e.g.*, disease vs. healthy) by quantitative analysis of known biological markers or copy number variant loci.

[121] Many nanoreporters, referred to as singular nanoreporters, are composed of one molecular entity. However, to increase the specificity of a nanoreporter and/or to improve the kinetics of its binding to a target molecule, a nanoreporter can be a dual nanoreporter composed of two molecular entities, each containing a different target-specific sequence that binds to a different region of the same target molecule. In a dual nanoreporter, at least one of the two molecular entities is labeled. The other molecular entity need not necessarily be labeled. Such unlabeled components of dual nanoreporters may be used as capture probes and optionally have affinity tags attached, such as biotin, which are useful to immobilize and/or stretch the complex containing the dual nanoreporter and the target molecule to allow visualization and/or imaging of the complex. For instance, in some embodiments, a dual nanoreporter with a 6-position nanoreporter code, uses one 6-position coded nanoreporter (also referred to herein as a reporter probe) and a capture probe. In some embodiments, a dual nanoreporter with a 6-position nanoreporter code can be used, using one capture probe with an affinity tag and one 6-position nanoreporter component. In some embodiments an affinity tag is optionally included and can be used to purify the nanoreporter or to immobilize the nanoreporter (or nanoreporter-target molecule complex) for the purpose of imaging.

[122] In some embodiments, the nucleotide sequences of the individual label attachment regions within each nanoreporter are different from the nucleotide sequences of the other label attachment regions within that nanoreporter, preventing

rearrangements, such recombination, sharing or swapping of the label polynucleotide sequences. The number of label attachment regions to be formed on a backbone is based on the length and nature of the backbone, the means of labeling the nanoreporter, as well as the type of label monomers providing a signal to be attached to the label attachment regions of the backbone. In some embodiments, the complementary nucleotide sequence of each label attachment region is assigned a specific detectable molecule.

[123] The disclosure also provides labeled nanoreporters wherein one or more label attachment regions are attached to a corresponding detectable molecule, each detectable molecule providing a signal. For example, in some embodiments, a labeled nanoreporter according to the disclosure is obtained when at least three detectable molecules are attached to three corresponding label attachment regions of the backbone such that these labeled label attachment regions, or spots, are distinguishable based on their unique linear arrangement. A "spot," in the context of nanoreporter detection, is the aggregate signal detected from the label monomers attached to a single label attachment site on a nanoreporter, and which, depending on the size of the label attachment region and the nature (*e.g.*, primary emission wavelength) of the label monomer, may appear as a single point source of light when visualized under a microscope. Spots from a nanoreporter may be overlapping or non-overlapping. The nanoreporter code that identifies that target molecule can comprise any permutation of the length of a spot, its position relative to other spots, and/or the nature (*e.g.*, primary emission wavelength(s)) of its signal. Generally, for each probe or probe pair described herein, adjacent label attachment regions are non-overlapping, and/or the spots from adjacent label attachment regions are spatially and/or spectrally distinguishable, at least under the detection conditions (*e.g.*, when the nanoreporter is immobilized, stretched and observed under a microscope, as described in U.S. Publication No. 2010/0112710, incorporated herein by reference).

[124] Occasionally, reference is made to a spot size as a certain number of bases or nucleotides. As would be readily understood by one of skill in the art, this refers to the number of bases or nucleotides in the corresponding label attachment region.

[125] The order and nature (*e.g.*, primary emission wavelength(s), optionally also length) of spots from a nanoreporter serve as a nanoreporter code that identifies the target molecule capable of being bound by the nanoreporter through the nanoreporter's target specific sequence(s). When the nanoreporter is bound to a target molecule, the

nanoreporter code also identifies the target molecule. Optionally, the length of a spot can be a component of the nanoreporter code.

[126] Detectable molecules providing a signal associated with different label attachment regions of the backbone can provide signals that are indistinguishable under the detection conditions ("like" signals), or can provide signals that are distinguishable, at least under the detection conditions (*e.g.*, when the nanoreporter is immobilized, stretched and observed under a microscope).

[127] The disclosure also provides a nanoreporter wherein two or more detectable molecules are attached to a label attachment region. The signal provided by the detectable molecules associated with said label attachment region produces an aggregate signal that is detected. The aggregate signal produced may be made up of like signals or made up of at least two distinguishable signals (*e.g.*, spectrally distinguishable signals).

[128] In one embodiment, a nanoreporter includes at least three detectable molecules providing like signals attached to three corresponding label attachment regions of the backbone and said three detectable molecules are spatially distinguishable. In another embodiment, a nanoreporter includes at least three detectable molecules providing three distinguishable signals attached to three neighboring label attachment regions, for example three adjacent label attachment regions, whereby said at least three label monomers are spectrally distinguishable.

[129] In other embodiments, a nanoreporter includes spots providing like or unlike signals separated by a spacer region, whereby interposing the spacer region allows the generation of dark spots, which expand the possible combination of uniquely detectable signals. The term "dark spot" refers to a lack of signal from a label attachment site on a nanoreporter. Dark spots can be incorporated into the nanoreporter code to add more coding permutations and generate greater nanoreporter diversity in a nanoreporter population. In one embodiment, the spacer regions have a length determined by the resolution of an instrument employed in detecting the nanoreporter.

[130] In other embodiments, a nanoreporter includes one or more "double spots." Each double spot contains two or more (*e.g.*, three, four or five) adjacent spots that provide like signals without being separated by a spacer region. Double spots can be identified by their sizes.

[131] A detectable molecule providing a signal described herein may be attached

covalently or non-covalently (*e.g.*, via hybridization) to a complementary polynucleotide sequence that is attached to the label attachment region. The label monomers may also be attached indirectly to the complementary polynucleotide sequence, such as by being covalently attached to a ligand molecule (*e.g.*, streptavidin) that is attached through its interaction with a molecule incorporated into the complementary polynucleotide sequence (*e.g.*, biotin incorporated into the complementary polynucleotide sequence), which is in turn attached via hybridization to the backbone.

[132] A nanoreporter can also be associated with a uniquely detectable signal, such as a spectral code, determined by the sequence of signals provided by the label monomers attached (*e.g.*, indirectly) to label attachment regions on the backbone of the nanoreporter, whereby detection of the signal allows identification of the nanoreporter.

[133] In other embodiments, a nanoreporter also includes an affinity tag attached to the reporter probe backbone, such that attachment of the affinity tag to a support allows backbone stretching and resolution of signals provided by label monomers corresponding to different label attachment regions on the backbone. Nanoreporter stretching may involve any stretching means known in the art including but not limited to, means involving physical, hydrodynamic or electrical means. The affinity tag may comprise a constant region.

[134] In other embodiments, a nanoreporter also includes a target-specific sequence coupled to the backbone. The target-specific sequence is selected to allow the nanoreporter to recognize, bind or attach to a target molecule. The nanoreporters described herein are suitable for identification of target molecules of all types. For example, appropriate target-specific sequences can be coupled to the backbone of the nanoreporter to allow detection of a target molecule. Preferably the target molecule is DNA (including cDNA), RNA (including mRNA and cRNA), a peptide, a polypeptide, or a protein.

[135] One embodiment of the disclosure provides increased flexibility in target molecule detection with label monomers described herein. In this embodiment, a dual nanoreporter comprising two different molecular entities, each with a separate target-specific region, at least one of which is labeled, bind to the same target molecule. Thus, the target-specific sequences of the two components of the dual nanoreporter bind to different portions of a selected target molecule, whereby detection of the spectral code

associated with the dual nanoreporter provides detection of the selected target molecule in a biomolecular sample contacted with said dual nanoreporter.

[136] The disclosure also provides a method of detecting the presence of a specific target molecule in a biomolecular sample comprising: (i) contacting said sample with a nanoreporter as described herein (*e.g.*, a singular or dual nanoreporter) under conditions that allow binding of the target-specific sequences in the dual nanoreporter to the target molecule and (ii) detecting the spectral code associated with the dual nanoreporter. Depending on the nanoreporter architecture, the dual nanoreporter may be labeled before or after binding to the target molecule.

[137] The uniqueness of each nanoreporter probe in a population of probe allows for the multiplexed analysis of a plurality of target molecules. For example, in some embodiments, each nanoreporter probe contains six label attachment regions, where each label attachment region of each backbone is different from the other label attachment regions in that same backbone. If the label attachment regions are going to be labeled with one of four colors and there are 24 possible unique sequences for the label attachment regions and each label attachment region is assigned a specific color, each label attachment region in each backbone will consist of one of four sequences. There will be 4096 possible nanoreporters in this example. The number of possible nanoreporters can be increased, for example, by increasing the number of colors, increasing the number of unique sequences for the label attachment regions and/or increasing the number of label attachment regions per backbone. Likewise the number of possible nanoreporters can be decreased by decreasing the number of colors, decreasing the number of unique sequences for the label attachment regions and/or decreasing the number of label attachment regions per backbone.

[138] In certain embodiments, the methods of detection are performed in multiplex assays, whereby a plurality of target molecules are detected in the same assay (a single reaction mixture). In a preferred embodiment, the assay is a hybridization assay in which the plurality of target molecules are detected simultaneously. In certain embodiments, the plurality of target molecules detected in the same assay is, at least 2, at least 5 different target molecules, at least 10 different target molecules, at least 20 different target molecules, at least 50 different target molecules, at least 75 different target molecules, at least 100 different target molecules, at least 200 different target molecules, at least 500

different target molecules, or at least 750 different target molecules, or at least 1000 different target molecules. In other embodiments, the plurality of target molecules detected in the same assay is up to 50 different target molecules, up to 100 different target molecules, up to 150 different target molecules, up to 200 different target molecules, up to 300 different target molecules, up to 500 different target molecules, up to 750 different target molecules, up to 1000 different target molecules, up to 2000 different target molecules, or up to 5000 different target molecules. In yet other embodiments, the plurality of target molecules detected is any range in between the foregoing numbers of different target molecules, such as, but not limited to, from 20 to 50 different target molecules, from 50 to 200 different target molecules, from 100 to 1000 different target molecules, from 500 to 5000 different target molecules, and so on and so forth.

[139] Additional disclosure regarding nanoreporters can be found in International Publication No. WO 07/076129 and WO 07/076132, the contents of which are incorporated herein in their entireties. Further, the term nucleic acid probes and nanoreporters can include the rationally designed (*e.g.* synthetic sequences) described in International Publication No. WO 2010/019826, incorporated herein by reference in its entirety.

Kits

[140] Kits include a composition containing at least a first probe and a restriction enzyme. The first probe includes a first molecule containing a first label attachment region to which are attached one or more label monomers that emit light constituting a first signal; a second label attachment region, which is non-over-lapping with the first label attachment region, to which are attached one or more label monomers that emit light constituting a second signal; and a first target-specific sequence attached to the first molecule, wherein the target-specific sequence specifically hybridizes to a target DNA sequence. In certain embodiments of the kit, the first probe further includes an affinity tag. In other embodiments of the kit, the first probe includes a second molecule containing a second target-specific sequence; and an affinity tag; wherein the first molecule and the second molecule specifically hybridize to the same target DNA sequence at different sites.

[141] In other embodiments of the kit, the first molecule is a reporter probe or a capture

probe. In other embodiments, the second molecule is a reporter probe or a capture probe. Reporter probes and capture probes are provided in the kit individually or in a mixture.

[142] The restriction enzyme can be either a restriction endonuclease or a DNase. Preferably the restriction enzyme is AluI or BfaI.

[143] The kit optionally includes a second probe including a third molecule containing a third label attachment region to which are attached one or more label monomers that emit light constituting a third signal; a fourth label attachment region, which is non-overlapping with the third label attachment region, to which are attached one or more label monomers that emit light constituting a fourth signal; and a third target-specific sequence attached to the third molecule, wherein the target-specific sequence specifically hybridizes to a control DNA sequence. In certain embodiments the second probe includes a fourth molecule containing a fourth target-specific sequence and an affinity tag; wherein the third molecule and the fourth molecule specifically hybridize to the same control DNA sequence at different sites on the sequence.

[144] In other embodiments of the kit, the third molecule is a reporter probe or a capture probe. In other embodiments, the fourth molecule is a reporter probe or a capture probe. Reporter probes and capture probes are provided in the kit individually or in a mixture.

[145] In preferred embodiments of the kits, the labels and label monomers are fluorescent.

[146] Kits further include a control DNA sequence of known copy number. In other embodiments, kits contain a control probe to ensure that equivalent amounts of DNA are introduced or loaded into the nCounter® system.

[147] Kits include instructions for handling the enclosed compositions and protocols for performing singular or multiplexed fragmenting and denaturing reactions, as well as the contacting, stretching, and measuring steps described herein using the enclosed compositions. Furthermore, the instructions provide guidance for preparing the resultant tagged fragmented and hybridized genomic DNA molecule(s) for detection using the nCounter® Analysis System.

Nucleic Acids

[148] Also disclosed herein are isolated nucleic acid molecules that can be used as controls for genomic copy number assays. These nucleic acid molecules include the

sequences shown in Table 1. Of the nucleic acid sequences shown above in Table 1, SEQ ID NOs: 2, 5, 7, 12, 13, 17, 19, 24, 25, 28, 32, 36, 38, 40, 44, 46, 50, 52, 56, 58, 62 and 66 are the preferred sequence for each corresponding chromosome. Of these sequences, SEQ ID NOs: 2, 5, 13, 19, 28, 46, 50, 56, 58 and 66 are particularly preferred for use as controls.

[149] Also included in the invention are nucleic acid fragments sufficient for use as controls in genomic copy number assays. These sequences can be present in the genomic sample itself or can be added to separate control samples. Probes can also be made to detect these sequences. These probes, themselves can be nucleic acid molecules comprising any of SEQ ID NOs: 1-66 or any complement thereof. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs, and derivatives, fragments and homologs thereof. The nucleic acid molecule may be single-stranded or double-stranded, but preferably is comprised double-stranded DNA.

[150] The term "probes", as utilized herein, refers to nucleic acid sequences of variable length, preferably between at least about 10 nucleotides (nt), 100 nt, or as many as approximately, *e.g.*, 6,000 nt, depending upon the specific use. Probes are used in the detection of identical, similar, or complementary nucleic acid sequences. In specific embodiments, these probe sequences are used to construct target specific portions of nanoreporters described above.

[151] The term "isolated" nucleic acid molecule, as utilized herein, is one, which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5'- and 3'-termini of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecules described herein can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell/tissue from which the nucleic acid is derived (*e.g.*, brain, heart, liver, spleen, *etc.*). Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material or culture medium when produced by

recombinant techniques, or of chemical precursors or other chemicals when chemically synthesized.

[152] A nucleic acid molecule described herein can be isolated using standard molecular biology techniques and the sequence information provided herein. Nucleic acid molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, *et al.*, (eds.), MOLECULAR CLONING: A LABORATORY MANUAL 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989; and Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993.)

[153] In another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule that is a complement of the nucleotide sequence shown in SEQ ID NOs: 1-66, or a portion of this nucleotide sequence (*e.g.*, a fragment that can be used as a probe or primer). A nucleic acid molecule that is complementary to the nucleotide sequence shown SEQ ID NOs: 1-66 is one that is sufficiently complementary that it can hydrogen bond with little or no mismatches, thereby forming a stable duplex.

[154] As used herein, the term “complementary” refers to Watson-Crick or Hoogsteen base pairing between nucleotides units of a nucleic acid molecule, and the term “binding” means the physical or chemical interaction between two polypeptides or compounds or associated polypeptides or compounds or combinations thereof. Binding includes ionic, non-ionic, van der Waals, hydrophobic interactions, and the like. A physical interaction can be either direct or indirect. Indirect interactions may be through or due to the effects of another polypeptide or compound. Direct binding refers to interactions that do not take place through, or due to, the effect of another polypeptide or compound, but instead are without other substantial chemical intermediates.

[155] Fragments provided herein are defined as sequences of at least 6 (contiguous) nucleic acids, a length sufficient to allow for specific hybridization in the case of nucleic acids and are at most some portion less than a full length sequence. Fragments may be derived from any contiguous portion of a nucleic acid or amino acid sequence of choice. Derivatives are nucleic acid sequences from the native compounds either directly or by modification or partial substitution. Analogs are nucleic acid sequences that have a structure similar to, but not identical to, the native compound but differs from it in

respect to certain components or side chains. Analogs may be synthetic or from a different evolutionary origin and may have a similar or opposite metabolic activity compared to wild type. Homologs are nucleic acid sequences or amino acid sequences of a particular gene that are derived from different species.

[156] Derivatives and analogs may be full length or other than full length, if the derivative or analog contains a modified nucleic acid, as described below. Derivatives or analogs of the nucleic acids of the invention include, but are not limited to, molecules comprising regions that are substantially homologous to the nucleic acids of the invention, in various embodiments, by at least about 70%, 80%, or 95% identity (with a preferred identity of 80-95%) over a nucleic acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to the complement of a sequence encoding the aforementioned proteins under stringent, moderately stringent, or low stringent conditions. See *e.g.* Ausubel, *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993, and below.

[157] As used herein, the phrase “stringent hybridization conditions” refers to conditions under which a probe, primer or oligonucleotide will hybridize to its target sequence, but to substantially no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures than shorter sequences.

[158] Stringent conditions are known to those skilled in the art and can be found in Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Preferably, the conditions are such that sequences at least about 65%, 70%, 75%, 85%, 90%, 95%, 98%, or 99% homologous to each other typically remain hybridized to each other. A non limiting example of stringent hybridization conditions are hybridization in a high salt buffer comprising 6X SSC, 50 mM Tris HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2X SSC, 0.01% BSA at 50°C.

Probe Pair Selection

[159] Genotyping of individuals based on the relative copy number of particular

genomic regions can be accomplished using a collection of probe pairs specifically designed as described below.

[160] First, a list of genomic regions is obtained with the publically available reference genome build number, chromosome, start, and end coordinates. From this list, a custom track file is generated to be used for creation of a custom user track that can be viewed within a browser, for example, the UCSC genome browser, over the Internet.

[161] After loading the track file into the genome browser, unmasked raw DNA sequences are downloaded using the genome table browser. This is generally downloaded as a multi-FASTA file containing all the regions sequences together, but sometimes it is downloaded as a single sequence FASTA file. The multi-FASTA file containing the region sequences is manipulated to strip extraneous characters from the header of each FASTA entry, leaving only necessary information such as region name, chromosome, start, and end positions.

[162] Then the multi-FASTA file of region sequences is split into separate FASTA files, one file for each region. Each region file is then passed to a computer program that creates *in silico* restriction fragments of various sizes, depending on the location of restriction enzyme recognition sites in the sequence. The size of the resulting DNA fragments will vary from about 0.1 kb to about 10 kb, with an approximate average size of 0.5 kb.

[163] When all of the regions have been processed, the resulting fragment sequences are concatenated into one big file again for loading into a database of DNA fragments. A computer program is used to read the file of region coordinates and the file of DNA fragments in order to create a data structure in the database, linking the restriction fragment sequences to the regions. When all of the fragment sequences have been loaded into the database, the Gauntlet program generates probe pairs, each probe consisting of approximately 35-50 nucleotides, specifically designed to work in the nanoString nCounter® system. Many probe pairs are created per restriction fragment during the process, with the majority failing to meet rigorous specifications for the design of matched probe pairs.

[164] Those probes that pass the physical structure and matching criteria are loaded into the database to be further scored for fitness within the CNV assay. Every passed probe for the project is sent to a local licensed version of the BLAT program to

determine the location(s) with respect to the publically available reference genome (*e.g.* hg18 or hg19) so that we can unambiguously map the location(s) and determine their potential for cross hybridization to other regions of the genome.

[165] Fitness scoring is performed on the Reporter probe of each probe pair (35-50 nucleotides in length) based on: (i) the length of the restriction fragment the probe sequence is within that we know works best in the nCounter® system. This is based on a mathematical model of performance as determined by in-house experimentation. (ii) the location of the probe within the region to be analyzed. The location score is based on the number of probe pairs the customer has requested per region when they submitted them for the assay design. (iii) the results of the BLAT scoring, which gives us a measure of whether we can unambiguously map the Reporter probe within the same reference genome sequence.

[166] The unique algorithm that was developed for fitness scoring is described in detail below. This process allows for an expansion of the number of zones (bins) per region to facilitate selection of the requested number of probe pairs evenly distributed over the entire region using the probes that will work best in the nCounter® system according to our mathematical model of fitness.

[167] The following is the flow of our unique process of probe selection for the custom CNV assay: The user specifies the value (N) of the number of probes requested per region and the maximum value (MAX) of zones to try for an iterative processing of each region. Data is gathered from the database and arranged into data structures amenable to the process. Then, for every region, and for every iteration from N to MAX, a scoring matrix is created the exact length of the region using a natural mathematical function (absolute value of a sine wave) with the cycles specified relative to N, and increasing by the value (S) at the end of each iteration cycle.

[168] For every Reporter probe, a fitness score is calculated using the value of the sine wave, the value of the fragment length model, and an adjusted BLAT score. As the algorithm passes through the entire region length of sequence from end to end, each probe score is tested against the highest score seen so far in the zone. If the score for the probe at that position is higher than the one saved previously, the probe is replaced with the higher scoring probe. When the algorithm has reached the end of each zone, the highest scoring probe is added to the list of probes to be included in the assay.

[169] When the algorithm has reached the entire length of the region, the program tests if the number of probes requested (N) has been satisfied, and IF NOT, the value of N is changed to the next incremental value of N by adding S, and the process begins all over again. The cycles continue until the maximum value of zones (MAX) has been reached.

EXAMPLES

Example 1: Quantitation of Copy Number Variations.

[170] Multiple probes for designed for the X (9) and Y (9) chromosomes, as well as for chromosome 18 (6) and chromosome 21(3). Cells lines were provided with known chromosomal aberrations. Samples included cells with 1-5 copies of the X chromosome, normal males and females, and cells with trisomy at chromosome 21 and 18.

[171] Genomic DNA from the samples was digested with AluI (1hr @ 100ng/ μ l). 100ng of genomic DNA was used per assay. The genomic DNA was denatured prior to hybridization (5 min @ 95°C, snap cool 2 min). All experiments were performed in triplicate.

[172] For samples with cells with 1-5 copies of the X chromosome, the samples were normalized to probes on chromosome 18 (*see* Figure 1). For trisomy detection, normalization was done to the Y chromosome in the male samples (*see* Figure 2).

[173] The assay for multiple X chromosomes was repeated. Multi-X cell line genomic DNA purchased from Coriell cell repository. 1 μ g of each sample was digested with 10U of AluI enzyme in a 50 μ l digest at 37°C for 2 hours. The digested DNA was heat denatured at 95°C for 5 minutes and snap cooled on ice.

[174] 100 ng each digested/denatured sample was hybridized with the codeset CNV2 under standard nCounter® conditions for 16 hours. In addition to probes to other chromosomes, the CNV2 codeset contains 235 probes with 3 probes designed to bind to chromosome X. Standard conditions for the nCounter® assay are: 30 μ l hybridization in 5X SSPE/0.1% Tween 20, 25 pM reporter probe, 100 pM capture probe, 100 ng genomic DNA, 65°C, with a heated lid for 16 hours. Raw counts were normalized to the average of 66 probes to invariant genomic regions, to correct for genome-equivalents input into each assay. Normalized counts were averaged for each sample triplicate. Average counts for each probe are then divided by the corresponding count for the reference sample (NA10851, Coriell Cell Repository) to generate a copy number estimate.

[175] Copy number estimate is then averaged for the 3 probes to chromosome X. The graph shows the average copy number estimate and standard deviation for 3 probes to chromosome X (see Figure 3). Figures 1-3 show proof of concept that nanoreporters as described above, can be used to ascertain genomic copy number.

Example 2: Precision Counting of Gene Copies in Normal and Cancerous Colon and Breast Tissues.

[176] Hybridizations were performed in triplicate with normal and tumorous colon and breast tissues, with GPCR and Kinase panels (24 total hybridizations) according to the nCounter® probe pair methods described above. As shown in Figure 4, the genes were binned based on expression level, and the average %CV (coefficient of variance, standard deviation and mean) was calculated for all the genes detected in each bin. The total number of measurements (n) is indicated. Even for the 173 measurements of genes expressed at very low levels, the %CV averaged less than 15%. Likewise, small fractional fold changes can be detected according to these methods as shown in Figure 5. This demonstrates the precision of the nCounter® system in the counting of gene copies.

Example 3: Precision Counting of Autosomal Mutations.

[177] 78 different autosomal loci, consisting of 25 HapMapped CNV regions and other regions of interest, together with 23 invariant regions (one per chromosome), were analyzed with a single CodeSet according to the nCounter® method described above. It is easy to identify the loci that vary in copy number.

[178] Samples were, from top to bottom, NA07019, NA12877, NA10487. All the HapMap overlapping regions are 2X in these individuals. NA12877 was male; notice the single X dose in region with index 102.

Example 4: Probe Pair Selection.

[179] *Sequence Preparation:*

[180] A list of genomic regions was obtained. The list could be produced from many sources. For example, the list came, in some instances, from a commercial source and in others from scrutiny of genomic regions known to be involved in a particular disease of interest through a scientific literature search. The list of regions contained specific data concerning the publically available human reference genome that was used to identify the region, including the build identifier, chromosome number, start, and end coordinates.

[181] From the list of regions, a custom track file was generated to be used for creation of a custom user track that can be viewed, for example, within the UCSC genome browser over the Internet. After loading the track file into the genome browser, unmasked raw DNA sequences were downloaded using the genome table browser. This file was generally downloaded as a multi-FASTA file containing all the regions sequences concatenated together, but sometimes it was downloaded as a single sequence FASTA file if only one region is collected.

[182] The multi-FASTA file containing the specific DNA sequences from the regions is manipulated to strip extraneous characters from the header of each FASTA entry, leaving only necessary information such as region name, chromosome, start, and end positions. This can be accomplished using the custom Perl program `replace.pl`.

[183] The multi-FASTA file of region sequences were then split into separate files, one file for each region using the custom Perl program `splitfa.pl`. Each file was named using the sequence name found in the header of the FASTA entry in the multi-FASTA file.

[184] Each FASTA sequence file was then passed to the custom Perl program `fragment.pl` within a Linux bash shell script. The `fragment.pl` program created *in silico* restriction fragments of various sizes, depending on the location of restriction enzyme recognition sites in the sequence. The size of the resulting DNA fragments varied from about 0.1 kb to about 10 kb, with an approximate average size of 0.5 kb. Parameters set within `fragment.pl` allowed for the exclusion of fragments smaller or larger than the desired length.

[185] When all of the sequence files had been processed, the resulting sequence fragments were concatenated into one larger file for loading into a database of DNA fragments by the custom Perl program `milk.pl`. This program connected to a local MySQL CNV database, to create the appropriate project within the database, and linked the data to the specific organism and genome build. It then proceeded to load the DNA sequence fragments into the database for the design of probes. The `milk.pl` program also read a file of region coordinates in order to create the correct data structure in the database, linking the restriction fragment sequences to the regions.

[186] *Probe Design:*

[187] When all of the fragment sequences had been loaded into the database, the custom Perl program `CNV_start_pipeline.pl` ran multiple instances of the custom Perl

program gauntlet.pl, that generated probe pairs specifically designed to work in the nanoString nCounter® system. Each specific probe consisted of approximately 35-50 nucleotides, with probe pairs being matched for T_m. Many probe pairs were created for each restriction fragment during the process, with the majority failing to meet rigorous specifications for the design of matched probe pairs. Those probes that pass the physical structure and matching criteria were loaded into the CNV database to be scored for fitness within the CNV assay.

[188] *BLAT Scoring:*

[189] BLAT scoring was performed on each probe pair by concatenating the reporter probe sequence and the ghost probe sequence (each approximately 35-50 nucleotides in length). The combined reporter-ghost probe sequence was sent to a local licensed version of the BLAT program to determine the location(s) with respect to the publically available reference genome (*e.g.* hg18 or hg19). This was done to unambiguously map the probes against the reference genome and determine the potential for cross-hybridization to other regions of the genome. The output of the BLAT program for each probe pair was stored in the CNV database for subsequent scoring.

[190] The BLAT score for each probe pair within a project was accomplished by running the custom Perl program CNV_BLAT_score.pl, that created a score in the arbitrary range of 0-100 based on the number of “hits” within a specified combination of “percent identity” (PID) and “alignment length” (AL), parameters set within the program, the location of the “hit” on the combined reporter-ghost probe sequence, and the expected number of “hits” for a particular region in the genome. Note that “hits” within the reporter probe portion of the combined sequence are weighted as more severe than those on the ghost probe portion due to technical considerations of detecting the labeled “spot” tag on the reporter probe.

[191] *Probe Selection:*

[192] When BLAT scores had been determined and loaded into the CNV database, the selection of the “best” probes for each region was accomplished using the custom Perl program butter.pl. This program took into consideration the following parameters for picking the best probes for a given region: (i) the length of the restriction fragment the probe sequence is within that we know works best in the nCounter® system. This was based on a mathematical model of performance as determined by in-house

experimentation, (ii) the location of the probe within the region to be analyzed, and (iii) the BLAT score as determined above in "BLAT scoring".

[193] The custom Perl program butter.pl used a unique algorithm that was developed for fitness scoring of probe pairs. The algorithm included a process that allows for an expansion of the number of zones (bins) per region to facilitate selection of the requested number of probe pairs evenly distributed over the entire region using the probes that would work best in the nCounter® system according to our mathematical model of fitness. The location score was based on the number of probe pairs that had been requested per region when they submitted them for the assay design. For example, if the desired number of probes to a region was 1, then the best probe pair would be the one that (i) resides on the optimal size restriction fragment (high fragment score), (ii) is directly in the center (equal spacing from either end) of the defined region (high spacing score), and (iii) has the expected number of "hits" (high BLAT score).

[194] The following is the flow of our unique process of probe selection for the custom CNV assay:

[195] The user specified the value of the number of probes requested per region (N) and the maximum value of zones to try for an iterative processing of each region (MAX). Data was gathered from the database and arranged into data structures amenable to the process. For each region the following steps were performed.

[196] For each iteration from N to MAX, a scoring matrix was created the exact length (L) of the region (in nucleotides). Then, using a natural mathematical function (absolute value of a sine wave) with the cycles specified relative to N, a value ranging from 0 to 1 was assigned to every position of the matrix. For example, if the length of the region was 1kb (1000 nucleotides) and the number of desired probes was 1, then $L=1000$ and $N=1$, then the value in the matrix position $1000/2 = 500$ is equal to 1.0 (the upper limit of the absolute value of a sine function). Therefore, the best position score possible for a probe pair would be at position 500. If a probe pair were located at position 500 with all other parameters being equal amongst the other probe pairs available for the zone (ideal fragment length and ideal BLAT score), the 1 best probe pair selected would be the one located right in the center of the region, which is what we want.

[197] For each zone (N), the following steps were performed. For each probe pair, a fitness score was calculated using the value of the fragment length model, the value of

the sine wave at the position of the probe pair, and the BLAT score. As the algorithm passed through the entire region length of sequence from end to end, each probe pair score was tested against the highest score seen so far in the zone (there are N zones). If the score for the probe pair at that position was higher than the one saved previously, the probe pair was replaced with the higher scoring one. When the algorithm reached the end of each zone, the highest scoring probe pair is added to the list of those to be included in the assay. Then the next probe pair was scored.

[198] For the next zone, when the algorithm reached the entire length of the region, the program tests if the number of probes requested (N) has been satisfied, and IF NOT, the value of N is changed to the next incremental value of N by adding S, and the process begins all over again. The cycles continue until the maximum value of zones (MAX) has been reached. In the next iteration ($N = N + S$ unless $N = \text{MAX}$). The value (N) is increased by (S) at the end of every iteration, until MAX is reached. This was then performed for each successive region.

Example 5. Gene Copy Number Assay Protocol.

[199] *AluI Restriction Digestion*

[200] A restriction enzyme fragmentation was set up. 200-600 ng of DNA in in 7 μL of sample was placed a 0.2 mL-0.5 mL PCR tube. Genomic DNA was generally at a concentration of at least 29 ng/ μL prior to addition to the fragmentation reaction.

[201] 7 μL containing DNA 600 ng was dissolved in RNase free water, Tris pH 8.0 or similar. To this was added 1 μL 10X AluI Fragmentation Buffer; 1 μL 10X CNV DNA Prep Control; 1 μL AluI Fragmentation Enzyme; up to 10 μL of total volume.

[202] The digestion was incubated at at 37° C for at least 2 hours in a heat block or thermalcycler with heated lid turned on. Samples generally were denatured upon completion of restriction digestion.

[203] The final hybridization reaction contained the following components: 10 μL nanoreporters, 10 μL hybridization buffer, a total volume of 5 μL of sample DNA, and 5 μL Capture ProbeSet.

[204] *Hybridization Reaction*

[205] Aliquots of both reporter probes and capture probes were removed from the freezer and thawed on benchtop at room temperature. The tubes were inverted or flicked several times to mix well and spin down reagent. A master mix was created containing

130 μ L of the reporter probes and 130 μ L of hybridization buffer. Hybridization buffer was added directly to nanoreporter tube. Capture probes were not added to the master mix. The master mix was inverted to mix and spun down.

[206] 12 tubes were labeled. 20 μ L of mastermix was added to each of the 12 tubes.

[207] *Thermocycler*

[208] AluI digestion tubes were denatured at 95°C for 5 minutes. The thermocycler was pre-heated to 65°C with heated lid turned on and “forever” time setting. The AluI digestion tubes were then immediately placed on ice for 2 minutes to minimize DNA renaturation and then briefly spun down.

[209] 5 μ L AluI-digested DNA sample was added to the hybridization tube. The remainder of the AluI-digested sample was generally stored at –20° C for future use.

[210] 5 μ L of capture probe was added to each tube immediately before placing at 65°C. Tubes were capped and mixed the reagents by flicking with your finger to ensure complete mixing. Tubes were briefly spin down at < 1000 g and immediately placed in the 65°C thermocycler. The hybridization assays were incubated for at least 16 hours and were left at 65°C until ready for processing. Maximum hybridization time did not exceed 30 hours.

Example 6. Optimal Size Selection of Restriction Fragments.

[211] During the probe design process, target regions were analyzed for AluI sites (based on the human reference genome sequence) and the sizes of AluI fragments were predicted. One nCounter® CNV probe was designed per AluI fragment. Figure 7 shows the relationship between AluI fragment length in base pairs (x-axis) and the counts obtained via hybridization in the nCounter® system (y-axis). Based on this data, the probe design algorithm selected the optimal size fragments per genomic region.

Example 7. Determination of Copy Number Variations (CNV) using nCounter® copy number assay.

[212] The nCounter® copy number assay was used to measure the copy number of 20 genomic regions in 50 human genomic DNA samples containing known copy number variations (CNVs). Fifty human genomic DNAs were purchased from Coriell Cell Repository. The presence of CNVs in these samples was previously determined by genome-wide analysis using microarray methodology and the data is publically available at the public website Database of Genomic Variants (<http://projects.tcag.ca/variation/>).

[213] Six hundred nanograms of genomic DNA were processed via the nCounter® Copy number assay manual. Briefly, 600ng of DNA was digested with restriction enzyme Alu1, sample was denatured at 95° C for 5 minutes and added directly to an nCounter® hybridization reaction. The nCounter® CodeSet used in this experiment contained 60 probes complementary to 20 genomic regions that were selected based on known variations across these samples as well as control probes. Hybridization occurred in solution for 16 hours at 65° C. Hybridized samples were purified and imaged using nCounter® PrepStation and Digital Analyzer.

[214] Raw data was normalized using the average signal for 10 invariant control probes. This step removes slight variations in DNA input amounts. Copy number calls were calculated by dividing the normalized counts of the test samples by the normalized counts in the reference and multiplying by 2 for autosomal chromosomes (1-22). The reference sample was NA10851 purchased from Coriell. The graph in Figure 8 shows a comparison of the copy number value (Y-axis) for a region of chromosome 7 between the nCounter® assay (light gray bars) and the public data (dark gray bars, determined by microarray). The nCounter® copy number calls were determined by averaging the copy number calls for the 3 probes designed to this region. There was 100% concordance in copy number calls in this region, across the 50 samples. Several examples of samples with heterozygous (1 copy) and homozygous deletions (zero copies) in this region are shown.

Example 8. Karyotype Panel.

[215] The Human Karyotype Panel used below consists of 338 probe pairs designed to target known invariant regions for molecular karyotyping of the human genome. The panel has 8 probe pairs distributed across each arm of the 22 autosomes, excluding the p-arms of acrocentric chromosomes, for a total of 313 autosomal probe pairs. In addition, there are 16 X-specific and 9 Y-specific probe pairs that may be used for gender determination. The Human Karyotype Panel is provided with 10 invariant control probe pairs designed to well-characterized invariant regions on separate chromosomes to be used for normalization of digital count data, eliminating sample-to-sample variation.

[216] Figure 9 shows copy number calls (y axis) for all 313 autosomal probe pairs (x axis) within the Human Karyotype Panel. One hundred and two (102) "normal" human HapMap DNA samples purchased from the Coriell Institute for Medical Research were

tested using the standard CNV assay protocol, described above. Normalized digital counts were compared to the male HapMap sample NA10851 to determine relative copy number calls. For each HapMap sample, the copy number call value is shown as a black cross. Lines marked as "1" represent a z-score of 1 ($P < 0.32$) and lines marked as "2" represent a z-score of 2 ($P < 0.05$) assuming a Gaussian distribution about the expected copy number of 2 and standard deviation of 0.2. The standard deviation of copy number calls for each probe pair is shown at the bottom of the graph, overlaying the y axis for both copy number calls and standard deviation. Probe pairs are sorted by ascending standard deviation. A cut-off value of 0.2 for standard deviation is demarcated by a gray dotted line.

OTHER EMBODIMENTS

[217] While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. Genbank and NCBI submissions indicated by accession number cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference. While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of detecting a DNA sequence in a genome comprising:
 - (a) providing a first sample containing genomic DNA;
 - (b) fragmenting the genomic DNA;
 - (c) denaturing the genomic DNA;
 - (d) providing a first nanoreporter comprising a first probe comprising
 - (i) a first label attachment region to which are attached one or more label monomers that emit light constituting a first signal;
 - (ii) a second label attachment region, which is non-over-lapping with the first label attachment region, to which are attached one or more label monomers that emit light constituting a second signal; and
 - (iii) a first target-specific sequence attached to the first probe, wherein the target-specific sequence specifically hybridizes to the genomic DNA sequence to be detected;
 - (e) contacting the first probe with the fragmented genomic DNA wherein the contact is made under conditions sufficient for hybridization of the first target specific sequence to a fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected
 - (f) stretching the first probe hybridized to the at least one fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected using a flow-stretch, receding meniscus, or electro-stretch technique, thereby spatially separating said label monomers, and
 - (g) measuring a signal from the first probe, wherein said signal uniquely identifies the at least one fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected.
2. The method of claim 1, wherein the first nanoreporter further comprises a second probe comprising
 - (i) a second target-specific sequence; and

(ii) an affinity tag;

wherein the first probe and the second probe specifically hybridize to the same fragment of the fragmented genomic DNA at different sites on the fragment.

3. The method of claim 1, wherein the first probe further comprises an affinity tag.
4. The method of claim 1, wherein the genomic DNA is mammalian genomic DNA.
5. The method of claim 4, wherein the mammal is a human.
6. The method of claim 1, wherein the genomic DNA sample is unamplified.
7. The method of claim 1, wherein step (e) is performed in solution.
8. The method of claim 1, wherein the fragmentation is performed by restriction enzyme digestion.
9. The method of claim 8, wherein the restriction enzyme is AluI.
10. The method of claim 8, wherein the restriction enzyme is BfaI.
11. The method of claim 1, wherein the fragmentation is performed chemically, by mechanical shearing or sonication.
12. A method of determining the copy number of the DNA sequence to be detected of claim 1 further comprising
 - (a) providing a reference sample comprising fragmented genomic DNA wherein the copy number of the genomic sequence the first target specific sequence specifically hybridizes to in the reference sample is known;
 - (b) contacting the first probe with the reference sample wherein the contact is made under conditions sufficient for hybridization of the first target specific sequence to a fragment of the fragmented genomic DNA comprising the genomic DNA sequence to

be detected;

(c) stretching the first probe hybridized to the at least one fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected using a flow-stretch, receding meniscus, or electro-stretch technique, thereby spatially separating said label monomers;

(d) measuring a signal from the first probe, wherein said signal uniquely identifies the at least one fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected; and

(e) comparing the signal from the first sample to the signal from the reference sample, wherein the copy number of the first sample is determined by correlating the signal from the first sample with the signal from the reference sample.

13. The method of claim 12, wherein the reference sample is a synthetic nucleic acid sample.

14. The method of claim 12, wherein the reference sample is a biological genomic DNA sample.

15. A method of normalizing the signal generated in claim 12 further comprising

(a) providing at least a second nanoreporter comprising a third probe comprising

(i) a third label attachment region to which are attached one or more label monomers that emit light constituting a third signal;

(ii) a fourth label attachment region, which is non-over-lapping with the third label attachment region, to which are attached one or more label monomers that emit light constituting a fourth signal; and

(iii) a third target-specific sequence attached to the third probe, wherein the target-specific sequence specifically hybridizes to a first DNA fragment from a copy number invariant region of the genome;

(b) contacting the third probe with the fragmented genomic DNA from the first sample and the reference sample wherein the contact is made under conditions sufficient for hybridization of the third target specific sequence to the first DNA fragment from a

copy number invariant region of the genome;

(c) stretching the third probe hybridized to the first DNA fragment from a copy number invariant region of the genome using a flow-stretch, receding meniscus, or electro-stretch technique, thereby spatially separating said label monomers;

(d) measuring a signal from the third probe, wherein said signal uniquely identifies the first DNA fragment from a copy number invariant region of the genome; and

(e) comparing the signal from the the second nanoreporter contacted with the first sample and the second nanoreporter contacted with the reference sample, wherein the number of multiples of the quantity of signal from the second nanoreporter contacted with the first sample compared to the quantity of signal from the second nanoreporter contacted with the reference sample normalizes the signal from the first nanoreporter contacted with the first sample.

16. The method of claim 15, wherein the second nanoreporter further comprises a fourth probe comprising

- (i) a fourth target-specific sequence; and
- (ii) an affinity tag;

wherein the third probe and the fourth probe specifically hybridize to the same first DNA fragment from a copy number invariant region of the genome; at different sites on the fragment.

17. The method of claim 15, wherein the first DNA fragment from a copy number invariant region of the genome comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-66.

18. The method of claim 15, wherein the first DNA fragment from a copy number invariant region of the genome comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 2, 5, 7, 12, 13, 17, 19, 24, 25, 28, 32, 36, 38, 40, 44, 46, 50, 52, 56, 58, 62 and 66.

19. The method of claim 15, wherein the first DNA fragment from a copy number

invariant region of the genome e comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 2, 5, 13, 19, 28, 46, 50, 56, 58 and 66.

20. The method of claim 15, wherein the third probe further comprises an affinity tag.

21. The method of claim 15, wherein the genomic DNA is mammalian genomic DNA.

22. The method of claim 21, wherein the mammal is a human.

23. The method of claim 1, wherein the signal generated from the first nanoreporter hybridized to the at least one fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected comprises a mixture of two or more different label monomers.

24. The method of claim 15, wherein the signal generated from the second nanoreporter hybridized to the first DNA fragment from a copy number invariant region of the genome comprises a mixture of two or more different label monomers.

25. The method of claim 1, wherein said labels are fluorescent.

26. The method of claim 15, wherein said labels are fluorescent.

27. A method of detecting a DNA sequence in a genome comprising:

- (a) providing a first sample containing genomic DNA;
- (b) fragmenting the genomic DNA;
- (c) denaturing the genomic DNA;
- (d) providing a first nanoreporter that specifically hybridizes to the genomic DNA sequence to be detected;
- (e) contacting the first nanoreporter with the fragmented genomic DNA wherein the contact is made under conditions sufficient for hybridization of the first nanoreporter

to the genomic DNA sequence to be detected;

(f) stretching the first nanoreporter hybridized to the at least one fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected using a flow-stretch, receding meniscus, or electro-stretch technique; and

(g) measuring a signal from the first nanoreporter, wherein said signal uniquely identifies the at least one fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected.

28. A method of determining the copy number of the DNA sequence to be detected of claim 27 further comprising

(a) providing a reference sample comprising fragmented genomic DNA wherein the copy number of the genomic sequence the first nanoreporter specifically hybridizes to in the reference sample is known;

(b) contacting the first nanoreporter with the reference sample wherein the contact is made under conditions sufficient for hybridization of the first nanoreporter to a fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected;

(c) stretching the first nanoreporter hybridized to the at least one fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected using a flow-stretch, receding meniscus, or electro-stretch technique,

(d) measuring a signal from the first nanoreporter, wherein said signal uniquely identifies the at least one fragment of the fragmented genomic DNA comprising the genomic DNA sequence to be detected; and

(e) comparing the signal from the first sample to the signal from the reference sample, wherein the copy number of the first sample is determined by correlating the signal from the first sample with the signal from the reference sample.

29. A method of normalizing the signal generated in claim 28 further comprising

(a) providing at least a second nanoreporter;

(b) contacting the second nanoreporter with the the fragmented genomic DNA from the first sample and the reference sample wherein the contact is made under conditions sufficient for hybridization of the second nanoreporter to a first DNA fragment

from a copy number invariant region of the genome;

(c) stretching the second nanoreporter hybridized to the first DNA fragment from a copy number invariant region of the genome using a flow-stretch, receding meniscus, or electro-stretch technique;

(d) measuring a signal from the second nanoreporter, wherein said signal uniquely identifies the first DNA fragment from a copy number invariant region of the genome; and

(e) comparing the signal from the the second nanoreporters contacted with the first sample and the second nanoreporter contacted with the reference sample, wherein the number of multiples of the quantity of signal from the second nanoreporter contacted with the first sample compared to the quantity of signal from the second nanoreporter contacted with the reference sample normalizes the signal from the first nanoreporter contacted with the first sample.

30. The method of claim 29, wherein the first DNA fragment from a copy number invariant region of the genome comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-66.

31. A method of detecting two or more DNA sequences in a genome comprising:

(a) providing a first sample containing genomic DNA;

(b) fragmenting the genomic DNA;

(c) denaturing the genomic DNA;

(d) providing a two or more nanoreporters that each specifically hybridize to a distinct genomic DNA sequence to be detected;

(e) contacting the two or more nanoreporters with the fragmented genomic DNA wherein the contact is made under conditions sufficient for hybridization of the two or more nanoreporters to the genomic DNA sequence to be detected;

(f) stretching the two or more nanoreporters hybridized to its corresponding distinct genomic DNA sequence using a flow-stretch, receding meniscus, or electro-stretch technique, and

(g) measuring a signal from the two or more nanoreporters, wherein said signal uniquely identifies each of the corresponding distinct genomic DNA sequences thereby

detecting two or more DNA sequences in a genome.

32. A method of determining the copy number of the DNA sequence to be detected of claim 31 further comprising

(a) providing a reference sample comprising fragmented genomic DNA wherein the copy number of the genomic sequence the first target specific sequence specifically hybridizes to in the reference sample is known;

(b) contacting the first nanoreporter with the reference sample wherein the contact is made under conditions sufficient for hybridization of the two or more nanoreporters each fragment of the fragmented genomic DNA comprising the genomic DNA sequences to be detected;

(c) stretching the two or more nanoreporters hybridized to each fragment of the fragmented genomic DNA comprising the genomic DNA sequences to be detected using a flow-stretch, receding meniscus, or electro-stretch technique,

(d) measuring signals from the two or more nanoreporters, wherein said signal uniquely identifies each of the fragments of the fragmented genomic DNA comprising the genomic DNA sequences to be detected;

(e) comparing the signal from the first sample to the signal from the reference sample, wherein the copy number of the first sample is determined by correlating the signal from the first sample with the signal from the reference sample.

33. A method of normalizing the signal generated in claim 32 further comprising

(a) providing at least one invariable sequence specific nanoreporter;

(b) contacting the at least one copy number invariant sequence specific nanoreporter with the fragmented genomic DNA from the first sample and the reference sample wherein the contact is made under conditions sufficient for hybridization of the at least one invariable sequence specific nanoreporter to a first DNA fragment from a copy number invariant region of the genome;

(c) stretching the second nanoreporter hybridized to the the first DNA fragment from a copy number invariant region of the genome using a flow-stretch, receding meniscus, or electro-stretch technique;

(d) measuring a signal from the second nanoreporter, wherein said signal

uniquely identifies the first DNA fragment from a copy number invariant region of the genome; and

(e) comparing the signal from the the second nanoreporters contacted with the first sample and the second nanoreporter contacted with the reference sample, wherein the number of multiples of the quantity of signal from the second nanoreporter contacted with the first sample compared to the quantity of signal from the second nanoreporter contacted with the reference sample normalizes the signal from the first nanoreporter contacted with the first sample.

34. The method of claim 33, wherein the first DNA fragment from a copy number invariant region of the genome comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-66.

35. A kit, comprising

- (a) a first nanoreporter comprising a first probe comprising
 - (i) a first label attachment region to which are attached one or more label monomers that emit light constituting a first signal;
 - (ii) a second label attachment region, which is non-over-lapping with the first label attachment region, to which are attached one or more label monomers that emit light constituting a second signal; and
 - (iii) a first target-specific sequence attached to the first probe, wherein the target-specific sequence specifically hybridizes to a target DNA sequence; and
- (b) a restriction enzyme.

36. A composition comprising an isolated nucleic acid molecule comprising at least 50 nucleotides of a sequence selected from the group consisting of SEQ ID NO: 1-66.

37. A method of selecting probe pairs for detection of a genomic sequence comprising:

- (a) providing the genomic sequence;
- (b) performing *in silico* restriction fragmentation of the genomic sequence;
- (c) generating *in silico* probe pairs for every position on the *in silico*

restriction fragments, wherein each member of each pair is 35-50 nucleotides in length, and wherein each member of each set of pairs is complementary to a contiguous sequence;

- (d) discarding sets of probe pairs wherein the melting temperatures of the probe pairs differ by more than 5° C;
 - (e) subjecting the remaining probe pairs to BLAT scoring; and
 - (f) discarding sets of probe pairs with the lowest 75% of BLAT scores;
- thereby selecting probe pairs for detection of a genomic sequence.

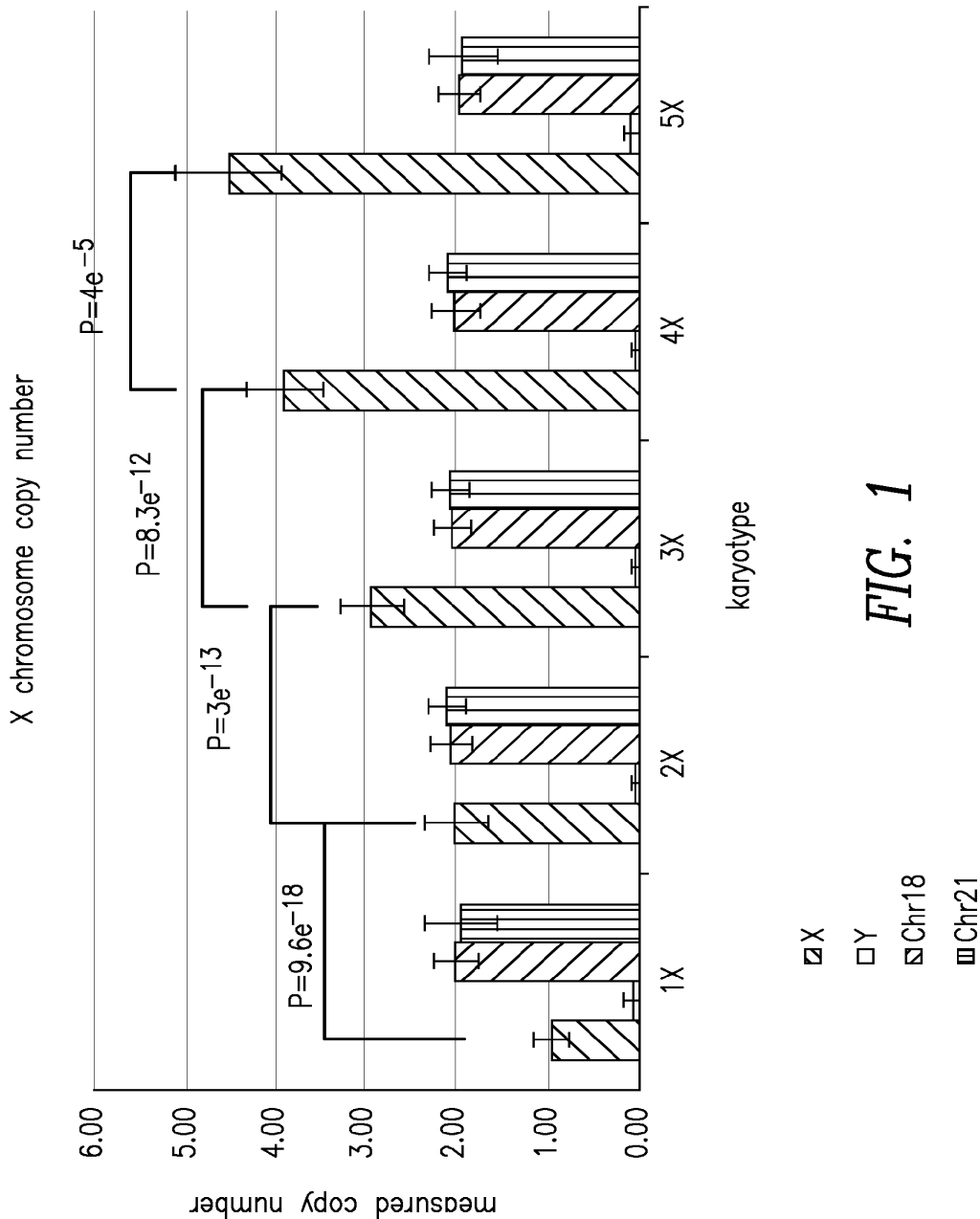


FIG. 1

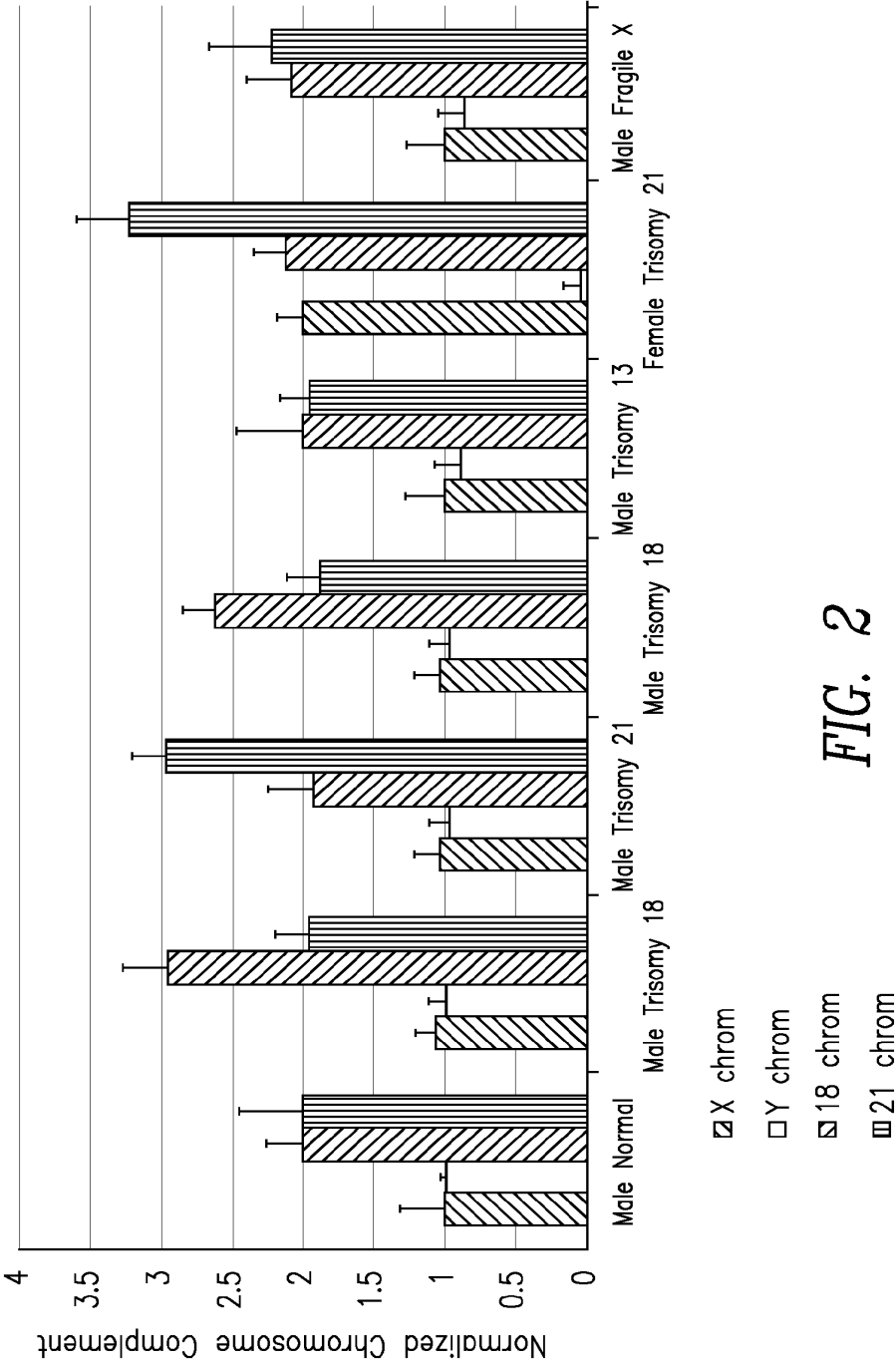


FIG. 2

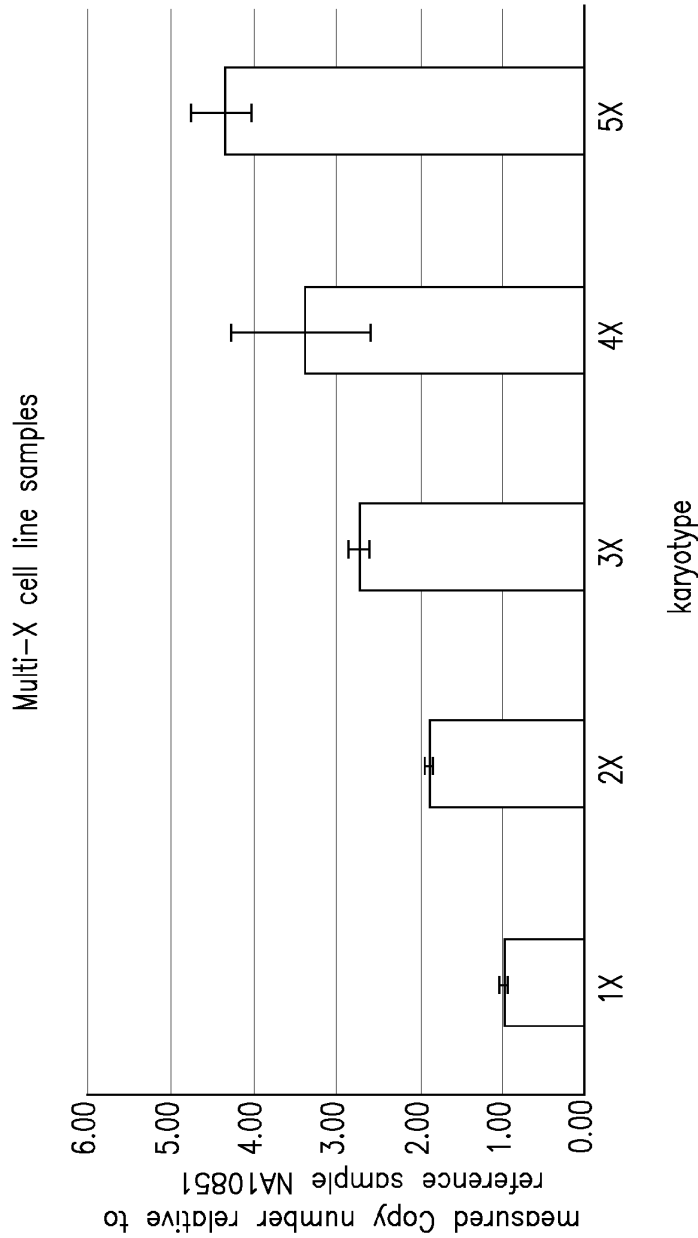


FIG. 3

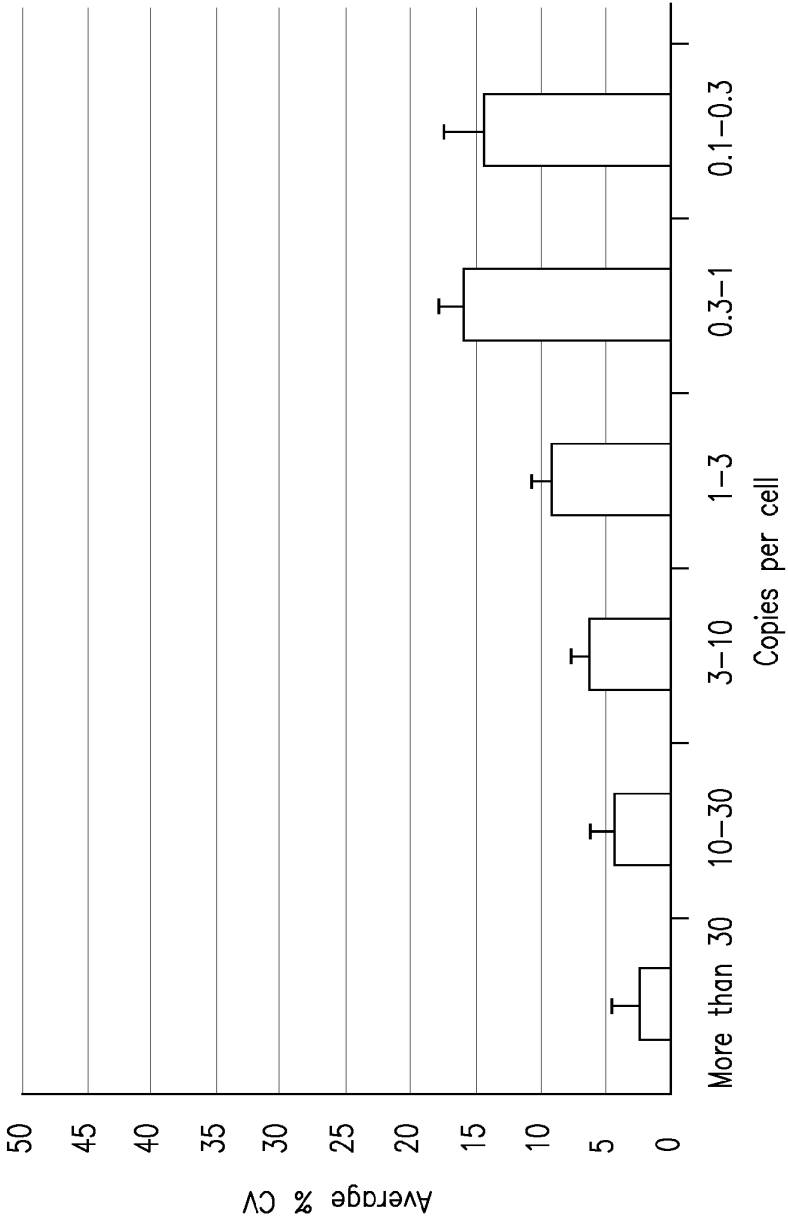


FIG. 4

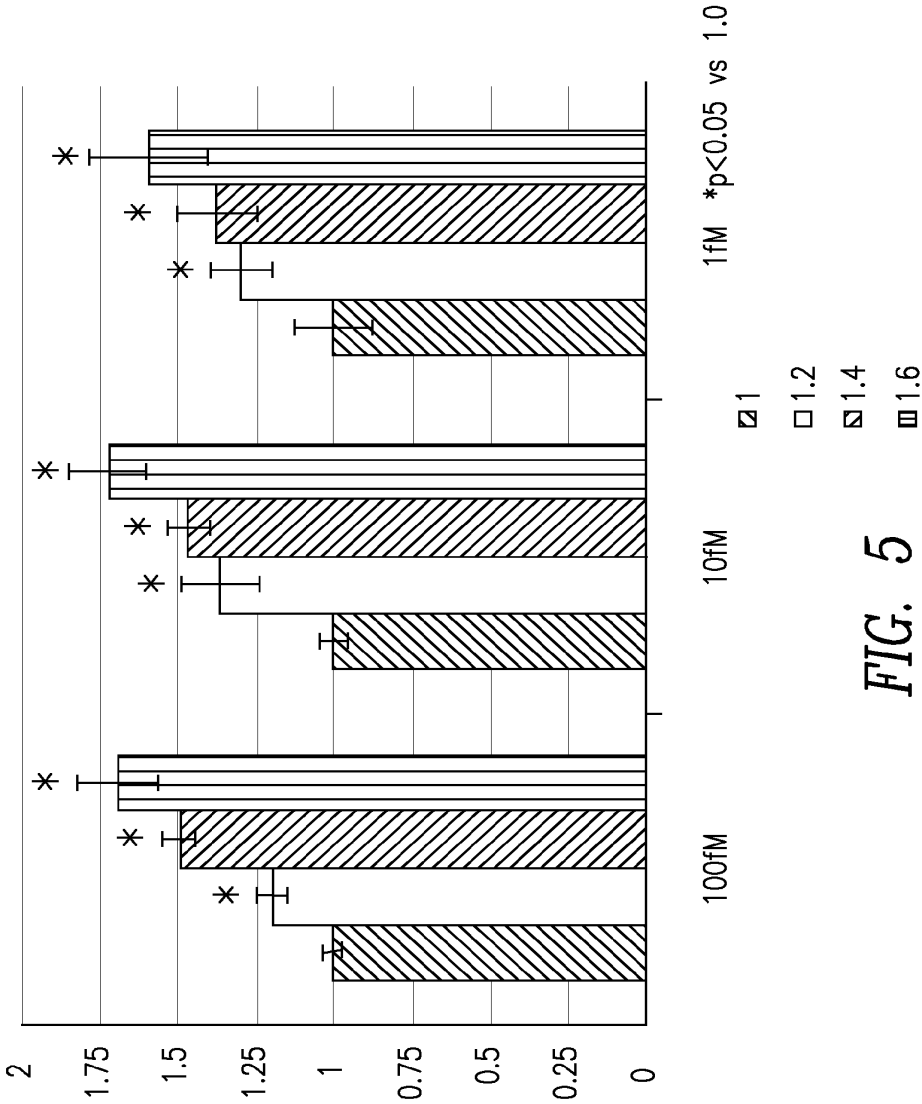


FIG. 5

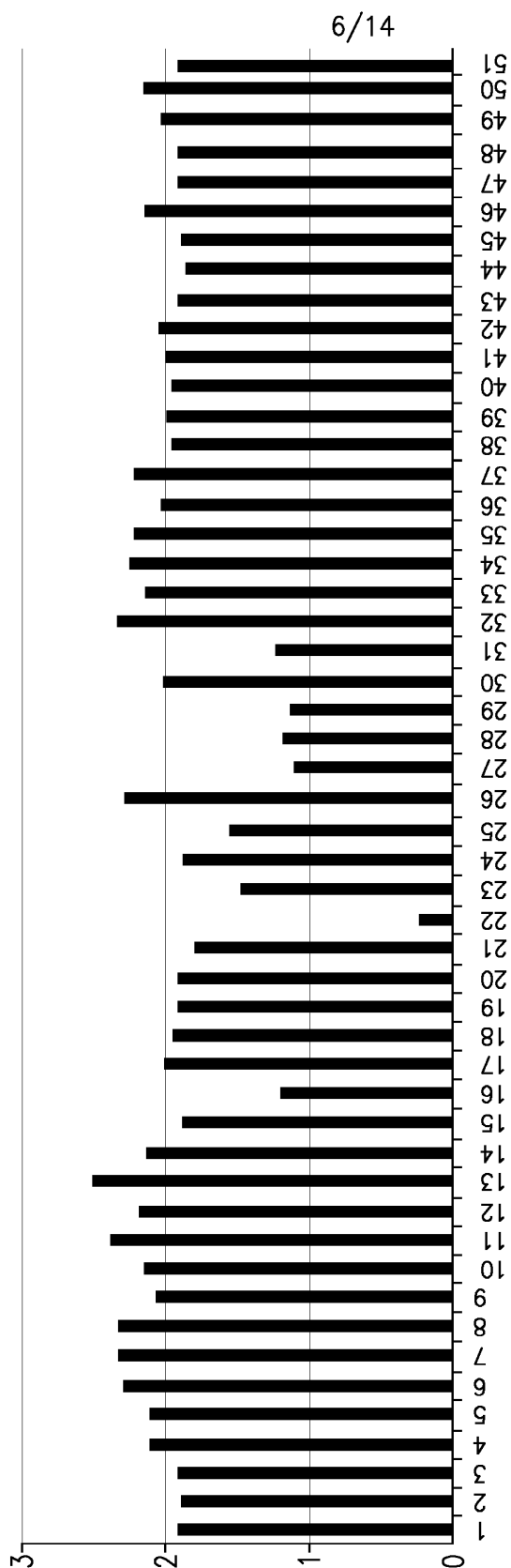


FIG. 6 1-1

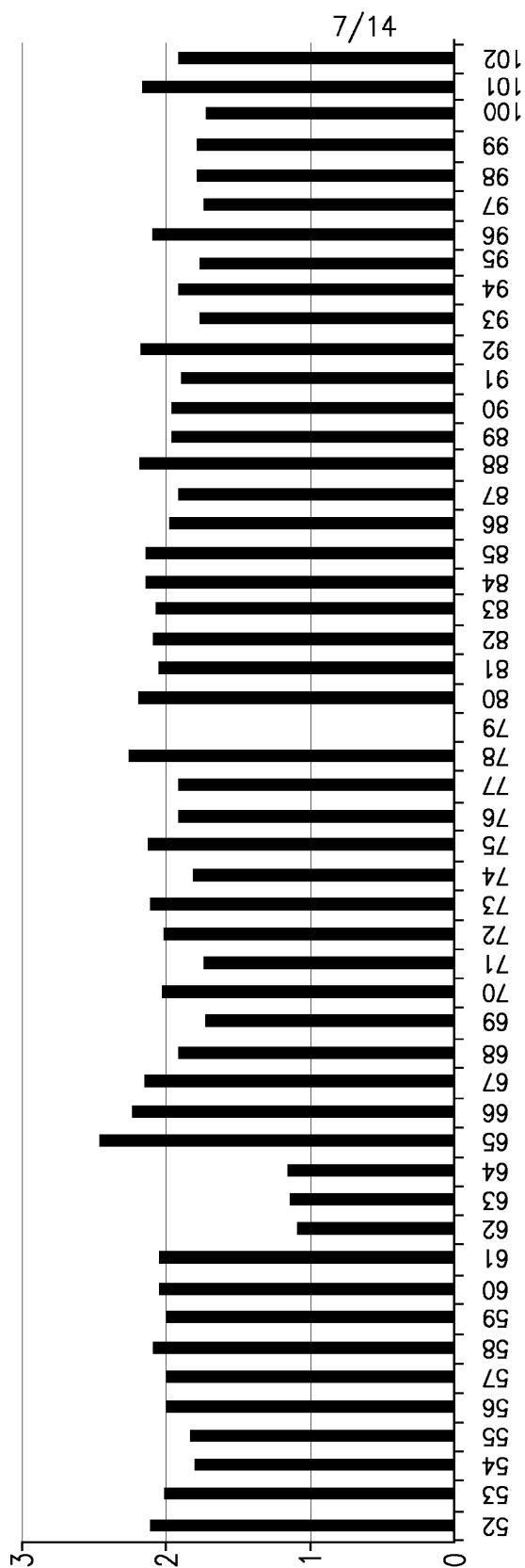


FIG. 6 1-2

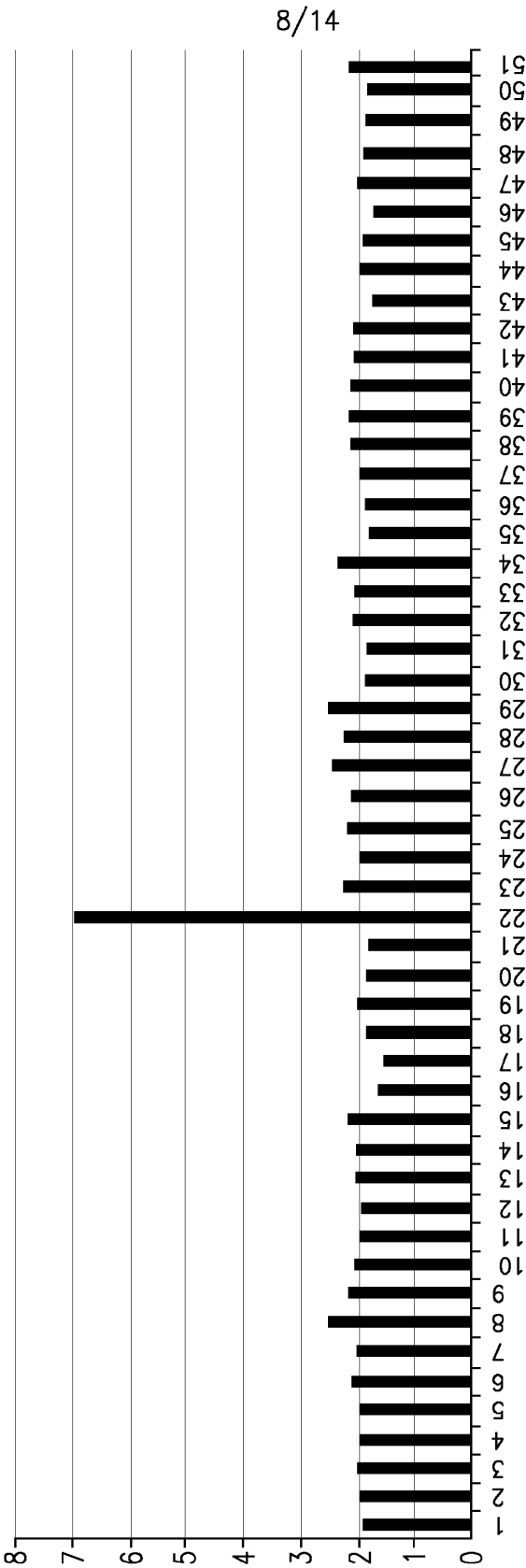


FIG. 6 2-1

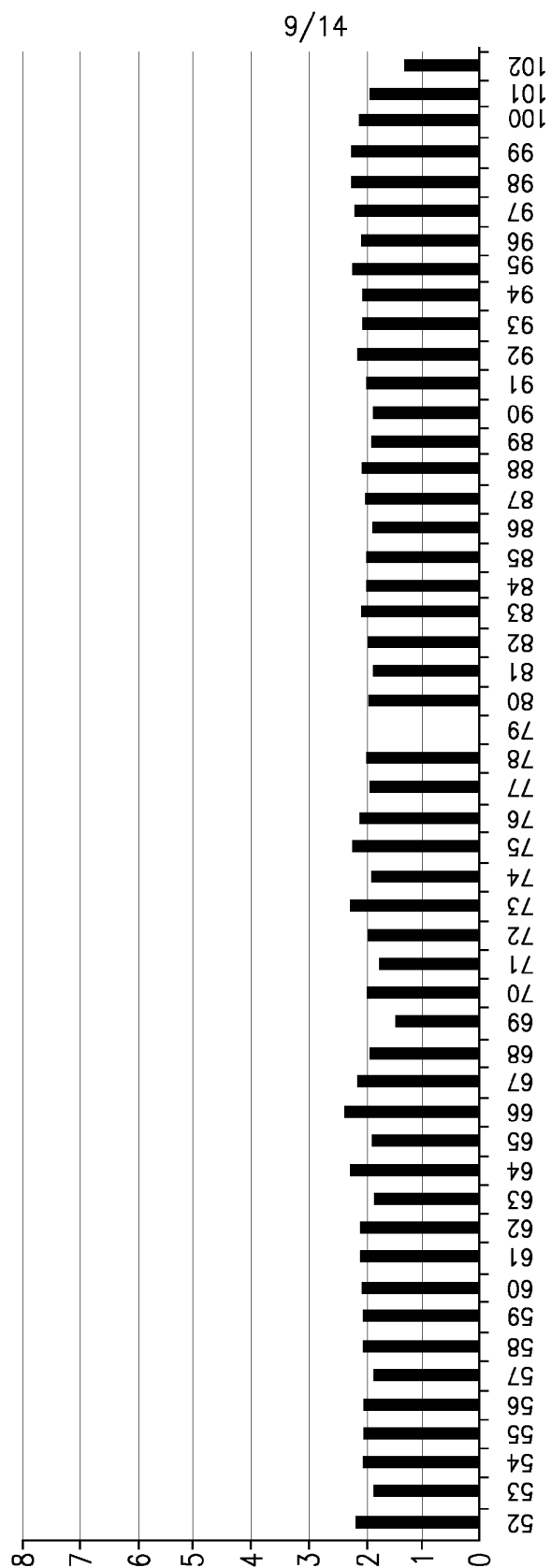


FIG. 6-2-2

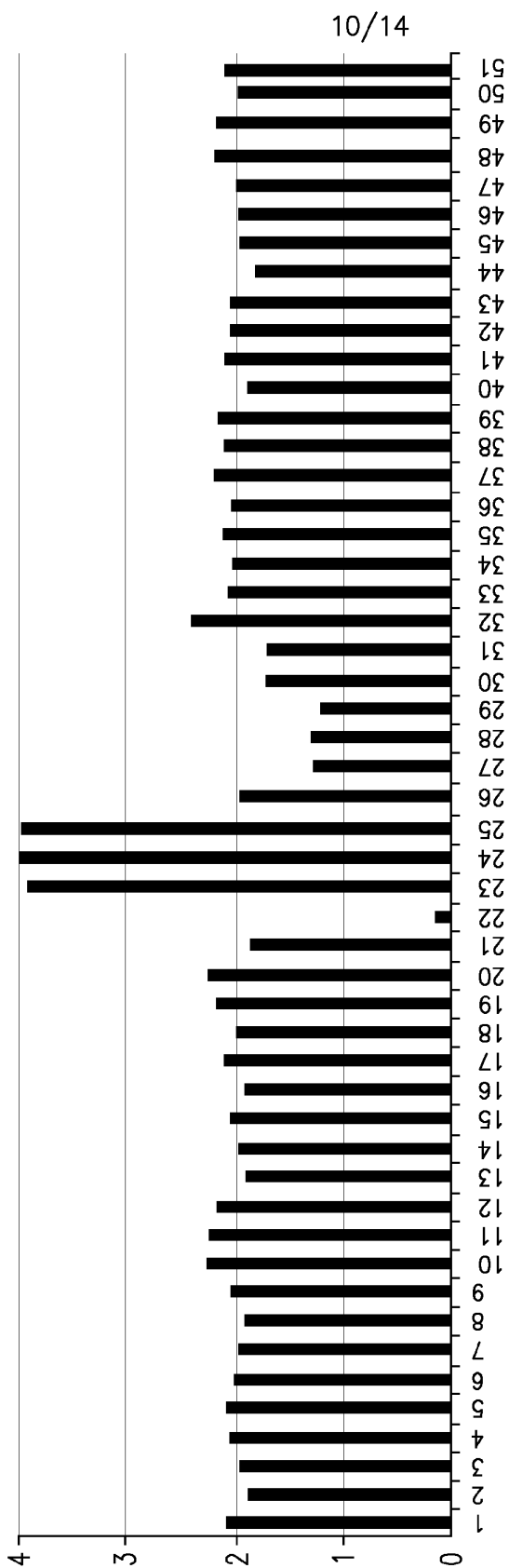


FIG. 6-3-1

SUBSTITUTE SHEET (RULE 26)

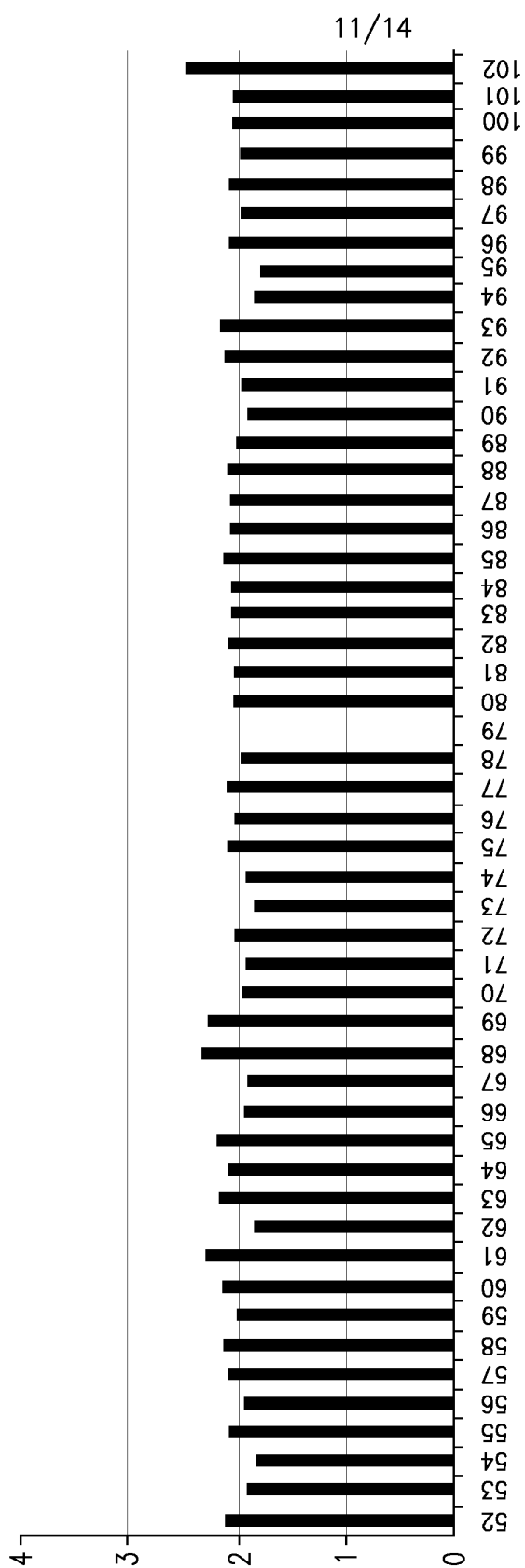
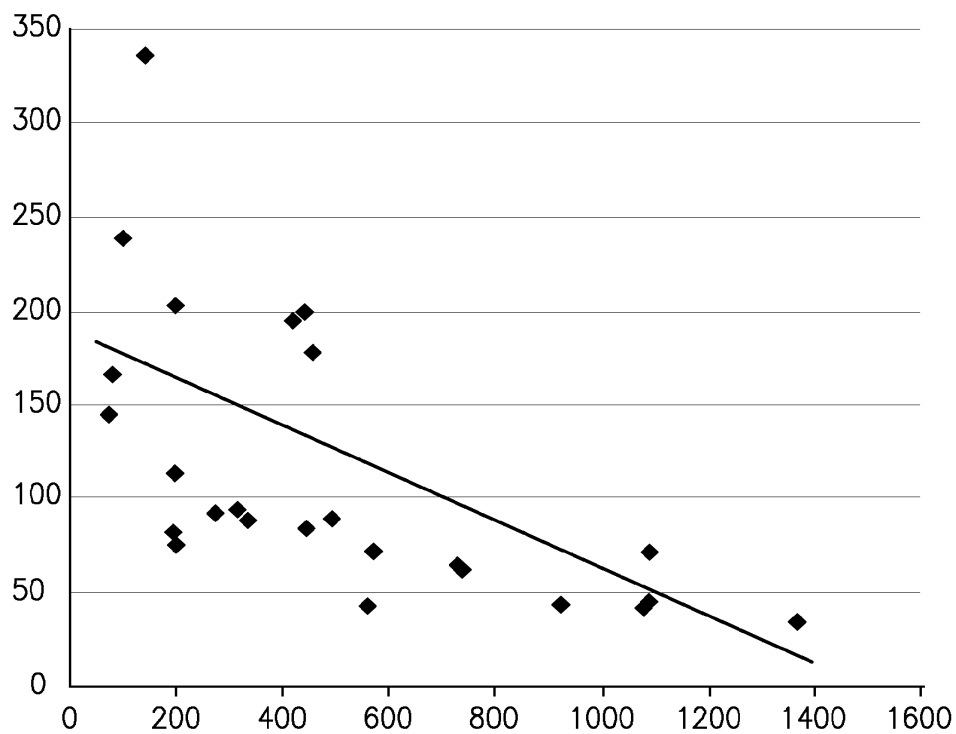


FIG. 6-3-2

12/14

*FIG. 7*

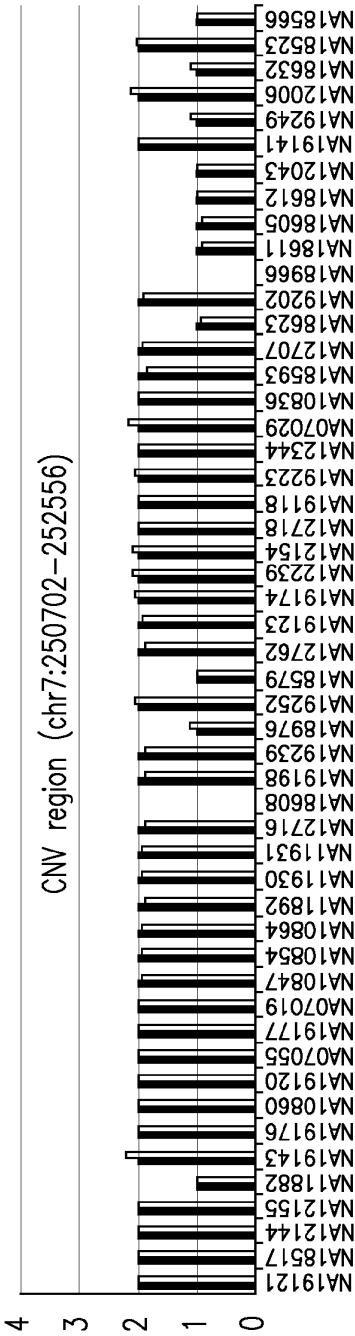
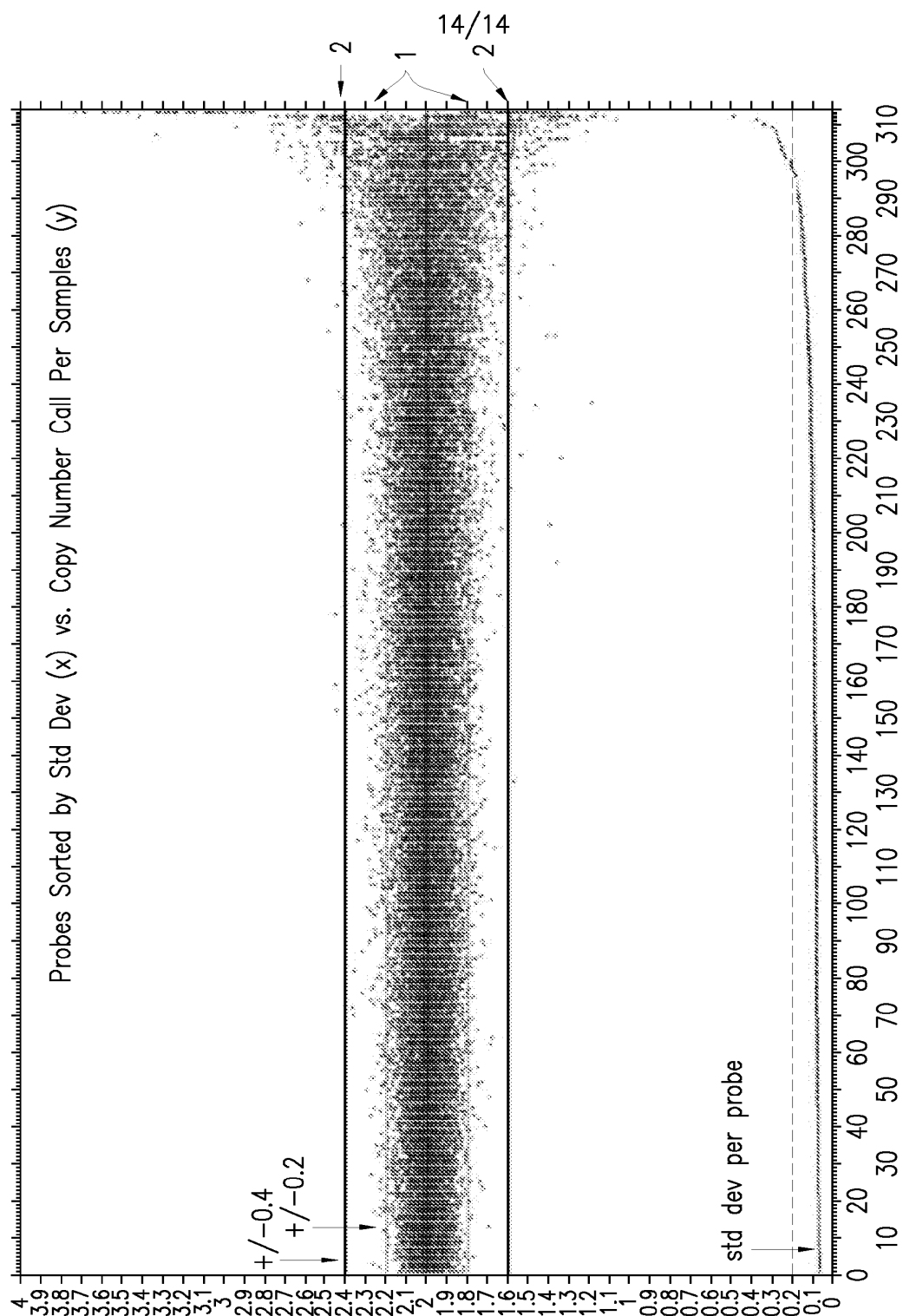


FIG. 8





(43) International Publication Date
22 September 2011 (22.09.2011)

PCT

(10) International Publication Number
WO 2011/116088 A3

(51) International Patent Classification:
C12Q 1/68 (2006.01) *C12N 15/11* (2006.01)

(21) International Application Number:
PCT/US2011/028657

(22) International Filing Date:
16 March 2011 (16.03.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/314,491 16 March 2010 (16.03.2010) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD,
SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG,
ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE DETECTION OF GENOMIC FEATURES

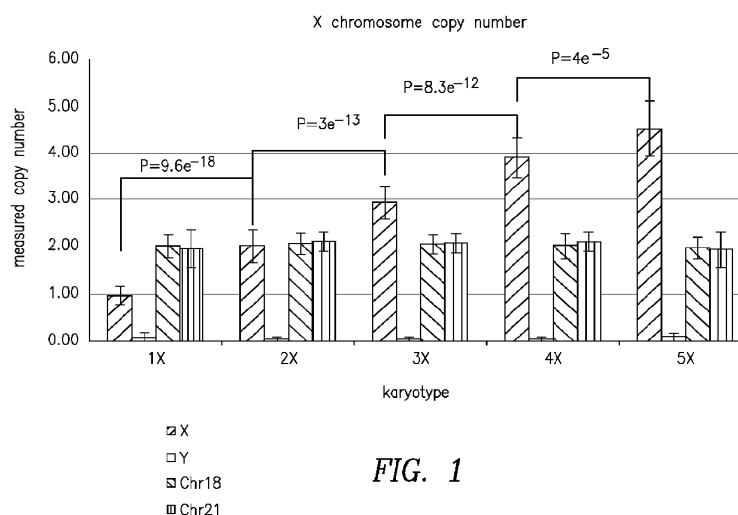


FIG. 1

(57) Abstract: The invention provides compositions and methods for the detection of gene copy number and/or chromosome copy number in a multiplexed reaction. The assays and kits described herein are applicable for the identification, diagnosing, and monitoring of disorders including, but not limited to cancer, developmental and degenerative disease, neurological disorders, and stem cell disorders.

WO 2011/116088 A3



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report:
2 February 2012

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/028657**A. CLASSIFICATION OF SUBJECT MATTER*****C12Q 1/68(2006.01)i, C12N 15/11(2006.01)i***

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12Q 1/68; C40B 40/06; G01N 33/53

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

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

cKOMPASS(KIPO internal), Pubmed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007-076129 A2 (NANOSTRING TECHNOLOGIES, INC.) 05 July 2007 See claims 1-7, 11; page 9, line 7-22, page 55, line 6-11.	1-14, 23, 25, 27, 28 , 31, 32, 35
Y		15, 16, 20-22, 24, 26 , 29, 33
A		17-19, 30, 34, 36, 37
Y	JEON, J. et al. 'A comprehensive profile of DNA copy number variations in a Korean population: identification of copy number invariant regions among Koreans' Experimental and Molecular Medicine. Vol.41(9), pp.618-628 (September 2009) See the abstract; Table 3.	15, 16, 20-22, 24, 26 , 29, 33
A	US 2010-0047924 A1 (WEBSTER, P. et al.) 25 February 2010 See the abstract.	1-37
A	WO 2007-076132 A2 (NANOSTRING TECHNOLOGIES, INC.) 05 July 2007 See the abstract.	1-37



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

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Date of the actual completion of the international search

30 NOVEMBER 2011 (30.11.2011)

Date of mailing of the international search report

30 NOVEMBER 2011 (30.11.2011)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 189 Cheongsu-ro,
Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

KIM, JI YUN

Telephone No. 82-42-481-8288



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2011/028657

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 2009-521688 A	04.06.2009
		JP 2009-521688 T	04.06.2009
		US 2010-0261026 A1	14.10.2010
		WO 2007-076132 A3	07.09.2007

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 May 2012 (03.05.2012)

PCT

(10) International Publication Number
WO 2012/058638 A2

(51) International Patent Classification:
C12Q 1/68 (2006.01)

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(21) International Application Number:
PCT/US2011/058458

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date:
28 October 2011 (28.10.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/408,358 29 October 2010 (29.10.2010) US

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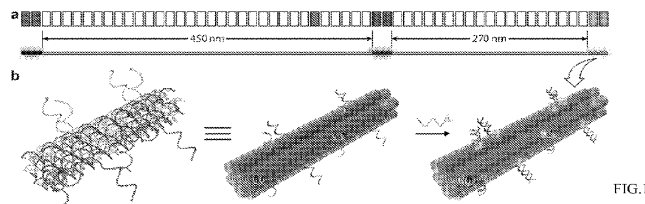
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

— with sequence listing part of description (Rule 5.2(a))

(54) Title: NUCLEIC ACID NANOSTRUCTURE BARCODE PROBES



(57) Abstract: Provided herein are, inter alia, barcode probes comprised of transiently or stably fluorescently labeled nucleic acid nanostructures that are fully addressable and able to be read using standard fluorescent microscope and methods of use thereof including methods of use as detectable labels for probes.

WO 2012/058638 A2

NUCLEIC ACID NANOSTRUCTURE BARCODE PROBES

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 61/408358, filed on October 29, 2010, entitled "DNA NANOSTRUCTURE BARCODE PROBES", the entire contents of which are incorporated by reference herein.

REFERENCE TO A COMPACT DISK APPENDIX

A computer program listing is appended to this disclosure and is hereby incorporated herein by this reference. The appendix includes the file programlisting.txt which includes listings for 6ht-v5-1color-1.json and 6ht-v6-2color-1.json.

BACKGROUND OF INVENTION

A major challenge in modern biology and nanotechnology is to observe, identify and differentiate a large number of different molecular species in real time. Fluorescent microscopy is a powerful tool for non-destructively and dynamically monitoring many individual molecular events. However, the multiplexing ability of fluorescent imaging is limited by the number of spectrally non-overlapping fluorophores available. There is therefore a great need for novel addressable fluorescent probes useful in multiplex detection systems.

BRIEF SUMMARY OF INVENTION

The invention provides, inter alia, nucleic acid barcode probes that comprise a nucleic acid nanostructure comprising one or more fluorescently labeled regions that may be stably or transiently bound (and thus labeled) with fluorophore-bearing oligonucleotides. The barcode probes may further comprise a target binding moiety. The invention also provides methods of use for such barcode probes including but not limited to their use in analyte detection assays (e.g., assays for detecting and optionally quantitating one or more analytes). The nature of the fluorescent signals (e.g., the wavelength or "color", intensity, etc.) and the pattern (or orientation, or arrangement or geometry) of such signals on the barcode can also be used to identify particular analytes

in a sample. This facilitates multiplexed assays in which a plurality of analytes are detected simultaneously (or at a minimum with a single sample or a single aliquot from a sample).

In one aspect, the invention provides a method of detecting a target comprising:
5 contacting a sample with a nucleic acid barcode probe, and determining whether the nucleic acid barcode probe binds to one or more components in the sample, wherein binding of the nucleic acid barcode probe to one or more components of the sample indicates presence of a target in the sample, and wherein the nucleic acid barcode probe comprises a nucleic acid nanostructure comprising a target binding moiety and at least
10 two fluorescently labeled regions.

In some embodiments, the method further comprises identifying the target based on the color and/or orientation of the fluorescently labeled regions of the nucleic acid barcode probe bound to one or more components of the sample.

In some embodiments, whether the nucleic acid barcode probe binds to one or
15 more components in the sample comprises contacting the nucleic acid barcode probe with soluble, transiently binding fluorophore-bearing oligonucleotides.

In some embodiments, the nucleic acid barcode probe comprises stably bound fluorophore-bearing oligonucleotides.

In another aspect, the invention provides a method of detecting a target
20 comprising contacting the target with a nucleic acid barcode probe, under conditions sufficient for the target to bind to the nucleic acid barcode probe; separating the target from material that is not bound to the target; and detecting the presence of the nucleic acid barcode probe bound to the target, wherein the nucleic acid barcode probe comprises a nucleic acid nanostructure comprising a target binding moiety and at least
25 two fluorescently labeled regions.

In some embodiments, the method further comprises identifying the target based on the color and/or orientation of the fluorescently labeled regions of the nucleic acid barcode probe bound to the target.

In some embodiments, detecting the presence of the nucleic acid barcode probe
30 bound to the target comprises contacting the nucleic acid barcode probe with soluble, transiently bound fluorophore-bearing oligonucleotides.

In some embodiments, the nucleic acid barcode probe comprises stably bound fluorophore-bearing oligonucleotides.

In another aspect, the invention provides a nucleic acid barcode probe comprising a nucleic acid nanostructure, such as a DNA barcode probe comprising a DNA
5 nanostructure, having at least two fluorescently-labeled regions. In some embodiments, the nanostructure comprises at least three fluorescently-labeled regions, and the orientation is determinable due to asymmetric spacing of the fluorescently-labeled regions. The locations of each of the fluorescently-labeled regions on the nanostructure are such that a pattern of the fluorescent labels is determinable based on the emission of
10 visible light by the fluorescently-labeled regions. In some embodiments, the orientation of the barcode probe is determinable based on the emission of visible light by the fluorescently-labeled regions.

In some embodiments, each of the fluorescently-labeled regions has a center that is located at least 200 nm from the centers of the other fluorescently-labeled regions. In
15 some embodiments, each of the fluorescently-labeled regions has a center that is located at least 250 nm from the centers of the other fluorescently-labeled regions. In some embodiments, each of the fluorescently-labeled regions has a center that is located at least about 25 nm, at least about 50 nm, or at least about 75 nm, or at least about 100 nm, or at least 150 nm from the centers of the other fluorescently-labeled regions.

20 In some embodiments, the nanostructure comprises a scaffold strand and plurality of staple strands. In some embodiments, the scaffold strand has a sequence derived from M13 bacteriophage. In some embodiments, the fluorescently-labeled regions of the DNA nanostructure comprise fluorophore-labeled staple strands. In some embodiments, the fluorophore-labeled staple strand is a transiently binding fluorophore-labeled staple strand. In some embodiments, the fluorophore-labeled staple strand is
25 transiently binding at room temperature. In some embodiments, the fluorophore-labeled staple strand is 7-12 nucleotides in length. In some embodiments, the fluorophore-labeled staple strand is about 9 nucleotides in length. In some embodiments, the fluorophore-labeled staple strand is a stably binding fluorophore-labeled staple strand.
30 In some embodiments, the fluorophore-labeled staple strand is a stably binding fluorophore-labeled staple strand at room temperature. In some embodiments, the

fluorophore-labeled staple strand is at least 18 nucleotides in length, including in some embodiments 18-25 nucleotides in length.

In some embodiments, the fluorophore-labeled staple strands are directly labeled. In some embodiments, the fluorophore-labeled staple strands are indirectly labeled.

- 5 In some embodiments, the fluorophore-labeled staple strands have a staple domain hybridized to a scaffold strand and a handle domain hybridized to a fluorophore-labeled oligonucleotide. In some embodiments, the handle domain is 7-12 nucleotides in length. In some embodiments, the handle domain is about 9 nucleotides in length. In some embodiments, the handle domain is at least 18 nucleotides in length. In some
10 embodiments, the handle domain is 18-25 nucleotides in length.

In some embodiments, the nanostructure is a nanotube. In some embodiments, the nanostructure is prepared using a DNA origami method. In some embodiments, the nanostructure comprises a single-stranded DNA tile. In some embodiments, the nanostructure comprises DNA hairpins.

- 15 In some embodiments, the barcode probe further comprises a target binding moiety. In some embodiments, the target binding moiety is a single-stranded nucleic acid complementary to a nucleic acid target. In some embodiments, the target binding moiety is an antibody. In some embodiments, the target binding moiety is a protein or peptide.
- 20 In some embodiments, wherein the nanostructure, once assembled, is sufficiently immutable in a resting state that the pattern of the fluorescent regions can be detected using light microscopy in that resting state. In some embodiments, the resting state comprises absence of an applied electric field.

- In another aspect, the invention provides a composition comprising a plurality of
25 any of the foregoing nucleic acid nanostructure barcode probes. In some embodiments, some or all members of the plurality are different from other members in the plurality. The members may differ from each other based on the target binding moiety and the signal and orientation (arrangements) of the barcode. In some embodiments, the plurality is equal to or less than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19,
30 20, 25, 30, 40, 50, 100, 200 or more. In some instances, the plurality is equal to or less than 216.

In another aspect, the invention provides a method of identifying a target nucleic acid comprising contacting the target nucleic acid with any of the foregoing barcode probes under conditions such that the target nucleic acid binds to the barcode probe; separating the target nucleic acid from material that is not bound to the target nucleic acid; and detecting the presence of the barcode probe bound to the target nucleic acid.

In another aspect, the invention provides a method of identifying a target protein or cell comprising contacting the target protein or cell with any of the foregoing barcode probes under conditions such that the target protein or cell binds to the barcode probe; separating the target protein or cell from material that is not bound to the target protein or cell; and detecting the presence of the barcode probe bound to the target protein or cell.

In another aspect, the invention provides a method of identifying a target protein or cell comprising contacting the target protein or cell with any of the foregoing barcode probes under conditions such that the target protein or cell binds to the barcode probe; separating the target protein or cell from material that is not bound to the target protein or cell; and detecting the presence of the barcode probe bound to the target protein or cell.

In another aspect, the invention provides a method of detecting a target comprising contacting a sample with any of the foregoing nucleic acid barcode probes, and determining whether the nucleic acid barcode probe binds to one or more components in the sample, wherein binding of the nucleic acid barcode probe to one or more components in the sample indicates presence of a target in the sample.

In some embodiments, the method further comprises removing components in the sample that are not bound to the nucleic acid barcode probe following the contacting step.

In some embodiments, the target is a nucleic acid, a protein, a peptide, or a cell, or a combination thereof.

In some embodiments, the presence of the barcode probe is detected by fluorescent microscopy.

In some embodiments, the presence of the barcode probe is detected without exposing the DNA barcode probe to an electric field.

In some embodiments, each probe comprises a nucleic acid nanostructure having at least two fluorescently-labeled regions and a target binding moiety, wherein the locations of each of the fluorescently-labeled regions on the nanostructure are such that a pattern of the fluorescent labels of the barcode probe and the identity of the target binding moiety is determinable based on the emission of visible light by the fluorescently-labeled regions; and each of the fluorescently-labeled regions has a center that is located at least 200 nm from the centers of the other fluorescently-labeled regions.

In another aspect, the invention provides a population of nucleic acid barcode probes such as DNA barcode probes, wherein each probe comprises a nucleic acid nanostructure such as a DNA nanostructure having at least two fluorescently-labeled regions and a target binding moiety, wherein the locations of each of the fluorescently-labeled regions on the nucleic acid nanostructure are such that a pattern of the fluorescent labels of the nucleic acid barcode probe and the identity of the target binding moiety is determinable based on the emission of visible light by the fluorescently-labeled regions.

In some embodiments, each of the fluorescently-labeled regions has a center that is located at least about 25 nm, at least about 50 nm, at least about 100 nm, at least about 200 nm, or at least about 250 nm from the centers of the other fluorescently-labeled regions.

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

BRIEF DESCRIPTION OF DRAWINGS

The patent or application file contains at least one Figure executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee. Publication of the application includes gray-scale renderings of the Figures. Color versions of these Figures are available upon request.

FIG. 1. Design of the DNA nanotube based barcode. (A) Two schematic drawings of the Blue--Red-Green (BRG, "--" and "-" denotes larger and smaller inter-zone distance in the barcode, respectively) barcode with a segment diagram on the top and a 3D view at the bottom. The main-body of the barcode is a DNA nanotube formed from by dimerizing two origami monomers, each consisting of 28 segments with 42-bp

(13.6 nm) length. The grey segment in the middle represents the junction where the two monomers are joined together through cross-hybridization between their scaffolds and staples. Three 84-bp zones of the nanotube are fluorescently labeled (shown as blue, red and green segments) to produce the BRG barcode with an inter-zone distance of 450-nm between the first two zones and 270-nm between the last two. Note that each zone is only labeled with one fluorophore species. The resulting barcodes are thus referred as single-labeled-zone barcodes. (B) 3D cartoons showing the details of one fluorescently labeled zone. Left: a scaffold-plus-staple model of such an 84-bp zone before labeling. Each of the twelve 63-base-long staples (shown in rainbow colors) contains two parts: the 42-base region at the 5'-end weaves through three double-helices to fold the scaffold (shown in black) into a six-helix bundle nanotube; and the 21-base extension at the 3'-end protrudes out for fluorescent labeling. Middle: an identical but simplified model to emphasize the six-helix bundle structure (each helix shown as a semi-transparent grey cylinder) and the positioning of the twelve 21-base staple extensions (each shown as a light-grey curl). Right: Cartoon representation of a "green" 84-bp zone. The labeling is achieved by hybridizing the Cy3 (shown the glowing green spheres at the 3'-ends) modified strands to the staple extensions.

FIG. 2. Single-labeled-zone fluorescent barcodes. (A) Superimposed TIRF microscopy images of five barcode species (top) and the statistics from manual counting (bottom). From left to right are the BBB, BRG, BRR, GRG and RGB barcodes with a representative image on top of the corresponding bar-graph. Each bar-graph is generated based on the manual sorting and counting of the objects found in a $50 \times 50 \mu\text{m}^2$ image (~40 barcodes, the exact sample size N is noted beside the corresponding bar-graph). (B) A representative image of the equimolar mixture of 27 barcode species. (C) Statistics obtained by analyzing twenty-seven $50 \times 50 \mu\text{m}^2$ images of the 27 barcode mixture (~1,500 barcodes in total). Left: barcode counts of the 27 species (average count of 55 with a standard deviation of 9). A representative TIRF image ($1.4 \times 0.7 \mu\text{m}^2$) of each barcode type is placed underneath the corresponding bar. Right: sorting result of the observed objects shown as a pie-chart. Color scheme used for the bar-graphs and the pie-chart (unrelated to the pseudo-colors of the fluorophores): blue: correct barcodes (qualified barcode with expected identity); green: incorrect barcodes (qualified barcode

with unexpected identity); red: monomer nanotubes (one spot or two connecting spots); purple: barcodes with wrong geometry (i.e., bending angle $<120^\circ$); and orange: barcodes containing at least one spot with two colors. In the 27-barcode pool, correct vs. incorrect barcodes were not distinguishable because all barcode types are expected. As a result the bars and pie representing the qualified barcodes in (C) are shown in blue. Scale bars: 5 μm .

FIG. 3. Representative TIRF and software reconstructed images of BRG and GRG nano-barcodes. (A) TIRF image of BRG nano-barcodes. (B) Software constructed image of (A), inset showing calculation of barcode bending angle. (C) TIRF image of BRG nano-barcodes. (D) Software constructed image of (C). (E) Theoretical designed distances between each region of BRG (upper) and GRG (lower) nano-barcodes. Scale bar: 10 pixels or $0.714 \mu\text{m}$.

FIG. 4. Schematic illustration and result of a 21-mer oligonucleotide detection using nano-barcodes. (A) A GRG barcode with a capture probe is biotinylated as a result of the target binding and a nude BRG barcode stays untouched. Note that the drawing is not to scale. (B) TIRF images of nano-barcodes immobilized on streptavidin coated glass cover-slip. Left: with target; Right: without target. (C) Statistical detection result showing the average barcode counts per $71.4 \times 71.4 \mu\text{m}^2$ area. Error bars represent the standard deviation.

FIG. 5. Dual-labeled-zone fluorescent barcodes. (A) Typical TIRF microscopy images of five selected barcode species, shown both in separate channels and after superimposing. Scale bar: $5 \mu\text{m}$. (B) Statistics obtained by analyzing two $50 \times 50 \mu\text{m}^2$ images of each barcode species (~ 85 barcodes, the exact sample size N is noted beside the corresponding bar-graph). The barcode types are noted under the x-axis of the diagram. Color scheme (unrelated to the pseudo-colors of the fluorophores): blue: correct barcodes (correct geometry and color identity); green: incorrect barcodes (correct geometry but incorrect color identity); red: monomer nanotubes (one spot or two connecting spots); and purple: barcodes with wrong geometry (i.e., bending angle $<120^\circ$). (C) Computer-aided barcode counting results of the 72-barcode pool ($N=2,617$) and the 216-barcode pool ($N=7,243$) plotted as bar-graphs with descending barcode counts from left to right (data not shown). A computer-generated reference barcode image is placed underneath the corresponding bar. (D) A table containing one

representative TIRF image ($1.4 \times 0.7 \mu\text{m}^2$) for each of the 216 dual-labeled-zone barcode species.

FIG. 6. Super-resolution fluorescent barcodes. (A) Scheme of DNA-PAINT used for super-resolution barcode imaging. The 400 nm nanotube consists of 4 binding zones spaced by ~ 114 nm. Each zone can be decorated with the desired combination of “docking” sequences for red, green or blue imager strands. The orthogonal imager strands bind transiently to their respective “docking” sites on the nanotube, creating the necessary “blinking” for super-resolution reconstruction (B) Top: Segment diagram (similar to the one used in FIG. 1) of the DNA nanotube monomers used for creating five barcodes for super-resolution imaging. Bottom: super-resolution images of the five barcodes shown in each channel separately and as an overlay of all channels. Scale bar: 100 nm. (C) Super-resolution image showing all five barcodes in one mixture. Scale bar: 500 nm.

FIG. 7. Tagging yeast cells with the GRG barcodes as in situ imaging probes. (A) Cartoon illustrating the tagging mechanism. The biotinylated barcodes are anchored on the yeast cell through streptavidin molecules bound to biotinylated polyclonal antibodies coated on the yeast surface. Only two of the ten biotinylated staples on the barcode are shown here for clarity. (B) Overlaid microscope images (acquired in bright field and TIRF) of the yeast cells treated with the barcodes. Top: Yeast cells treated as illustrated in (A). Bottom: Negative control: yeast cells treated with non-biotinylated barcodes. Scale bars: 5 μm .

FIG. 8. Fluorescent barcode with non-linear geometry. (A) A schematic of three identical ~ 400 -nm long DNA nanotubes are linked to the outer edge of a DNA ring with diameter of ~ 60 nm through the hybridization between staple extensions. The ring and the end of the tube are labeled by Cy3 (green) and Cy5 (red), respectively. (B) A representative TIRF microscope image of the barcode shown in (a). Scale bar: 5 μm .

DETAILED DESCRIPTION OF INVENTION

Provided herein are nucleic acid (e.g., DNA) nanostructure barcode probes that are fully addressable and able to be read using standard fluorescent microscope.

Previously described molecular barcodes are constructed using one of two strategies: (1) By combining multiple spectrally non-overlapping fluorophores in a

controlled molar ratio to generate a mixed color signature; or (2) by separating fluorophores beyond the diffraction limit (~200 nm) and arranging them in a specific geometric pattern. The first category of barcode has been made, for example, from dendrimeric DNA (*see, e.g., Li et al., Nat. Biotechnol.* 23:885-889 (2005)), self-
5 assembled 2D DNA arrays (*see, e.g., Lin et al., Nano Lett.* 7:507-512 (2007)) and quantum dots (*see, e.g., Han et al., Nat. Biotechnol.* 19:631-635 (2001)). The successful construction and decoding of such barcodes heavily depends on both the fluorescent labeling efficiency and the imaging instrument's ability to precisely detect different fluorescent intensity levels.

10 In contrast, barcodes constructed according to the second strategy are more robust, and can be constructed and detected even when the labeling efficiency and imaging conditions are sub-optimal. Furthermore, when such methods are used, the ability to multiplex increases exponentially with each additional fluorescent spot that is incorporated. Examples of barcodes that fall in this category include rare-earth doped
15 glass microfibers (~100 μm long) (*see, e.g., Dejneka et al., Proc. Nat. Acad. Sci. USA* 100:389-393 (2003)) and double-stranded linear DNA with one strand fluorescently tagged at specific locations (2–5 μm long) (*see, e.g., Xiao et al., Nat. Methods* 6:199-201 (2009) and Geiss et al., *Nat. Biotechnol.* 26:317-325 (2008)). However, existing methods using this strategy are limited both in the addressability of the fluorescent spots
20 and because, in the absence of specialized equipment, the labeled barcodes will fold into a conformation that brings the fluorescent spots within the diffraction limit of visible light, rendering the barcode unreadable using a fluorescent microscope.

The instant inventors recognized that the problems associated with existing molecular barcode strategies could be addressed by using nucleic acid nanostructures
25 such as DNA nanostructures to create novel molecular barcode probes. Nucleic acids such as DNA may be folded into predetermined one-, two- or three-dimensional nanostructures using a variety of techniques, such as DNA origami (Rothmund US-2007/0117109 A1), single-stranded tiles (Yin et al., "Programming DNA Tube Circumferences," *Science* (2008): 321: 824-826), DNA hairpins (Yin et al. US-
30 2009/0011956 A1; Yin et al., "Programming biomolecular self-assembly pathways," *Nature* (2008) 451:318-323), and others.

In general, the DNA origami process involves the folding of one or more long, “scaffold” DNA strands into a particular shape using a plurality of rationally designed “staple” DNA strands. The sequences of the staple strands are designed such that they hybridize to particular portions of the scaffold strands and, in doing so, force the scaffold strands into a particular shape. Methods useful in the making of DNA origami structures can be found, for example, in U.S. Pat. App. Pub. Nos. 2007/0117109, 2008/0287668, 2010/0069621 and 2010/0216978, each of which is incorporated by reference in its entirety. Staple design can be facilitated using, for example, caDNAno software, available on the internet at the cadnano website.

In certain embodiments, a DNA nanostructure barcode probe may include a DNA nanostructure made of one or more scaffold strands held in a specific shape by rationally designed staple strands. The sequence listing provides the nucleotide sequence of a scaffold strand, as SEQ ID NO:1, that may be used to construct an exemplary DNA origami barcode probe. The sequence listing also provides nucleotide sequences of staple strands, as SEQ ID NOs: 13-361, that may be used to construct an exemplary DNA origami barcode probe, together with the scaffold strand represented by SEQ ID NO:1. As will be discussed in greater detail herein, SEQ ID NOs: 13-186 represent nucleotide sequences of staple strands used to form a front monomer and SEQ ID NOs: 187-361 represent nucleotide sequences of staple strands used to form a rear monomer in an exemplary DNA origami barcode probe. As used herein, the term “DNA nanostructures” is used for convenience and it is to be understood that the invention contemplates nucleic acid nanostructures generally. The nanostructures of the invention may be linear (e.g., nanorods) or non-linear (e.g., star-shaped, triangular, etc.).

The DNA nanostructure has at least two non-overlapping, fluorescently-labeled regions. In certain embodiments, the DNA nanostructure barcode probe has at least 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 non-overlapping, fluorescently-labeled regions.

The fluorophore pattern of the probe is determined using light microscopy. In some embodiments, each of the fluorescently labeled regions can be visibly distinguished using a fluorescent light microscope. In some of these embodiments, the center of each fluorescently labeled region is separated from the centers of other fluorescently labeled regions by a distance greater than the visible light diffraction limit of visible light (*i.e.* at least 200 nm). In certain embodiments, therefore, each

fluorescently labeled region is at least 200 nm from any other fluorescently labeled region. In some embodiments, each fluorescently labeled region is at least 250 nm from any other fluorescently labeled region.

In some embodiments, even higher resolution is achievable and the
5 fluorescently labeled regions may be spaced apart from each other at even shorter distances (i.e., a distance of less than 200 nm). Accordingly, in some embodiments, the distance between the fluorescently labeled regions may be equal to or about 175 nm, 150 nm, 125 nm, 100 nm, 75 nm, 50 nm, 25 nm, or smaller distances. When the
10 fluorescently labeled regions are spaced apart at distances that are less than the diffraction limit of visible light, the barcoded probes are imaged using super-resolution techniques such as Point Accumulation for Imaging in Nanoscale Topography (PAINT, DNA-PAINT), Stimulated Emission Depletion Microscopy (STED), Reversible Saturable Optical Fluorescence Transitions (RESOLFT), Stochastic Optical
15 Reconstruction Microscopy (STORM, dSTORM), Photoactivated Localization Microscopy (PALM), Blink Microscopy (BM), and any other form of super-resolution microscopy.

It is to be understood that the term “fluorescently-labeled region” embraces regions that are stably labeled and those that are transiently labeled with fluorophore-bearing moieties such as fluorophore-bearing oligonucleotides that are complementary to
20 a handle domain or docking strand (or sequence), as described in greater detail herein. In some instances, the barcode probes of the invention are provided with such fluorophore-bearing oligonucleotides bound thereto, and therefore these probes would be fluorescent. In other instances, the barcode probes of the invention are provided without such
25 fluorophore-bearing oligonucleotides bound thereto, and therefore these probes may not be fluorescent until they are bound to a fluorophore-bearing oligonucleotide. In these latter instances, a probe may be provided together with a plurality of fluorophore-bearing oligonucleotides that are specific for (e.g., typically, complementary to) the handle domains or docking strands of the probe. The probes and the oligonucleotides may be provided in a kit, optionally with each in a separate container within the kit.

30 The positions of the fluorescently labeled regions can be selected such that the orientation of the DNA nanostructure barcode may be determinable through visualization of the barcode on a fluorescent microscope (typically by some form of asymmetry in the

arrangement of the labeled regions or by some arrangement convention, such a particular color or pattern reserved to indicate an end of the barcode). In some instances, orientation information is unnecessary and the barcode pattern need not be absolutely unique. Thus, barcodes with even just two labels may be used, and the presence and/or
5 intensity of various labels provides the information required.

In some instances, the fluorescently labeled regions are arranged in a linear manner. An examples is shown in, for example, FIG. 1. The fluorescently labeled regions may however be arranged in a non-linear manner as well. An example is shown in FIG. 8. Other non-linear arrangements will be apparent to those of ordinary skill in
10 the art and are embraced by the invention. In some instances, a non-linear orientation (or arrangement or geometry) of the fluorescently labeled regions is used to detect and/or identify analytes. In some instances, the signal (including for example the color or color combination) of non-linearly arranged fluorescently labeled regions is used to detect and/or identify analytes. In still other instances, orientation and signal are used together
15 to detect and/or identify analytes. Thus, it is to be understood that the nanostructure may be linear or non-linear and/or the arrangement of the fluorescently labeled regions may be linear or non-linear.

The DNA nanostructure, once assembled, is sufficiently immutable in a resting state (i.e., in the absence of external influence from e.g. an electrical field) that the spatial
20 pattern of the fluorescent regions can be detected using light microscopy in that resting state. Portions of the nanostructure may be flexible, such as unlabeled portions. In some embodiments, a probe may include a (relatively) rigid portion carrying label and an unlabeled flexible portion. in some embodiments, a probe may have two rigid labeled regions connected by a deformable linker.

25 In certain embodiments, the DNA nanostructure of the DNA barcode probe can be of any one-, two- or three dimensional shape that is able to support at least three fluorescently labeled regions at least 200 nm apart from each other. As stated herein, however, the invention is not so limited as nanostructures having fluorescently labeled regions spaced at distances of less than 200 nm from each other are also contemplated.

30 In certain embodiments, the DNA nanostructure is a nanotube. In some embodiments, the nanotube is at least 200, 300, 400, 500, 600, 700 or 800 nm long. In certain embodiments, the DNA nanostructure is a six helix bundle dimer nanotube.

Description of DNA nanotube design (via DNA origami) can be found in, for example, Douglas *et al.*, *Proc. Natl. Acad. Sci. USA* 104:6644-6648 (2006) and U.S. Pat. App. Pub. No. 2010/0216978, each of which is incorporated by reference in its entirety.

In some embodiments, the DNA barcode probes are designed such that the
5 orientation of the DNA barcode probe is determinable based on the emission of visible light by the fluorescently-labeled regions. Any property of the barcode can be used to render the orientation of the DNA barcode can be determinable. For example, if the DNA barcode probe has a substantially one-dimensional (linear) structure, such as a nanotube, the fluorescently labeled regions can be positioned asymmetrically along the
10 DNA nanostructure. The orientation of a substantially one-dimensional (linear) DNA barcode probe can also be made determinable by asymmetrically using a particular fluorophore or combination of fluorophores to label one side of the DNA nanostructure consistently. If the DNA nanostructure is two- or three-dimensional, the orientation of the DNA barcode probe can also be rendered determinable based, for example, on an
15 asymmetry of the shape of the structure itself.

In certain embodiments, the fluorescently labeled regions of the DNA barcode probe are generated by labeling specific staples of the DNA nanostructure with a fluorescent moiety. The staples can be directly labeled or indirectly labeled. As used
herein, the term “directly labeled” refers to a nucleic acid that is covalently bonded to a
20 detectable moiety. In contrast, the term “indirectly labeled” refers to a nucleic acid that is attached to a detectable moiety through one or more non-covalent interactions.

In certain embodiments, certain staples of the DNA nanostructure are directly labeled with a fluorescent moiety. In such embodiments, the staple can be, for example, synthesized with a particular fluorescent moiety attached, or covalently bonded to a
25 fluorescent moiety prior to its incorporation into the DNA nanostructure.

Any combination of fluorescent moieties may be used in a single barcode, provided the fluorescent signal from each labeled region is detectable. Preferably, the combination of fluorescent moieties is chosen so that there is no energy transfer between the fluorescent moieties (i.e., the fluorophore combination used on a single barcode
30 probe does not contain pairs of fluorophores that act together as a donor-acceptor pair).

In some embodiments, certain staples of the DNA nanostructure are indirectly labeled with a fluorescent moiety. In such embodiments, such staples can be synthesized

to have at least two domains, a staple domain and a handle domain. The staple domain is a region (or nucleotide sequence) of the staple that hybridizes to the scaffold strand to contribute to the formation and stability of the DNA nanostructure. The handle domain contains additional nucleic acid sequence that is not necessary for the creation of the DNA nanostructure. Before, during or after the formation of the DNA nanostructure, the handle sequences are available to be hybridized by oligonucleotides having a complementary DNA sequence. Thus, such staples can be indirectly labeled by hybridizing the handle domain to another nucleic acid that has a nucleic acid sequence complementary to the handle and that is itself either directly or indirectly labeled with a fluorescent moiety.

In some embodiments, each fluorescent region of the DNA barcode probe includes at least one fluorescently labeled staple. In certain embodiments, the fluorescently labeled region may include a plurality of fluorescently labeled staples. For example, in certain embodiments, each fluorescently labeled region may include at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more fluorescently labeled staples. In regions designed to have multiple staples labeled, all the staples may be labeled by a single type of fluorophore, or the staples may be labeled by a combination of fluorophore types. For example, in certain embodiments, a fluorescently labeled region is designed to be labeled by multiple types of fluorophores present at a predetermined ratio. An example of this latter type of labeling, referred to as dual-labeling, is demonstrated in the Examples. In dual-labeling, a single region is labeled with two fluorophores in a predetermined ratio, to yield a fluorescent signal that is distinguishable from either of the contributing fluorophores. In this way, the variety of barcode probes is increased.

In still other embodiments, the barcode probe may comprise one or more regions that are transiently labeled with fluorophore-bearing oligonucleotide strands. These embodiments may be used when the fluorescently labeled regions are within 200 nm of each other. In some embodiments, all the regions contributing to the barcode will be designed to be transiently labeled. Transient labeling of a region is achieved by using a nanostructure comprised of staple strands with handle domains that are shorter in length than those used for more permanent binding of a fluorescently labeled oligonucleotide. As an example, permanent (or stable) binding of fluorophore-bearing oligonucleotides to a handle domain of a staple strand can be achieved using

oligonucleotides and handle domains that are about 21 nucleotides in length. When shorter oligonucleotides and handle domains are used, the strength of binding between the two is reduced and accordingly they are more likely to dissociate than are longer strands. At room temperature, oligonucleotides and handle domains that are about 9
5 nucleotides in length associate with each other only transiently. As will be understood in the art, at higher temperatures, the length of the oligonucleotide and handle domain will typically be increased in order to achieve the same association/dissociation kinetics.

Accordingly, the invention contemplates handle domains that are directly or indirectly labeled with fluorophores as well as those that are transiently labeled with
10 fluorophores. The length of the handle domain (and similarly its complementary oligonucleotide) will depend upon the nature of the binding (i.e., whether it is intended to be permanent or transient binding), and the reaction conditions such as but not limited to temperature, salt concentration, and the like. Such lengths may range, without limitation, from about 5 nucleotides to 30 nucleotides, or from about 7 nucleotides to about 25
15 nucleotides, or from about 9 nucleotides to about 21 nucleotides.

In some embodiments, the DNA barcode probe may further include a target binding moiety that acts as a binding partner for the target (or analyte) of interest. As used herein, the term "binding" refers to an association between at least two molecules due to, for example, electrostatic, hydrophobic, ionic and/or hydrogen-bond interactions
20 under physiological conditions. Such a target binding moiety can be, for example, without limitation, a nucleic acid such as an oligonucleotide, a protein or peptide such as an antibody or antibody fragment, a carbohydrate or a polysaccharide, or a small molecule. The target binding moiety and the target to which it binds can also be viewed in a receptor and ligand relationship. In certain embodiments, the DNA barcode probe
25 may include multiple target capture moieties, which may be identical or different.

The target capture moiety can be attached to the DNA nanostructure of the DNA barcode probe using any method known in the art. For example, the target capture moiety can be covalently bonded to a staple strand or a scaffold strand. The capture moiety can also be indirectly attached to either a staple strand or the scaffold strand by,
30 for example, hybridizing to a handle domain of a staple strand, as described above.

In certain embodiments, the DNA barcode probe may include a target binding moiety that is an oligonucleotide or other nucleic acid capable of hybridizing to a target

nucleic acid. In general, an oligonucleotide is capable of hybridizing to a target nucleic acid if it includes a nucleic acid sequence that is substantially complementary a sequence of the target nucleic acid. In certain embodiments, the oligonucleotide may include a sequence that is perfectly complementary to a target (*i.e.* that is able to base pair at every
5 nucleotide with the target sequence). In some embodiments, the oligonucleotide is less than perfectly complementary to the target but is still able to hybridize to a target nucleic acid under certain conditions. Thus, in certain embodiments the sequence of the oligonucleotide is at least 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% complementary to a sequence of the target nucleic acid. In certain
10 embodiments, the DNA barcode probe may include a target binding moiety that is an aptamer.

In certain embodiments, the DNA barcode probe may include a target binding moiety that is an antibody. As used herein, the term "antibody" includes full-length antibodies and any antigen binding fragment (*i.e.*, "antigen-binding portion") or single
15 chain thereof. The term "antibody" includes, but is not limited to, a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen binding portion thereof. Antibodies may be polyclonal or monoclonal; xenogeneic, allogeneic, or syngeneic; or modified forms thereof (*e.g.*, humanized, chimeric).

20 As used herein, the phrase "antigen-binding portion" of an antibody, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen. The antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent
25 fragment consisting of the V_H , V_L , CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH1 domains; (iv) a Fv fragment consisting of the V_H and V_L domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) Nature 341:544 546), which consists of a V_H domain; and (vi) an
30 isolated complementarity determining region (CDR) or (vii) a combination of two or more isolated CDRs which may optionally be joined by a synthetic linker. Furthermore, although the two domains of the Fv fragment, V_H and V_L , are coded for by separate

genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_H and V_L regions pair to form monovalent molecules (known as single chain Fv (scFv); see *e.g.*, Bird *et al.* (1988) Science 242:423 426; and Huston *et al.* (1988) Proc. Natl. Acad. Sci. USA 85:5879

5 5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

In certain embodiments the target binding moiety is a protein or peptide. For
10 example, a protein or peptide can be used to bind the DNA barcode probe to the protein's ligand. DNA barcodes having protein or peptide target binding moieties can also be used, for example, to identify antibodies or receptors such as but not limited to cell surface receptors such as but not limited to T cell receptors and B cell receptors and intracellular receptors such as but not limited to hormone receptors that are able to bind
15 to an epitope present on the protein or peptide.

In certain embodiments, the target binding moiety is a small molecule. DNA barcode probes having small molecule target binding moieties can, for example, be used to identify molecular or cellular targets of small molecules of interest. Furthermore, libraries of small molecules, where each small molecule is individually tagged with a
20 DNA barcode, can be used in small molecule library screens to identify small molecules that specifically bind to a target of interest.

DNA barcode probes may be provided as a population of distinct species. The number of distinct barcode probes in the population is limited only by the multiplexing capability of the particular barcodes in the population. In certain embodiments, the
25 population contains at least 10, 50, 100, 500, 1000, 2000, 3000, 4000, 5000, 10^4 , 50000, 10^5 , 10^5 , 10^6 , 10^7 , 10^8 , 10^9 , 10^{10} , 10^{11} distinct barcode probes. The population may contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more distinct species. The population may contain less than or equal to about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100
30 or more distinct species. In some embodiments, the population comprises 216 distinct barcode probes. The barcode probes described herein are sufficiently adaptable and expandable to permit creation of such large-scale populations of distinguishable species.

Methods of Use

The DNA nanostructure barcode probes can be used, inter alia, in any assay in which existing molecular barcode technologies are used. For example, the DNA barcode probes can be used according to the methods described in U.S. Pat. App. Pub. No. 5 2010/0015607, the content of which is incorporated by reference in its entirety.

Typically assays include detection assays including diagnostic assays, prognostic assays, patient monitoring assays, screening assays, biowarfare assays, forensic analysis assays, prenatal genomic diagnostic assays, and the like. The assay 10 may be an in vitro assay or an in vivo assay. The sample being analyzed may be a biological sample, such as blood, sputum, lymph, mucous, stool, urine and the like. The sample may be an environmental sample such as a water sample, an air sample, a food sample, and the like. The assay may be carried out with one or more components of the binding reaction immobilized. Thus, the targets or the barcodes may be immobilized. 15 The assay may be carried out with one or more components of the binding reaction non-immobilized. The assays may involve detection of a number of targets in a sample, essentially at the same time, in view of the multiplexing potential offered by the barcode probes of the invention. As an example, an assay may be used to detect a particular cell type (e.g., based on a specific cell surface receptor) and a particular genetic mutation in 20 that particular cell type. In this way, an end user may be able to determine how many cells of a particular type carry the mutation of interest, as an example.

In certain embodiments, a method of identifying a target nucleic acid may include contacting the target nucleic acid with a DNA barcode having an oligonucleotide target capture moiety that includes a nucleic acid sequence capable of hybridizing to a 25 sequence of the target nucleic acid. In certain embodiments, the target nucleic acid is contacted with a DNA barcode probe under conditions such that the target nucleic acid binds to the DNA barcode probe. In some embodiments, the target nucleic acid is then separated from at least some material that is not bound to the target nucleic acid. In certain embodiments the presence of the target nucleic acid is then determined by 30 detecting the presence of the DNA barcode probe bound to the target nucleic acid. The detection of the DNA barcode probe can be accomplished by any appropriate method known in the art, including through fluorescent microscopy.

In some embodiments, the above-described method may further include immobilizing a capture probe containing a nucleic acid sequence complementary to a second target nucleic acid sequence to a solid support. In some embodiments the target nucleic acid is contacted with both the capture probe and the DNA barcode probe. The target nucleic acid can be contacted by the capture probe first, the DNA barcode probe first, or by both probes simultaneously. The capture probe can be immobilized on the solid support before hybridizing to the target nucleic acid, after hybridizing to the target nucleic acid, or simultaneously with hybridizing to the target nucleic acid. In such embodiments, the presence of the target nucleic acid will cause the formation of a tertiary complex that includes the capture probe, the target nucleic acid and the DNA barcode probe, immobilized to a solid support. As described above, the presence of the target nucleic acid is then determined by detecting the presence of the DNA barcode probe by any appropriate method known in the art, including through fluorescent microscopy

In certain embodiments, a method of identifying a target protein or cell may include contacting the target protein or cell with a DNA barcode probe described herein. In certain embodiments, the DNA probe has a protein, peptide or antibody target capture moiety. In some embodiments, the DNA barcode probe is contacted to a target cell or protein under conditions such that the target cell or protein binds to the DNA barcode probe. In some embodiments, the method further includes the step of separating the target protein or cell from at least some material that is not bound to the target protein or cell. In certain embodiments, the method further includes identifying a target protein or cell by detecting the presence of the DNA barcode probe bound to the target protein or cell. In some embodiments, the target protein is an antibody or receptor such as but not limited to a T cell receptor.

It will be appreciated that for some of the aspects and embodiments of the invention, it is preferable for the barcode probe and/or target to remain stationary during image acquisition, particularly if a super-resolution approach is being used and/or if the imaging technique requires superimposition of separately acquired images.

30

Super-Resolution Imaging

As discussed herein, in some aspects of the invention, the barcode probes comprise fluorescently labeled regions that are spaced at distances less than 200 nm (i.e., the diffraction limit of visible light). In some of these instances, the probe is contacted to a sample and once bound to one or more components of that sample it is exposed to soluble oligonucleotides each of which is specific for one of the regions and is labeled with fluorophores. Such soluble, transiently binding oligonucleotides may be referred to herein as “imager” strands. In some instances, the unbound components in the sample are removed prior to the addition of the fluorophore-bearing oligonucleotides. The presence of the barcode probe (and its identity based on its barcode) is then determined by imaging the remaining sample components using a series of single time lapsed images or a time lapsed movie in order to detect the binding of a fluorophore-bearing oligonucleotide to its complement on the probe. The complement on the probe may be referred to herein as a “docking” strand. The conditions are set such that at any given time only a single fluorophore-bearing oligonucleotide is bound to the barcode probe. If only a single fluorophore is bound at any given time, its color identity can be determined even if the neighboring regions are less than 200 nm away (since there would be no fluorophores bound to the neighboring regions at the same time). In this way, one is able to position adjacent “fluorescently labeled” regions at distances of less than 200 nm, and thereby generate an even greater diversity of barcodes. It is to be understood that in these embodiments, the fluorescently labeled regions are only transiently fluorescent and that the barcodes are only fluorescent when bound by imager strands.

In some embodiments, the imager and/or docking strands are about 5 to about 18 nucleotides in length, or about 6 to about 15 nucleotides in length, or about 7 to about 12 nucleotides in length. In some embodiments, the length is about 8, 9, 10, 11 or 12 nucleotides.

The art is familiar with other localization-based super-resolution fluorescence techniques including, for example, the STORM technique as described in U.S. Patent No. 7838302, the disclosure of which relating to STORM is incorporated by reference herein. The invention contemplates labeling of the nanostructure barcode probes in any manner sufficient for any super-resolution technique.

In other aspects of the invention, the nanostructure barcode probes of the invention may be used to calibrate and/or confirm calibration of fluorescence microscopy equipment, including standard or conventional fluorescence microscopes, confocal microscopes, super-resolution fluorescence microscopes, and the like. Accordingly, nanostructure barcode probes may be used as calibration standards (or tools). Of particular interest in these instances are the barcode probes having “fluorescently-labeled” regions that are spaced apart at less than the diffraction limit of visible light (i.e., less than about 200 nm). When used in this manner, the probes may or may not have a target binding moiety. As an example, they may comprise a target binding moiety such as biotin or streptavidin that facilitates their immobilization for imaging purposes.

EXAMPLES

Example 1: Creation of a DNA Barcode

DNA origami barcode probes were constructed by fluorescently labeling three separate regions of an 800-nm six-helix bundle dimer nanotube (FIG. 1). Each of the approximately 28 nm long fluorescently labeled regions was modified with twelve oligonucleotides attached to one of the three fluorophores (rhodamine-green, Cy3 or Cy5). The DNA origami barcode probe was designed to be asymmetric by placing the first two labeled regions further apart (approximately 460 nm apart) than the last two (approximately 270 nm apart). It is to be understood that other arrangements, including symmetric arrangements, are also contemplated by the invention.

The main structure of the DNA origami barcode probe is a DNA six-helix bundle nanotube dimer designed using the caDNAno software available at the cadnano website. The sequence of the scaffold strand used for each monomer is provided as SEQ ID NO:1. The sequences of the staples used in the construction of the DNA origami barcode are provided as SEQ ID NOs: 13-361. Certain selected staples were elongated (after rational design) to include 21-nt single stranded overhangs (handles) for fluorescent labeling. Table 1 provides the handle and anti-handle sequences used.

30

Table 1: DNA sequences used for fluorescently labeling nano-barcode.

Name	Sequence (SEQ. ID. NO.)
Handle 1	5'-TTCTTCTACCTACCTACATCAC-3' (SEQ ID NO:2)
Handle 2	5'-TAACATTCCTAACTTCTCATA-3' (SEQ ID NO:3)
"Blue" anti-handle 1	5'-GTGATGTAGGTGGTAGAGGAA/rhodamine green/-3' (SEQ ID NO:4)
"Green" anti-handle 1	5'-GTGATGTAGGTGGTAGAGGAATTT/Cy3/-3' (SEQ ID NO:5)
"Red" anti-handle 1	5'-GTGATGTAGGTGGTAGAGGAA/Cy5/-3' (SEQ ID NO:6)
"Blue" anti-handle 2	5'-TATGAGAAGTTAGGAATGTTA/Alexa Fluor 488/-3' (SEQ ID NO:7)
"Green" anti-handle 2	5'-TATGAGAAGTTAGGAATGTTA/Cy3/-3' (SEQ ID NO:8)
"Red" anti-handle 2	5'-TATGAGAAGTTAGGAATGTTA/Cy5/-3' (SEQ ID NO:9)

Accordingly, of the staple strands provided in the Sequence Listing, SEQ ID NOs: 16, 17, 70-73, 126-129, 182 and 183 are labeled "blue"; SEQ ID NOs: 195, 196, 239, 240, 251, 252, 295, 296, 307, 308, 351 and 352 are labeled "red"; and SEQ ID NOs: 216-219, 272-275 and 328-331 are labeled "green".

caDNA JSON files showing the arrangement of the front and rear monomers of the probe are provided in the computer program listing appendix as "6ht-v5-1color-1.json" and "6ht-v6-2color-1.json" respectively.

To assemble the DNA origami barcode probe, the front and rear monomers were each assembled and fluorescently labeled in a separate test tube and then mixed together to form the dimer. The assembly of each monomer is accomplished in one-pot reaction by mixing 100 nM scaffold strand derived from M13 bacteriophage (termed p7308) (SEQ ID NO:1) with a pool of oligonucleotide staple strands (SEQ ID NOs: 13-186 for the front monomer and 187-361 for the rear monomer; 600 nM of each; reverse-phase cartridge purified, Bioneer Inc.) in folding buffer containing 5 mM Tris, 1 mM EDTA, 20 mM MgCl₂, 50 mM NaCl (pH 8) and subjecting the mixture to a thermal-annealing ramp that cooled from 80°C to 60°C over the course of 80 minutes and then cooled from 60°C to 24°C over 15 hours. Excessive staples were removed by polyethylene glycol (PEG) fractionation before each monomer was incubated with anti-handles carrying appropriate fluorophores at 1:1.2 molar ratio for labeling. For

dimerization, a stoichiometric amount of the fluorescently labeled front and rear monomers were mixed and incubated at 37°C for 2 hours. The final product was purified by agarose gel (non-denaturing, 1.0%) electrophoresis. The purified nano-barcode can be stored at -20 °C for at least 3 months.

- 5 Although this example uses a barcode made of two monomers, a DNA barcode probe could include 3, 4, 5, or more monomers. The platform is therefore scalable to any desired level, and can provide any desired number of distinct probes.

Example 2: Detection of a Singly-Labeled DNA Barcode Using Fluorescent Microscopy

- 10 Two of the monomer nanotubes were folded and fluorescently labeled separately and combined together as described above to yield the nano-barcode. The final product was purified by agarose gel electrophoresis and directly deposited on a glass slide for imaging using a total internal reflection fluorescence microscope (TIRFM). In brief, 5 µL of the purified nano-barcode (~ 20 pM) was deposited on a
15 glass slide, sandwiched by a coverslip (No. 1.5, 18 x 18 mm², ~0.17 mm thick) and let sit for 5 minutes before being imaged on a Leica DM16000B TIRFM. The samples were imaged sequentially through three channels, each assigned a false color (blue, green and red). For the blue channel, the 488 nm laser beam was reflected by a dichroic mirror (430/505/575/670) and shined on the sample through a 100x objective (HCX PL APO
20 100x/1.47 oil CORR TIRF, Leica). The emission light was collected through the same objective, filtered through the same dichroic mirror and an external emission filter (525/36) and integrated for 800 ms on an EM-CCD camera (Hamamatsu C9100-02). For the green and red channels, similar configurations were used except for the excitation laser (561 and 635 nm, respectively), emission filter (605/52 and 705/72, respectively)
25 and exposure time (500 and 700 ms, respectively). The imaging process was automatically controlled by a Leica LAS software. The images were processed by *Image J* and a custom written software for decoding.

- The following false-colors were assigned to the fluorescently labeled regions: Alexa Fluor 488/rhodamine green (blue), Cy3 (green) and Cy5 (red). TIRFM images
30 resolved the DNA origami barcode as a strip of three distinct bright spots. Notably, the distance between blue and green spots is farther than that between green and red showing the asymmetry of the barcode (data not shown)

A DNA origami barcode system having three fluorescently labeled regions, each of which is labeled by one of three distinct fluorophores can generate 3^3 (27) distinct DNA origami barcode probes. All 27 possible DNA origami barcode probes were assembled separately and purified together by agarose gel electrophoresis.

5 Five distinct barcodes from the 27 members in the barcode family were randomly chosen for quality control experiments. The barcodes were assembled and purified separately and imaged under the same experimental conditions. Two distinct features of the barcode were clearly visible from the TIRF images (FIG. 2A, top panel): first, each fluorescently labeled zone on a barcode was resolved as a single-color spot
10 and each complete barcode consisted of three of such spots; Second, two of the neighboring spots were separated by a small gap while the other 7 two neighbors sat closely together. Therefore one can visually recognize and decode those geometrically encoded barcodes based on the color identity of the spots and their relative spatial positions, even without the aid of any specialized decoding software. Using a custom-
15 written software that localizes the center of each spot on the BRG barcodes, we measured the average center-to-center distance between the neighboring spots to be 433 ± 53 nm (mean $\pm$ s.d., N=70; larger distance) and 264 ± 52 nm (mean $\pm$ s.d., N=70; smaller distance), confirming the correct formation of the barcodes. These experimentally measured distances were slightly smaller than the designed values (478
20 nm and 298 nm). We attribute this discrepancy to random thermal bending of the nanotubes (persistence length of $\sim 1-2$ μ m), which has been observed previously by others^{23,28} and confirmed by us (data not shown) using transmission electron microscopy (TEM). It is important to note that unlike some other geometrically encoded barcoding systems (e.g., NanoString nCounter¹²), there was no molecular combing step involved in
25 the sample preparation. The separation between the fluorescent spots was exclusively created by the inherently rigid structure of the six-helix bundle nanotube. It is also notable that the spot intensities were not perfectly uniform across the whole image, which can be explained by factors such as the uneven illumination of the sample stage and differences in labeling efficiency. Nevertheless, the TIRF images proved that the
30 barcodes were successfully assembled and can be resolved unambiguously. We then manually investigated TIRF images with an area of 50×50 μ m² for the selected five

barcodes (FIG. 2A, bottom panel). The objects found within the images were first sorted into qualified (i.e., three single-color spots arranged in a nearly linear and asymmetric fashion as designed) and unqualified (i.e., all other objects) barcodes. The qualified 8 barcodes were further categorized into correct and incorrect (false-positive) barcodes based on the fluorescent signatures of the composing spots to reflect whether the barcode was the expected type. The unqualified barcodes were further sorted into (1) monomer nanotubes (single spot or two “kissing” spots), (2) barcode with “wrong” geometry (i.e., extreme bending), and (3) barcode containing at least one spot with multiple colors. Our statistics revealed that more than 70% of the visible objects were qualified barcodes, which we further determined to be exclusively the expected type (i.e., zero false-positive out of 188 qualified barcodes observed). The unqualified barcodes arose likely from folding defects, sample damage during handling and overlapping nanotubes on the surface, which can be largely reduced by optimizing the sample preparation and imaging protocol.

Typically, a number of different barcode species coexist in one pool. Thus it is important to examine the robustness of our system by mixing different types of barcode together. In an initial test, we synthesized BRG and RGB barcodes separately, mixed them together at equal molar ratio and co-purified them via gel electrophoresis. The TIRF analysis of the purified mixture confirmed the 1:1 stoichiometry of the two barcodes and the overall assembly success rate (qualified barcode/all objects) of ~80%, suggesting that both barcodes maintained their integrity in the mixing and co-purification process. In addition, over 98% of the qualified barcodes fell into one of the two expected types (BRG and RGB). The 2% false-positive rate was due to an unexpected barcode namely BGB, which could be attributed to a rare occasion when the front monomer of the BRG barcode lay in proximity of the rear monomer of the RGB barcode. This can be eliminated using a more stringent purification condition to minimize the amount of leftover monomers.

We next challenged the system by imaging a pool of all 27 members of the barcode family in which all species were mixed at equimolar amount. The TIRF images (FIG. 2B) showed that all types of barcodes were resolved. Statistics by sampling twenty-seven $50 \times 50 \mu\text{m}^2$ images (~1,500 barcodes in total) revealed an average count of 55 per barcode type with a standard deviation of 9 (FIG. 2C), fitting

well with the expected stoichiometry considering the pipetting and sampling error. The distribution of observed objects over the four categories (note that here correct vs. incorrect barcodes were not distinguishable as all 27 types were included) was consistent with the values measured from the single-type barcode samples. The above observations
5 suggest that the sub-micrometer-long DNA nanotube represents a reliable platform to construct geometrically encoded barcodes with built-in structural rigidity.

Software could be used to recognize and decode the image of different types of DNA origami barcode probes automatically. Typically, such software has three basic
10 steps: recognition, filtering and decoding. In the first step, the fluorescent spots are identified. For each fluorescent channel (blue, red or green), the software identifies fluorescent spots based on their intensity and size, then compares them to automatically determined thresholds using overall image intensity and pre-defined spot sizes. The
15 fluorescent spots below those thresholds are removed along with general background noise. After processing all three channels, a barcode image is constructed by merging spots identified in three channels. An example of such a barcode image is provided in FIG. 3. In the second step, the distances (calculated from (x,y) coordinates of fluorescent spots) between each region of DNA origami barcode probes and the barcode bending angle (based on the center spot) are calculated. The software then filters DNA origami
20 barcode probes and removes those with region distances that disagreed with the theoretical region distances or had a barcode bending angle smaller than a currently arbitrarily set threshold angle of 140 degrees. As an example, the BRG barcodes were filtered using three distance rules: (1) The distance between blue and green spot cannot be greater than 15 pixels (theoretical distance was 11 pixels); (2) The distance between
25 red and blue spot cannot be greater than 9 pixels (theoretical distance was 6.8 pixels); and (3) The distance between red and green spot cannot be greater than 6 pixels (theoretical distance was 4.2 pixels). The BRG barcodes that had a bending angle (at the red spot) smaller than 140 degrees were removed. In the last step, after all barcodes are identified and filtered, the software uses different criteria (based on theoretical distance
30 and color) to sort barcodes into specific types. Therefore, multiple types of DNA barcode probes can be decoded based on how they were originally designed. Besides the final constructed DNA barcode probe image, the software can output statistical information

regarding the (x,y) coordinates of each DNA barcode probe fluorescent spot, distances between adjacent spots, barcode bending angle, and barcode types.

The software described above was used to detect BRG and GRG DNA origami barcode probes. As shown in FIG. 3, the BRG and GRG DNA origami barcode probes were clearly identified by the automated decoding software. The software used a number of filters to select the valid DNA origami barcode probes. As a result, 88% and 85% of BRG and GRG nano-barcodes were counted. The software generated statistical information on BRG and GRG barcodes (Table 2) that showed that the measured distances between each region on those DNA origami barcode probes were in good agreement with the theoretical region distances as designed (FIG. 3E).

Table 2

Barcode type	Barcode identified	Barcode discarded	Barcode bending angle α (degree)	Distance 1 (pixel)	Distance 2 (pixel)
BRG	70	9	165.11 $\pm$ 10.08	6.18 $\pm$ 0.76	3.77 $\pm$ 0.74
GRG	81	15	161.51 $\pm$ 11.73	6.12 $\pm$ 0.95	3.95 $\pm$ 0.98

15

Example 3: Detection of an Oligonucleotide Target Using a DNA Barcode Probe

A 42-nt DNA oligonucleotide target was detected using a DNA origami barcode probe. Two different purified barcodes Green, Red, Green (GRG) with the 21-nt oligonucleotide target capture moiety specific for a 42-nt oligonucleotide target (Target 1, *see* Table 3 for sequences) and Blue, Red, Green (BRG) without a target capture moiety, were mixed at 1:1 ratio and diluted to 20 pM in folding buffer. Biotin probe specific for Target 1 (0.2 μ L of 100 nM) and Target 1 (0.4 μ L of 10 nM) was added to 100 μ L of the barcode mixture. In a separate test tube containing 100 μ L of the barcode mixture, 0.2 μ L of 100 nM biotin probe for Target 1 and 0.4 μ L of 1x folding buffer was added as a negative control. The above samples were both incubated at 37 °C overnight before being run through separate channels of a micro-fluidic cell with a streptavidin coated glass cover-slip (Xenopore) substrate. Both channels were then washed with 40 μ L of washing buffer (5 mM Tris-HCl pH 8.0, 500 mM NaCl) and imaged on a Leica TIRFM as described above. Ten images were taken in each channel

at random locations and the total number of DNA origami barcode probes was counted manually.

5

Table 3: DNA sequences used in oligonucleotide target detection

Name	Sequence (SEQ ID NO:)
Target oligo	5'-GAATCGGTCACAGTACAACCGCGCCGTAGGGCTG-ATCAAAGC-3' (SEQ ID NO:10)
Biotin probe	5'-/Biotin/ GCTTTGATCAGCCCTACGGCG-3' (SEQ ID NO:11)
Capture probe	5'-CGGTTGTACTGTGACCGATTTC-3' (SEQ ID NO:12)

In the presence of the target oligonucleotide, the biotin probe hybridized to one
21 nt sequence of the target oligonucleotide, while the GRG barcode hybridized to a
second 21 nt sequence of the target oligonucleotide. The BRG probe, however, lacking a
target capture moiety specific for the target oligonucleotide does not hybridize to the
target and therefore does not become bound by the biotin probe. (FIG. 4A). As a
consequence, when the detection reaction mixture was run through the streptavidin-
coated glass surface, the GRG barcode binds to the surface, while BRG barcode is
washed away. TIRF images and statistical analysis supported the specificity of the
detection (FIGs. 4B and C). In the presence of 40 pM oligonucleotide target, there were
~20 times more GRG barcodes than BRG barcodes bound to the surface. In the absence
of the target, both barcodes did not show significant surface binding.

20

Example 4: Dual-Labeled Barcode Probes

In order to enhance multiplexing capability even further, the sequence of six
staple extensions per zone was changed so that instead of using twelve identical
fluorescent oligonucleotides for labeling, a combination of up to two fluorophores was
used to create more unique fluorescence signatures (pseudo-colors) for each zone. Six
pseudo-colors (B, R, G, BG, BR, and GR) were generated by this “dual-labeling”
strategy using three spectrally differentiable fluorophores. Consequently, the total
number of distinct barcodes was raised from 27 to $6^3=216$, which represented an order
of magnitude increase in the multiplexing capability.

Similar to the single-labeled-zone barcode family, 5 members from the dual-labeled-zone barcode family were chosen for quality control purpose. The barcodes can be visually decoded either solely from the superimposed image or by examining all different channels simultaneously. For example, as shown in the first column of FIG. 5A, the barcode “BG--GR-BR” (“--” and “-” denotes larger and smaller inter-zone distance in the barcode, respectively) exhibited two spots each in the blue, green and red channels but with descending gaps between them, matching its design. In the superimposed image, the barcodes were seen as Cyan--Yellow-Pink, an expected consequence of color mixing caused by the dual-labeling strategy. In a similar fashion, we further verified the correct formation of the other four selected barcodes (FIG. 5A). Although the final pseudo-color from the dual-labeled zones was not always uniform (e.g., some yellow spots were green-tinted while the others were red-tinted) due to the inconsistent labeling efficiency and minor sample displacement during imaging, the fluorescence signature of any given spot could be identified by checking the raw images acquired from the three imaging channels. We manually analyzed two $50 \times 50 \mu\text{m}^2$ images of each dual-labeled-zone barcode and plotted the statistical data in FIG. 5B. Here, objects were sorted into qualified barcodes and unqualified barcodes based on their geometry and the qualified ones were further categorized as correct and incorrect. 75–95% of the objects were qualified barcodes, among which 80–90% were the correct type (percentage varies depending on the exact type of barcode). Compared to the single-labeled-zone barcode family, the percentage of qualified barcodes remained the same, while the false positive rate increased significantly from zero to 10–20%. This observed increased false positive rate is consistent with the expected decreased robustness of the dual-labeling strategy (as compared to single-labeling). In one design, a dual-labeled zone carried 6 staple extensions for each fluorophore species, only half as many as in a single-labeled zone.

As a result, the dual-labeled-zone barcode consisted of dimmer spots that were more susceptible to damages such as photo bleaching. In this sense, a single-labeled-zone barcode can be thought of as a redundantly encoded dual-labeled-zone barcode. For instance, a single-labeled-zone barcode can still be recognized as the correct type when six fluorophores were missing from each zone, a scenario in which the dual-labeled-zone barcode could be disqualified or categorized as incorrect. In the latter case, it will increase the false positive rate. In principle, the false positive rate can be decreased by

increasing the copy number of each fluorophore species in a dual-labeled zone. The five barcodes we examined have each of their zones labeled with two distinct fluorophore species, making them likely among the most error-prone members of the dual-labeled-zone barcode family. Therefore, we would expect a smaller false-positive rate on average
5 from the whole family.

We further tested the dual-labeled-zone barcoding system by imaging a mixture containing 72 barcode species that were individually assembled and co-purified. Custom MATLAB scripts were used to assist the decoding process in two steps. In step one, a three-channel (red, green, blue) TIRF image containing barcodes was pre-processed to
10 remove background and thresholded so that only pixels containing qualified barcodes remained. The resulting three-channel binary image was merged to generate a single-channel binary image. Next, the software identified the location and orientation of geometrically legitimate barcodes based on their shape in the binary image. In step two, for each barcode located in step one, the corresponding region of the three-channel image
15 was compared against a library of all possible reference barcodes. The observed barcode was assigned the identity of the reference barcode with the highest correlation. The fully automated decoding process (unsupervised mode) ended after the above two steps. In an optional supervised mode, the software presented the user with the observed barcode and its most likely identity for approval. Comparison between supervised and unsupervised
20 decoding results confirmed >80% agreement between the computer and the user. The computer-aided (supervised mode) analysis of thirty-six $64 \times 64 \mu\text{m}^2$ three-channel images registered ~2,600 qualified barcodes that belonged to 116 different species (FIG. 5C, top panel). The expected 72 species constituted ~98% of the total barcode population with an average barcode count of 36 per species and a standard deviation of 8. In
25 contrast, the unexpected species averaged only ~1.4 barcodes per species (maximum 4 counts).

Finally, we analyzed a mixture containing all the 216 members of the dual-labeled-zone barcode. Sixty $64 \times 64 \mu\text{m}^2$ images of this mixture were processed by the decoding software in the unsupervised mode. The fully automated analysis registered
30 ~34 barcode counts per species (~7,200 barcodes total) with a standard deviation of 17 (FIG. 5C, bottom panel). The relatively large standard deviation could be attributed to

the decoding error in the fully automated data analysis. Our study demonstrated that 216 barcode species were successfully constructed and resolved (FIG. 5D).

Example 5: Super-Resolution Barcode Probes

5 Barcodes with higher spatial information density were also generated using geometrically encoded super-resolution barcodes with fluorescent features spaced by ~100-nm.

 As a feasibility demonstration of the latter approach, we applied DNA-PAINT³¹, a recently developed super-resolution fluorescence technique, to image the
10 barcodes. Over the last years, several techniques have been developed that allow imaging beyond the diffraction limit using far-field fluorescence microscopy⁴⁰⁻⁴⁴. In most super-resolution implementations, fluorophores are switched between fluorescence ON- and OFF-states, so that individual molecules can be localized consecutively. In methods relying on targeted readout schemes such as in Stimulated Emission Depletion
15 Microscopy⁴⁵ (STED) or other Reversible Saturable Optical Fluorescence Transitions⁴⁰ (RESOLFT) techniques, fluorescence emission is actively confined to an area below the diffraction limit. Switching of fluorescent molecules can also be carried out stochastically such as in (direct) Stochastic Optical Reconstruction Microscopy^{46,47} (STORM, dSTORM), Photoactivated Localization Microscopy⁴⁸ (PALM) and Blink
20 Microscopy⁴⁹ (BM) where most fluorescent molecules are “prepared” in a dark state and only stochastically switched on to emit fluorescence. In Point Accumulation for Imaging in Nanoscale Topography⁵⁰ (PAINT), fluorescence switching is obtained by targeting a surface with fluorescent molecules. In all stochastic approaches, fluorescence from single molecules is localized^{51,52} in a diffraction-limited area to yield super-resolved images.
25 DNA-PAINT uses transient binding of fluorescently labeled oligonucleotides (imager strands) to complementary “docking” strands on DNA nanostructures to obtain switching between a fluorescence ON- and OFF-state, which is necessary for localization-based super-resolution microscopy (cf. FIG. 6A). By adjusting the length of the imager/docking strand duplex and the concentration of imager strands in solution,
30 fluorescence ON- and OFF-times can be tuned independently.

 For this study, we extended the DNA-PAINT technique to three-color imaging using orthogonal imager strand sequences coupled to three spectrally distinct dyes

(Atto488 for blue, Cy3b for green and Atto655 for red excitation). To demonstrate the feasibility of the three-color super-resolution barcode system, we designed a DNA nanotube monomer with 4 binding zones in a symmetric arrangement. The neighboring zones were separated by ~114 nm (i.e., well below the diffraction limit). Each binding zone consists of 18 staple strands, which can be extended to display three groups of orthogonal sequences (six per group) for the red, green or blue imager strands to bind. As a proof-of-principle experiment, we designed five different barcodes (FIG. 6A and top panel of B). The bottom panel of FIG. 6B shows the super-resolution reconstruction of the five barcodes for each channel separately as well as an overlay of all channels. FIG. 6C shows a larger area containing all five barcodes. The unique pattern of the barcodes in all three channels can be resolved. Some barcodes moved during the sequential imaging of all three color channels, but were still resolvable. Imaging could be improved by alternating excitation and faster image acquisition to prevent this effect. The transient, repetitive binding of imager strands to docking sequences on the nanotube not only creates the necessary “blinking” behavior for localization but also makes the imaging protocol more robust, as DNA-PAINT is not prone to photo-bleaching or incorrectly labeled strands. With the microscope setup we used, DNA-PAINT provides a resolution of ~46 nm (FWHM of a Gaussian fit to the reconstructed PSF) in the red, ~25 nm in the green and ~29 nm in the blue channel. The lower resolution in the red imaging channel is a result from weaker laser excitation power. When using a higher power TIRF system, a resolution of 24 nm, similar to the green and blue channel can be obtained. The obtainable resolution and imaging specificity suggests that 6 positions on one nanotube monomer could be robustly resolved while keeping the geometrical asymmetry of the barcode, which would lead to $6^7 = 279,936$ possible different barcodes. Furthermore the modularity of the nanotube design enables the customized reengineering of barcodes with inter-zone distances tailored to the resolving power of the used microscope, thus making it applicable for a wide range of microscope setups.

Example 6: In Situ Labeling

In a proof-of-principle experiment, the GRG barcode was used to tag wild-type *Candida albicans* yeast. The yeast cells were first mixed with a biotinylated polyclonal antibody specific to *C. albicans*, then coated with a layer of streptavidin, and finally

incubated with biotinylated GRG barcodes (FIG. 7A). TIRF microscopy revealed the barcodes attached to the bottom surface of the yeast cells (FIG. 7B, top panel). While some of the nanotubes landed awkwardly on the uneven cell walls of the yeast cells, a number of GRG barcodes can be clearly visualized. In contrast, no barcode tagging was
5 observed when non-biotinylated antibodies or barcodes were used to treat the yeasts (FIG. 7B, bottom panel), suggesting that little to no non-specific interaction existed between the barcode and the cell surface.

Example 7: Non-Linear Labeled Nanostructures

10 DNA nanostructures with non-linear geometry could be assembled to generate more sophisticated barcodes. FIG. 8 shows an example where three ~400 nm DNA tubes were linked to the outer edge of a ~60 nm DNA ring through hybridization between the staple extensions (FIG. 8A, inset). Fluorescently labeling the ring and the far end of the nanotubes generated a three-point-star-like structure clearly resolvable under
15 fluorescence microscopy. TIRF microscopy and TEM studies (FIG. 8B) revealed that about 50% of successfully folded barcodes featured three nanotubes surrounding the ring with roughly 120° angle between each other as designed, while many other barcodes had significantly biased angles between neighboring nanotubes due to the semi-flexible double-stranded DNA linker between the ring and the nanotubes. It is conceivable that
20 using similar design to connect three identical “satellite” linear barcodes to a central hub (here the three satellite barcodes may share the hub as a common fluorescently labeled zone), one can construct barcodes with triplicated encoding redundancy that feature outstanding reliability. In addition, more rigid linkers between the ring and the protrusions (e.g., multi-helix DNA with strand crossovers) could be employed to enforce
25 better-defined barcode geometry.

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EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more
than routine experimentation, many equivalents of the specific embodiments of the
subject matter described herein. Such equivalents are intended to be encompassed by the
25 following claims.

All publications, patents, and patent applications cited in this specification are
herein incorporated by reference to the same extent as if each individual publication or
patent application was specifically and individually indicated to be incorporated by
reference.

30 What is claimed is:

[illegible]

- 41 -

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[illegible]

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617,1,615], [1,618,1,616], [1,619,1,617], [1,620,1,618], [1,621,1,619], [1,622,1,620], [1,623,1,621], [1,624,1,622], [1,625,1,623], [1,626,1,624], [1,627,1,625], [1,628,1,626], [1,629,1,627], [1,630,1,628], [1,631,1,629], [1,632,1,630], [1,633,1,631], [1,634,1,632], [1,635,1,633], [1,636,1,634], [1,637,1,635], [1,638,1,636], [1,639,1,637], [1,640,1,638], [1,641,1,639], [1,642,1,640], [1,643,1,641], [1,644,1,642], [1,645,1,643], [2,645,1,644], [1,647,2,646], [1,648,1,646], [1,649,1,647], [1,650,1,648], [1,651,1,649], [1,652,1,650], [1,653,1,651], [1,654,1,652], [1,655,1,653], [1,656,1,654], [1,657,1,655], [1,658,1,656], [1,659,1,657], [1,660,1,658], [1,661,1,659], [1,662,1,660], [1,663,1,661], [1,664,1,662], [1,665,1,663], [1,666,1,664], [1,667,1,665], [1,668,1,666], [1,669,1,667], [1,670,1,668], [1,671,1,669], [1,672,1,670], [1,673,1,671], [1,674,1,672], [1,675,1,673], [1,676,1,674], [1,677,1,675], [1,678,1,676], [1,679,1,677], [1,680,1,678], [1,681,1,679], [1,682,1,680], [1,683,1,681], [1,684,1,682], [1,685,1,683], [1,686,1,684], [1,687,1,685], [1,688,1,686], [1,689,1,687], [1,690,1,688], [1,691,1,689], [1,692,1,690], [1,693,1,691], [1,694,1,692], [1,695,1,693], [1,696,1,694], [1,697,1,695], [1,698,1,696], [1,699,1,697], [1,700,1,698], [1,701,1,699], [1,702,1,700], [1,703,1,701], [1,704,1,702], [1,705,1,703], [1,706,1,704], [1,707,1,705], [1,708,1,706], [1,709,1,707], [1,710,1,708], [1,711,1,709], [1,712,1,710], [1,713,1,711], [1,714,1,712], [1,715,1,713], [1,716,1,714], [1,717,1,715], [1,718,1,716], [1,719,1,717], [1,720,1,718], [1,721,1,719], [1,722,1,720], [1,723,1,721], [1,724,1,722], [1,725,1,723], [1,726,1,724], [1,727,1,725], [1,728,1,726], [1,729,1,727], [1,730,1,728], [1,731,1,729], [1,732,1,730], [1,733,1,731], [1,734,1,732], [1,735,1,733], [1,736,1,734], [1,737,1,735], [1,738,1,736], [1,739,1,737], [1,740,1,738], [1,741,1,739], [1,742,1,740], [1,743,1,741], [1,744,1,742], [1,745,1,743], [1,746,1,744], [1,747,1,745], [1,748,1,746], [1,749,1,747], [1,750,1,748], [1,751,1,749], [1,752,1,750], [1,753,1,751], [1,754,1,752], [1,755,1,753], [1,756,1,754], [1,757,1,755], [1,758,1,756], [1,759,1,757], [1,760,1,758], [1,761,1,759], [1,762,1,760], [1,763,1,761], [1,764,1,762], [1,765,1,763], [1,766,1,764], [1,767,1,765], [1,768,1,766], [1,769,1,767], [1,770,1,768], [1,771,1,769], [1,772,1,770], [1,773,1,771], [1,774,1,772], [1,775,1,773], [1,776,1,774], [1,777,1,775], [1,778,1,776], [1,779,1,777], [1,780,1,778], [1,781,1,779], [1,782,1,780], [1,783,1,781], [1,784,1,782], [1,785,1,783], [1,786,1,784], [1,787,1,785], [1,788,1,786], [1,789,1,787], [1,790,1,788], [1,791,1,789], [1,792,1,790], [1,793,1,791], [1,794,1,792], [1,795,1,793], [1,796,1,794], [1,797,1,795], [1,798,1,796], [1,799,1,797], [1,800,1,798], [1,801,1,799], [1,802,1,800], [1,803,1,801], [1,804,1,802], [1,805,1,803], [1,806,1,804], [1,807,1,805], [1,808,1,806], [1,809,1,807], [1,810,1,808], [1,811,1,809], [1,812,1,810], [1,813,1,811], [1,814,1,812], [1,815,1,813], [1,816,1,814], [1,817,1,815], [1,818,1,816], [1,819,1,817], [1,820,1,818], [1,821,1,819], [1,822,1,820], [1,823,1,821], [1,824,1,822], [1,825,1,823], [1,826,1,824], [1,827,1,825], [1,828,1,826], [1,829,1,827], [1,830,1,828], [1,831,1,829], [1,832,1,830], [1,833,1,831], [1,834,1,832], [1,835,1,833], [1,836,1,834], [1,837,1,835], [1,838,1,836], [1,839,1,837], [1,840,1,838], [1,841,1,839], [1,842,1,840], [1,843,1,841], [1,844,1,842], [1,845,1,843], [1,846,1,844], [1,847,1,845], [1,848,1,846], [1,849,1,847], [1,850,1,848], [1,851,1,849], [1,852,1,850], [1,853,1,851], [1,854,1,852], [1,855,1,853], [1,856,1,854], [1,857,1,855], [1,858,1,856], [1,859,1,857], [1,860,1,858], [1,861,1,859], [1,862,1,860], [1,863,1,861], [1,864,1,862], [1,865,1,863], [1,866,1,864], [1,867,1,865], [1,868,1,866], [1,869,1,867], [1,870,1,868], [1,871,1,869], [1,872,1,870], [1,873,1,871], [1,874,1,872], [1,875,1,873], [1,876,1,874], [1,877,1,875], [1,878,1,876], [1,879,1,877], [1,880,1,878], [1,881,1,879], [1,882,1,880], [1,883,1,881], [1,884,1,882], [1,885,1,883], [1,886,1,884], [1,887,1,885], [1,888,1,886], [1,889,1,887], [1,890,1,888], [1,891,1,889], [1,892,1,890], [1,893,1,891], [1,894,1,892], [1,895,1,893], [1,896,1,894], [1,897,1,895], [1,898,1,896], [1,899,1,897], [1,900,1,898], [1

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[2,888,2,886], [2,889,2,887], [2,890,2,888], [2,891,2,889], [2,892,2,890], [2,893,2,891], [2,894,2,892], [2,895,2,893], [-1,-1,2,894], [2,897,-1,-1], [2,898,2,896], [2,899,2,897], [2,900,2,898], [2,901,2,899], [2,902,2,900], [2,903,2,901], [2,904,2,902], [2,905,2,903], [2,906,2,904], [2,907,2,905], [2,908,2,906], [2,909,2,907], [3,909,2,908], [2,911,3,910], [2,912,2,910], [2,913,2,911], [2,914,2,912], [2,915,2,913], [2,916,2,914], [2,917,2,915], [2,918,2,916], [2,919,2,917], [2,920,2,918], [2,921,2,919], [2,922,2,920], [2,923,2,921], [1,923,2,922], [2,925,1,924], [2,926,2,924], [2,927,2,925], [2,928,2,926], [2,929,2,927], [2,930,2,928], [2,931,2,929], [2,932,2,930], [2,933,2,931], [2,934,2,932], [2,935,2,933], [2,936,2,934], [2,937,2,935], [-1,-1,2,936], [2,939,-1,-1], [2,940,2,938], [2,941,2,939], [2,942,2,940], [2,943,2,941], [2,944,2,942], [2,945,2,943], [2,946,2,944], [2,947,2,945], [2,948,2,946], [2,949,2,947], [2,950,2,948], [2,951,2,949], [3,951,2,950], [2,953,3,952], [2,954,2,952], [2,955,2,953], [2,956,2,954], [2,957,2,955], [2,958,2,956], [2,959,2,957], [2,960,2,958], [2,961,2,959], [2,962,2,960], [2,963,2,961], [2,964,2,962], [2,965,2,963], [1,965,2,964], [2,967,1,966], [2,968,2,966], [2,969,2,967], [2,970,2,968], [2,971,2,969], [2,972,2,970], [2,973,2,971], [2,974,2,972], [2,975,2,973], [2,976,2,974], [2,977,2,975], [2,978,2,976], [2,979,2,977], [-1,-1,2,978], [2,981,-1,-1], [2,982,2,980], [2,983,2,981], [2,984,2,982], [2,985,2,983], [2,986,2,984], [2,987,2,985], [2,988,2,986], [2,989,2,987], [2,990,2,988], [2,991,2,989], [2,992,2,990], [2,993,2,991], [3,993,2,992], [2,995,3,994], [2,996,2,994], [2,997,2,995], [2,998,2,996], [2,999,2,997], [2,1000,2,998], [2,1001,2,999], [2,1002,2,1000], [2,1003,2,1001], [2,1004,2,1002], [2,1005,2,1003], [2,1006,2,1004], [2,1007,2,1005], [1,1007,2,1006], [2,1009,1,1008], [2,1010,2,1008], [2,1011,2,1009], [2,1012,2,1010], [2,1013,2,1011], [2,1014,2,1012], [2,1015,2,1013], [2,1016,2,1014], [2,1017,2,1015], [2,1018,2,1016], [2,1019,2,1017], [2,1020,2,1018], [2,1021,2,1019], [-1,-1,2,1020], [2,1023,-1,-1], [2,1024,2,1022], [2,1025,2,1023], [2,1026,2,1024], [2,1027,2,1025], [2,1028,2,1026], [2,1029,2,1027], [2,1030,2,1028], [2,1031,2,1029], [2,1032,2,1030], [2,1033,2,1031], [2,1034,2,1032], [2,1035,2,1033], [3,1035,2,1034], [2,1037,3,1036], [2,1038,2,1036], [2,1039,2,1037], [2,1040,2,1038], [2,1041,2,1039], [2,1042,2,1040], [2,1043,2,1041], [2,1044,2,1042], [2,1045,2,1043], [2,1046,2,1044], [2,1047,2,1045], [2,1048,2,1046], [2,1049,2,1047], [1,1049,2,1048], [2,1051,1,1050], [2,1052,2,1050], [2,1053,2,1051], [2,1054,2,1052], [2,1055,2,1053], [2,1056,2,1054], [2,1057,2,1055], [2,1058,2,1056], [2,1059,2,1057], [2,1060,2,1058], [2,1061,2,1059], [2,1062,2,1060], [2,1063,2,1061], [-1,-1,2,1062], [2,1065,-1,-1], [2,1066,2,1064], [2,1067,2,1065], [2,1068,2,1066], [2,1069,2,1067], [2,1070,2,1068], [2,1071,2,1069], [2,1072,2,1070], [2,1073,2,1071], [2,1074,2,1072], [2,1075,2,1073], [2,1076,2,1074], [2,1077,2,1075], [3,1077,2,1076], [2,1079,3,1078], [2,1080,2,1078], [2,1081,2,1079], [2,1082,2,1080], [2,1083,2,1081], [2,1084,2,1082], [2,1085,2,1083], [2,1086,2,1084], [2,1087,2,1085], [2,1088,2,1086], [2,1089,2,1087], [2,1090,2,1088], [2,1091,2,1089], [1,1091,2,1090], [2,1093,1,1092], [2,1094,2,1092], [2,1095,2,1093], [2,1096,2,1094], [2,1097,2,1095], [2,1098,2,1096], [2,1099,2,1097], [2,1100,2,1098], [2,1101,2,1099], [2,1102,2,1100], [2,1103,2,1101], [2,1104,2,1102], [2,1105,2,1103], [-1,-1,2,1104], [2,1107,-1,-1], [2,1108,2,1106], [2,1109,2,1107], [2,1110,2,1108], [2,1111,2,1109], [2,1112,2,1110], [2,1113,2,1111], [2,1114,2,1112], [2,1115,2,1113], [2,1116,2,1114], [2,1117,2,1115], [2,1118,2,1116], [2,1119,2,1117], [3,1119,2,1118], [2,1121,3,1120], [2,1122,2,1120], [2,1123,2,1121], [2,1124,2,1122], [2,1125,2,1123], [2,1126,2,1124], [2,1127,2,1125], [2,1128,2,1126], [2,1129,2,1127], [2,1130,2,1128], [2,1131,2,1129], [2,1132,2,1130], [2,1133,2,1131], [1,1133,2,1132], [2,1135,1,1134], [2,1136,2,1134], [2,1137,2,1135], [2,1138,2,1136], [2,1139,2,1137], [2,1140,2,1138], [2,1141,2,1139], [2,1142,2,1140], [2,1143,2,1141], [2,1144,2,1142], [2,11

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[2,243], [2,242,2,244], [2,243,2,245], [2,244,2,246], [2,245,2,247], [2,246,2,248], [2,247,2,249], [2,248,2,250], [2,249,2,251], [2,250,2,252], [2,251,2,253], [2,252,2,254], [2,253,2,255], [2,254,2,256], [2,255,2,257], [2,256,2,258], [2,257,2,259], [2,258,2,260], [2,259,2,261], [2,260,2,262], [2,261,2,263], [2,262,2,264], [2,263,2,265], [2,264,2,266], [2,265,2,267], [2,266,2,268], [2,267,2,269], [2,268,2,270], [2,269,2,271], [2,270,2,272], [2,271,2,273], [2,272,2,274], [2,273,2,275], [2,274,2,276], [2,275,2,277], [2,276,2,278], [2,277,2,279], [2,278,2,280], [2,279,2,281], [2,280,2,282], [2,281,2,283], [2,282,2,284], [2,283,2,285], [2,284,2,286], [2,285,2,287], [2,286,2,288], [2,287,2,289], [2,288,2,290], [2,289,2,291], [2,290,2,292], [2,291,2,293], [2,292,2,294], [2,293,2,295], [2,294,2,296], [2,295,2,297], [2,296,2,298], [2,297,2,299], [2,298,2,300], [2,299,2,301], [2,300,2,302], [2,301,2,303], [2,302,2,304], [2,303,2,305], [2,304,2,306], [2,305,2,307], [2,306,2,308], [2,307,2,309], [2,308,2,310], [2,309,2,311], [2,310,2,312], [2,311,2,313], [2,312,2,314], [2,313,2,315], [2,314,2,316], [2,315,2,317], [2,316,2,318], [2,317,2,319], [2,318,2,320], [2,319,2,321], [2,320,2,322], [2,321,2,323], [2,322,2,324], [2,323,2,325], [2,324,2,326], [2,325,2,327], [2,326,2,328], [2,327,2,329], [2,328,2,330], [2,329,2,331], [2,330,2,332], [2,331,2,333], [2,332,2,334], [2,333,2,335], [2,334,2,336], [2,335,2,337], [2,336,2,338], [2,337,2,339], [2,338,2,340], [2,339,2,341], [2,340,2,342], [2,341,2,343], [2,342,2,344], [2,343,2,345], [2,344,2,346], [2,345,2,347], [2,346,2,348], [2,347,2,349], [2,348,2,350], [2,349,2,351], [2,350,2,352], [2,351,2,353], [2,352,2,354], [2,353,2,355], [2,354,2,356], [2,355,2,357], [2,356,2,358], [2,357,2,359], [2,358,2,360], [2,359,2,361], [2,360,2,362], [2,361,2,363], [2,362,2,364], [2,363,2,365], [2,364,2,366], [2,365,2,367], [2,366,2,368], [2,367,2,369], [2,368,2,370], [2,369,2,371], [2,370,2,372], [2,371,2,373], [2,372,2,374], [2,373,2,375], [2,374,2,376], [2,375,2,377], [2,376,2,378], [2,377,2,379], [2,378,2,380], [2,379,2,381], [2,380,2,382], [2,381,2,383], [2,382,2,384], [2,383,2,385], [2,384,2,386], [2,385,2,387], [2,386,2,388], [2,387,2,389], [2,388,2,390], [2,389,2,391], [2,390,2,392], [2,391,2,393], [2,392,2,394], [2,393,2,395], [2,394,2,396], [2,395,2,397], [2,396,2,398], [2,397,2,399], [2,398,2,400], [2,399,2,401], [2,400,2,402], [2,401,2,403], [2,402,2,404], [2,403,2,405], [2,404,2,406], [2,405,2,407], [2,406,2,408], [2,407,2,409], [2,408,2,410], [2,409,2,411], [2,410,2,412], [2,411,2,413], [2,412,2,414], [2,413,2,415], [2,414,2,416], [2,415,2,417], [2,416,2,418], [2,417,2,419], [2,418,2,420], [2,419,2,421], [2,420,2,422], [2,421,2,423], [2,422,2,424], [2,423,2,425], [2,424,2,426], [2,425,2,427], [2,426,2,428], [2,427,2,429], [2,428,2,430], [2,429,2,431], [2,430,2,432], [2,431,2,433], [2,432,2,434], [2,433,2,435], [2,434,2,436], [2,435,2,437], [2,436,2,438], [2,437,2,439], [2,438,2,440], [2,439,2,441], [2,440,2,442], [2,441,2,443], [2,442,2,444], [2,443,2,445], [2,444,2,446], [2,445,2,447], [2,446,2,448], [2,447,2,449], [2,448,2,450], [2,449,2,451], [2,450,2,452], [2,451,2,453], [2,452,2,454], [2,453,2,455], [2,454,2,456], [2,455,2,457], [2,456,2,458], [2,457,2,459], [2,458,2,460], [2,459,2,461], [2,460,2,462], [2,461,2,463], [2,462,2,464], [2,463,2,465], [2,464,2,466], [2,465,2,467], [2,466,2,468], [2,467,2,469], [2,468,2,470], [2,469,2,471], [2,470,2,472], [2,471,2,473], [2,472,2,474], [2,473,2,475], [2,474,2,476], [2,475,2,477], [2,476,2,478], [2,477,2,479], [2,478,2,480], [2,479,2,481], [2,480,2,482], [2,481,2,483], [2,482,2,484], [2,483,2,485], [2,484,2,486], [2,485,2,487], [2,486,2,488], [2,487,2,489], [2,488,2,490], [2,489,2,491], [2,490,2,492], [2,491,2,493], [2,492,2,494], [2,493,2,495], [2,494,2,496], [2,495,2,497], [2,496,2,498], [2,497,2,499], [2,498,2,500], [2,499,2,501], [2,500,2,502], [2,501,2,503], [2,502,2,504], [2,503,2,505], [2,504,2,506], [2,505,2,507], [2,506,2,508], [2,507,2,509], [2,508,2,510], [2,509,2,511], [2,510,2,512], [2,511,2,513], [2,512,2,514], [2,513,2,515], [2,514,2,516], [2,515,2,517], [2,516,2,518], [2,517,2,519], [2,518,2,520], [2,519,2,521], [2,520,2,522], [2,521,2,523], [2,522,2,524], [2,523,2,525], [2,524,2,526], [2,525

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1,5,897],[5,896,5,898],[5,897,5,899],[5,898,5,900],[5,899,5,901],[5,900,5,902],[5,901,5,903],[5,902,5,904],[5,903,5,905],[5,904,5,906],[5,905,5,907],[5,906,5,908],[5,907,5,909],[5,908,0,909],[0,910,5,911],[5,910,5,912],[5,911,5,913],[5,912,5,914],[5,913,5,915],[5,914,5,916],[5,915,5,917],[5,916,5,918],[5,917,5,919],[5,918,5,920],[5,919,5,921],[5,920,5,922],[5,921,5,923],[5,922,4,923],[4,924,5,925],[5,924,5,926],[5,925,5,927],[5,926,5,928],[5,927,5,929],[5,928,5,930],[5,929,5,931],[5,930,5,932],[5,931,5,933],[5,932,5,934],[5,933,5,935],[5,934,5,936],[5,935,5,937],[5,936,-1,-1],[-1,-1,5,939],[5,938,5,940],[5,939,5,941],[5,940,5,942],[5,941,5,943],[5,942,5,944],[5,943,5,945],[5,944,5,946],[5,945,5,947],[5,946,5,948],[5,947,5,949],[5,948,5,950],[5,949,5,951],[5,950,0,951],[0,952,5,953],[5,952,5,954],[5,953,5,955],[5,954,5,956],[5,955,5,957],[5,956,5,958],[5,957,5,959],[5,958,5,960],[5,959,5,961],[5,960,5,962],[5,961,5,963],[5,962,5,964],[5,963,5,965],[5,964,4,965],[4,966,5,967],[5,966,5,968],[5,967,5,969],[5,968,5,970],[5,969,5,971],[5,970,5,972],[5,971,5,973],[5,972,5,974],[5,973,5,975],[5,974,5,976],[5,975,5,977],[5,976,5,978],[5,977,5,979],[5,978,-1,-1],[-1,-1,5,981],[5,980,5,982],[5,981,5,983],[5,982,5,984],[5,983,5,985],[5,984,5,986],[5,985,5,987],[5,986,5,988],[5,987,5,989],[5,988,5,990],[5,989,5,991],[5,990,5,992],[5,991,5,993],[5,992,0,993],[0,994,5,995],[5,994,5,996],[5,995,5,997],[5,996,5,998],[5,997,5,999],[5,998,5,1000],[5,999,5,1001],[5,1000,5,1002],[5,1001,5,1003],[5,1002,5,1004],[5,1003,5,1005],[5,1004,5,1006],[5,1005,5,1007],[5,1006,4,1007],[4,1008,5,1009],[5,1008,5,1010],[5,1009,5,1011],[5,1010,5,1012],[5,1011,5,1013],[5,1012,5,1014],[5,1013,5,1015],[5,1014,5,1016],[5,1015,5,1017],[5,1016,5,1018],[5,1017,5,1019],[5,1018,5,1020],[5,1019,5,1021],[5,1020,-1,-1],[-1,-1,5,1023],[5,1022,5,1024],[5,1023,5,1025],[5,1024,5,1026],[5,1025,5,1027],[5,1026,5,1028],[5,1027,5,1029],[5,1028,5,1030],[5,1029,5,1031],[5,1030,5,1032],[5,1031,5,1033],[5,1032,5,1034],[5,1033,5,1035],[5,1034,0,1035],[0,1036,5,1037],[5,1036,5,1038],[5,1037,5,1039],[5,1038,5,1040],[5,1039,5,1041],[5,1040,5,1042],[5,1041,5,1043],[5,1042,5,1044],[5,1043,5,1045],[5,1044,5,1046],[5,1045,5,1047],[5,1046,5,1048],[5,1047,5,1049],[5,1048,4,1049],[4,1050,5,1051],[5,1050,5,1052],[5,1051,5,1053],[5,1052,5,1054],[5,1053,5,1055],[5,1054,5,1056],[5,1055,5,1057],[5,1056,5,1058],[5,1057,5,1059],[5,1058,5,1060],[5,1059,5,1061],[5,1060,5,1062],[5,1061,5,1063],[5,1062,-1,-1],[-1,-1,5,1065],[5,1064,5,1066],[5,1065,5,1067],[5,1066,5,1068],[5,1067,5,1069],[5,1068,5,1070],[5,1069,5,1071],[5,1070,5,1072],[5,1071,5,1073],[5,1072,5,1074],[5,1073,5,1075],[5,1074,5,1076],[5,1075,5,1077],[5,1076,0,1077],[0,1078,5,1079],[5,1078,5,1080],[5,1079,5,1081],[5,1080,5,1082],[5,1081,5,1083],[5,1082,5,1084],[5,1083,5,1085],[5,1084,5,1086],[5,1085,5,1087],[5,1086,5,1088],[5,1087,5,1089],[5,1088,5,1090],[5,1089,5,1091],[5,1090,4,1091],[4,1092,5,1093],[5,1092,5,1094],[5,1093,5,1095],[5,1094,5,1096],[5,1095,5,1097],[5,1096,5,1098],[5,1097,5,1099],[5,1098,5,1100],[5,1099,5,1101],[5,1100,5,1102],[5,1101,5,1103],[5,1102,5,1104],[5,1103,5,1105],[5,1104,-1,-1],[-1,-1,5,1107],[5,1106,5,1108],[5,1107,5,1109],[5,1108,5,1110],[5,1109,5,1111],[5,1110,5,1112],[5,1111,5,1113],[5,1112,5,1114],[5,1113,5,1115],[5,1114,5,1116],[5,1115,5,1117],[5,1116,5,1118],[5,1117,5,1119],[5,1118,0,1119],[0,1120,5,1121],[5,1120,5,1122],[5,1121,5,1123],[5,1122,5,1124],[5,1123,5,1125],[5,1124,5,1126],[5,1125,5,1127],[5,1126,5,1128],[5,1127,5,1129],[5,1128,5,1130],[5,1129,5,1131],[5,1130,5,1132],[5,1131,5,1133],[5,1132,4,1133],[4,1134,5,1135],[5,1134,5,1136],[5,1135,5,1137],[5,1136,5,1138],[5,1137,5,1139],[5,1138,5,1140],[5,1139,5,1141],[5,1140,5,1142],[5,1141,5,1143],[5,1142,5,1144],[5,1143,5,1145],[5,1144,5,1146],[5,1145,5,1147],[5,1146,-1,-1],[-1,-1,5,1149],[5,1148,5,1150],[5,1149,5,1151],[5,1150,5,1152],[5,1151,5,1153],[

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[illegible]

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7,5,305], [5,308,5,306], [5,309,5,307], [5,310,5,308], [5,311,5,309], [5,312,5,310], [5,313,5,311], [5,314,5,312], [5,315,5,313], [5,316,5,314], [5,317,5,315], [5,318,5,316], [5,319,5,317], [5,320,5,318], [5,321,5,319], [5,322,5,320], [5,323,5,321], [5,324,5,322], [5,325,5,323], [5,326,5,324], [5,327,5,325], [5,328,5,326], [5,329,5,327], [5,330,5,328], [5,331,5,329], [5,332,5,330], [5,333,5,331], [5,334,5,332], [5,335,5,333], [5,336,5,334], [5,337,5,335], [5,338,5,336], [5,339,5,337], [5,340,5,338], [5,341,5,339], [5,342,5,340], [5,343,5,341], [5,344,5,342], [5,345,5,343], [5,346,5,344], [5,347,5,345], [5,348,5,346], [5,349,5,347], [5,350,5,348], [5,351,5,349], [5,352,5,350], [5,353,5,351], [5,354,5,352], [5,355,5,353], [5,356,5,354], [5,357,5,355], [5,358,5,356], [5,359,5,357], [5,360,5,358], [5,361,5,359], [5,362,5,360], [5,363,5,361], [5,364,5,362], [5,365,5,363], [5,366,5,364], [5,367,5,365], [5,368,5,366], [5,369,5,367], [5,370,5,368], [5,371,5,369], [5,372,5,370], [5,373,5,371], [5,374,5,372], [5,375,5,373], [5,376,5,374], [5,377,5,375], [5,378,5,376], [5,379,5,377], [5,380,5,378], [5,381,5,379], [5,382,5,380], [5,383,5,381], [5,384,5,382], [5,385,5,383], [5,386,5,384], [5,387,5,385], [5,388,5,386], [5,389,5,387], [5,390,5,388], [5,391,5,389], [5,392,5,390], [5,393,5,391], [5,394,5,392], [5,395,5,393], [5,396,5,394], [5,397,5,395], [5,398,5,396], [5,399,5,397], [5,400,5,398], [5,401,5,399], [5,402,5,400], [5,403,5,401], [5,404,5,402], [5,405,5,403], [5,406,5,404], [5,407,5,405], [5,408,5,406], [5,409,5,407], [5,410,5,408], [5,411,5,409], [5,412,5,410], [5,413,5,411], [5,414,5,412], [5,415,5,413], [5,416,5,414], [5,417,5,415], [5,418,5,416], [5,419,5,417], [5,420,5,418], [5,421,5,419], [5,422,5,420], [5,423,5,421], [5,424,5,422], [5,425,5,423], [5,426,5,424], [5,427,5,425], [5,428,5,426], [5,429,5,427], [5,430,5,428], [5,431,5,429], [5,432,5,430], [5,433,5,431], [5,434,5,432], [5,435,5,433], [5,436,5,434], [5,437,5,435], [5,438,5,436], [5,439,5,437], [5,440,5,438], [5,441,5,439], [5,442,5,440], [5,443,5,441], [5,444,5,442], [5,445,5,443], [5,446,5,444], [5,447,5,445], [5,448,5,446], [5,449,5,447], [5,450,5,448], [5,451,5,449], [5,452,5,450], [5,453,5,451], [5,454,5,452], [5,455,5,453], [5,456,5,454], [5,457,5,455], [5,458,5,456], [5,459,5,457], [5,460,5,458], [5,461,5,459], [5,462,5,460], [5,463,5,461], [5,464,5,462], [5,465,5,463], [5,466,5,464], [5,467,5,465], [5,468,5,466], [5,469,5,467], [5,470,5,468], [5,471,5,469], [5,472,5,470], [5,473,5,471], [5,474,5,472], [5,475,5,473], [5,476,5,474], [5,477,5,475], [5,478,5,476], [5,479,5,477], [5,480,5,478], [5,481,5,479], [5,482,5,480], [5,483,5,481], [5,484,5,482], [5,485,5,483], [5,486,5,484], [5,487,5,485], [5,488,5,486], [5,489,5,487], [5,490,5,488], [5,491,5,489], [5,492,5,490], [5,493,5,491], [5,494,5,492], [5,495,5,493], [5,496,5,494], [5,497,5,495], [5,498,5,496], [5,499,5,497], [5,500,5,498], [5,501,5,499], [5,502,5,500], [5,503,5,501], [5,504,5,502], [5,505,5,503], [5,506,5,504], [5,507,5,505], [5,508,5,506], [5,509,5,507], [5,510,5,508], [5,511,5,509], [5,512,5,510], [5,513,5,511], [5,514,5,512], [5,515,5,513], [5,516,5,514], [5,517,5,515], [5,518,5,516], [5,519,5,517], [5,520,5,518], [5,521,5,519], [5,522,5,520], [5,523,5,521], [5,524,5,522], [5,525,5,523], [5,526,5,524], [5,527,5,525], [5,528,5,526], [5,529,5,527], [5,530,5,528], [5,531,5,529], [5,532,5,530], [5,533,5,531], [5,534,5,532], [5,535,5,533], [5,536,5,534], [5,537,5,535], [5,538,5,536], [5,539,5,537], [5,540,5,538], [5,541,5,539], [5,542,5,540], [5,543,5,541], [5,544,5,542], [5,545,5,543], [5,546,5,544], [5,547,5,545], [5,548,5,546], [5,549,5,547], [5,550,5,548], [5,551,5,549], [5,552,5,550], [5,553,5,551], [5,554,5,552], [5,555,5,553], [5,556,5,554], [5,557,5,555], [5,558,5,556], [5,559,5,557], [5,560,5,558], [5,561,5,559], [5,562,5,560], [5,563,5,561], [5,564,5,562], [5,565,5,563], [5,566,5,564], [5,567,5,565], [5,568,5,566], [5,569,5,567], [5,570,5,568], [5,571,5,569], [5,572,5,570], [5,573,5,571], [5,574,5,572], [5,575,5,573], [5,576,5,574], [5,577,5,575], [5,578,5,576], [5,579,5,577], [5,580,5,578], [5,581,5,579], [5,582,5,580], [5,583,5,581], [5,584,5,582], [5,585,5,583], [5,586,5,584], [5,587,5,585], [5,588,5,586], [5,589,5,587], [5,590,5,588], [5,5

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[illegible]

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CLAIMS

1. A method of detecting a target comprising:
contacting a sample with a nucleic acid barcode probe, and
determining whether the nucleic acid barcode probe binds to one or more
5 components in the sample,
wherein binding of the nucleic acid barcode probe to one or more components of
the sample indicates presence of a target in the sample, and wherein the nucleic acid
barcode probe comprises a nucleic acid nanostructure comprising a target binding moiety
and at least two fluorescently labeled regions.
10
2. The method of claim 1, further comprising identifying the target based on the
color and/or orientation of the fluorescently labeled regions of the nucleic acid barcode
probe bound to one or more components of the sample.
- 15 3. The method of claim 1 or 2, wherein whether the nucleic acid barcode probe
binds to one or more components in the sample comprises contacting the nucleic acid
barcode probe with soluble, transiently binding fluorophore-bearing oligonucleotides.
4. The method of claim 1 or 2, wherein the nucleic acid barcode probe comprises
20 stably bound fluorophore-bearing oligonucleotides.
5. A method of detecting a target comprising
contacting the target with a nucleic acid barcode probe, under conditions
sufficient for the target to bind to the nucleic acid barcode probe;
25 separating the target from material that is not bound to the target; and
detecting the presence of the nucleic acid barcode probe bound to the target,
wherein the nucleic acid barcode probe comprises a nucleic acid nanostructure
comprising a target binding moiety and at least two fluorescently labeled regions.
- 30 6. The method of claim 5, further comprising identifying the target based on the
color and/or orientation of the fluorescently labeled regions of the nucleic acid barcode
probe bound to the target.

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7. The method of claim 5 or 6, wherein detecting the presence of the nucleic acid barcode probe bound to the target comprises contacting the nucleic acid barcode probe with soluble, transiently bound fluorophore-bearing oligonucleotides.
- 5 8. The method of claim 5 or 6, wherein the nucleic acid barcode probe comprises stably bound fluorophore-bearing oligonucleotides.
9. A composition comprising
- 10 a sample, and
- a nucleic acid barcode probe comprising a nucleic acid nanostructure having at least two fluorescently-labeled regions, wherein:
- the locations of each of the fluorescently-labeled regions on the nucleic acid nanostructure are such that a pattern of the fluorescent labels is determinable based on
- 15 the emission of visible light by the fluorescently-labeled regions.
10. The composition of claim 9, wherein the nucleic acid nanostructure comprises a scaffold strand and a plurality of staple strands.
- 20 11. The composition of claim 9 or 10, wherein the fluorescently-labeled regions comprise fluorophore-labeled staple strands.
12. The composition of claim 11, wherein the fluorophore-labeled staple strands comprise (a) a staple domain hybridized to a scaffold strand and (b) a handle domain.
- 25 13. The composition of claim 12, wherein the handle domain is hybridized to a fluorophore-labeled oligonucleotide.
14. The composition of any one of claims 9-13, wherein the nucleic acid
- 30 nanostructure is a DNA nanostructure.
15. The composition of claim 14, wherein the DNA nanostructure is a nanotube.

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16. The composition of any of claims 9-15, wherein the nucleic acid nanostructure comprises at least three fluorescently-labeled regions or at least four fluorescently-labeled regions.
- 5
17. The composition of claim 16, wherein orientation of the at least three or at least four fluorescently labeled regions is determinable based on asymmetric spacing of the fluorescently-labeled regions.
- 10
18. The composition of any of claims 9-17, wherein each of the fluorescently-labeled regions has a center that is located at least about 50 nm or at least about 100 nm from the centers of the other fluorescently-labeled regions.
- 15
19. The composition of any of claims 9-18, wherein each of the fluorescently-labeled regions has a center that is located at least 200 nm from the centers of the other fluorescently-labeled regions.
- 20
20. The composition of any one of claims 9-19, wherein the center of each of the fluorescently-labeled regions is located at least 250 nm from the center of any other fluorescently labeled region.
21. The composition of any one of claims 9-20, wherein the nucleic acid nanostructure further comprises a target binding moiety.
- 25
22. The composition of claim 21, wherein the target binding moiety is a single-stranded nucleic acid.
23. The composition of claim 21, wherein the target binding moiety is an antibody.
- 30
24. The composition of claim 21, wherein the target binding moiety is a protein or peptide.

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25. A method of identifying a target nucleic acid comprising:
contacting the target nucleic acid with a nucleic acid barcode probe of any one of the claims 9-24, under conditions such that the target nucleic acid binds to the nucleic acid barcode probe;
- 5 separating the target nucleic acid from material that is not bound to the target nucleic acid; and
detecting the presence of the nucleic acid barcode probe bound to the target nucleic acid.
- 10 26. A method of identifying a target protein or cell comprising:
contacting the target protein or cell with a nucleic acid barcode probe of any one of claims 9-24, under conditions such that the target protein or cell binds to the nucleic acid barcode probe;
- 15 separating the target protein or cell from material that is not bound to the target protein or cell; and
detecting the presence of the nucleic acid barcode probe bound to the target protein or cell.
- 20 27. A method of identifying a target protein or cell comprising:
contacting the target protein or cell with a nucleic acid barcode probe of any one of claims 9-24, under conditions such that the target protein or cell binds to the nucleic acid barcode probe;
- 25 separating the target protein or cell from material that is not bound to the target protein or cell; and
detecting the presence of the nucleic acid barcode probe bound to the target protein or cell.
28. A method of detecting a target comprising:
contacting a sample with a nucleic acid barcode probe of any one of claims 9-24,
- 30 and
determining whether the nucleic acid barcode probe binds to one or more components in the sample.

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wherein binding of the nucleic acid barcode probe to one or more components in the sample indicates presence of a target in the sample.

29. The method of claim 28, further comprising removing components in the sample
5 that are not bound to the nucleic acid barcode probe following the contacting step.

30. The method of claim 28 or 29, wherein the target is a nucleic acid, a protein, a peptide, or a cell, or a combination thereof.

10 31. The method of any one of claims 25-30, wherein the presence of the nucleic acid barcode probe is detected by fluorescent microscopy.

32. The method of any one of claims 25-30, wherein the presence of the nucleic acid barcode probe is detected without exposing the nucleic acid barcode probe to an electric
15 field.

33. A population of nucleic acid barcode probes, wherein each probe comprises a nucleic acid nanostructure having at least two fluorescently-labeled regions and a target binding moiety,
20 wherein the locations of each of the fluorescently-labeled regions on the nucleic acid nanostructure are such that a pattern of the fluorescent labels of the nucleic acid barcode probe and the identity of the target binding moiety is determinable based on the emission of visible light by the fluorescently-labeled regions.

25 34. The population of claim 33, wherein each of the fluorescently-labeled regions has a center that is located at least about 50 nm, at least about 100 nm, at least about 200 nm, or at least about 250 nm from the centers of the other fluorescently-labeled regions.

30

FIG.1

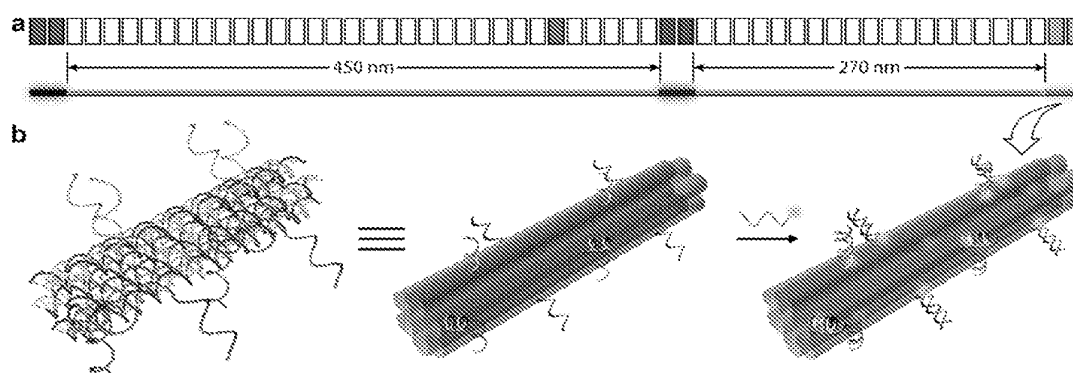


FIG. 2

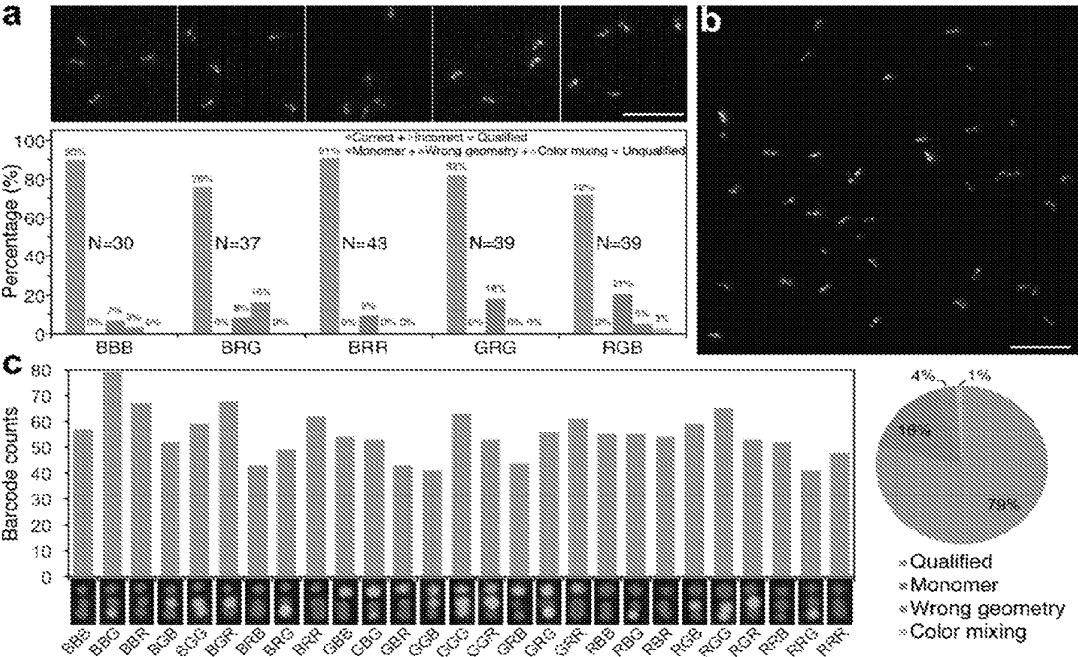


FIG. 3

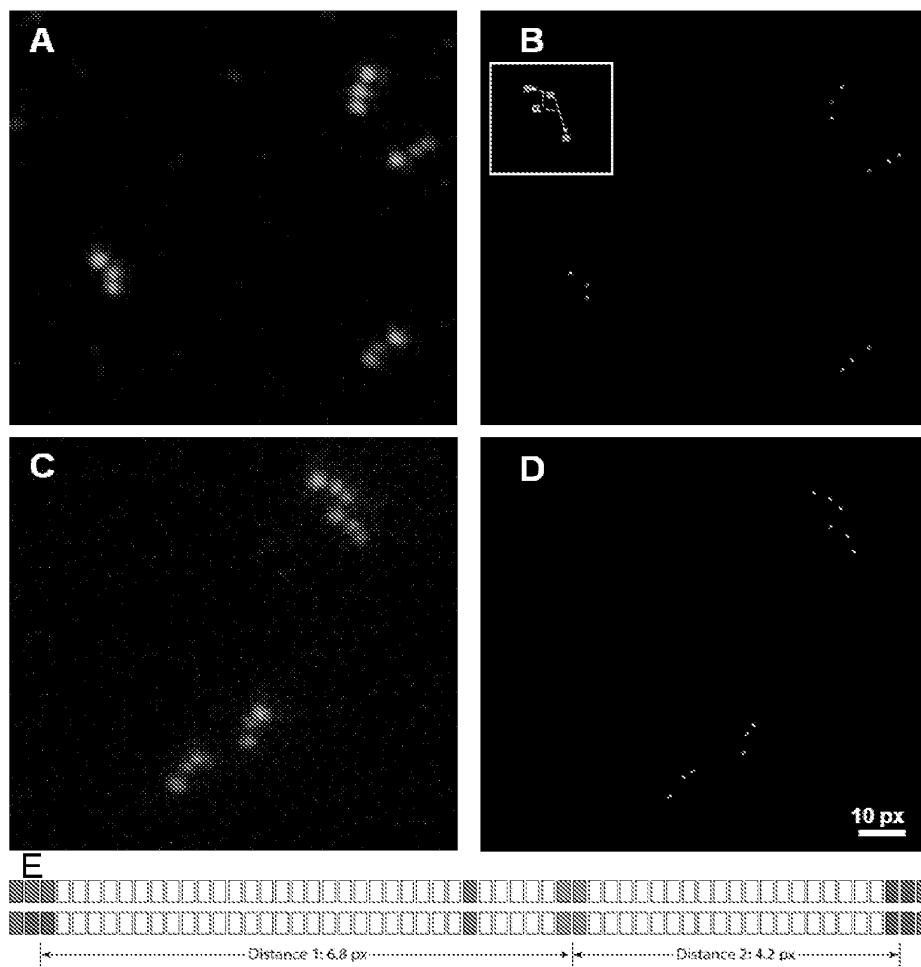


FIG. 4

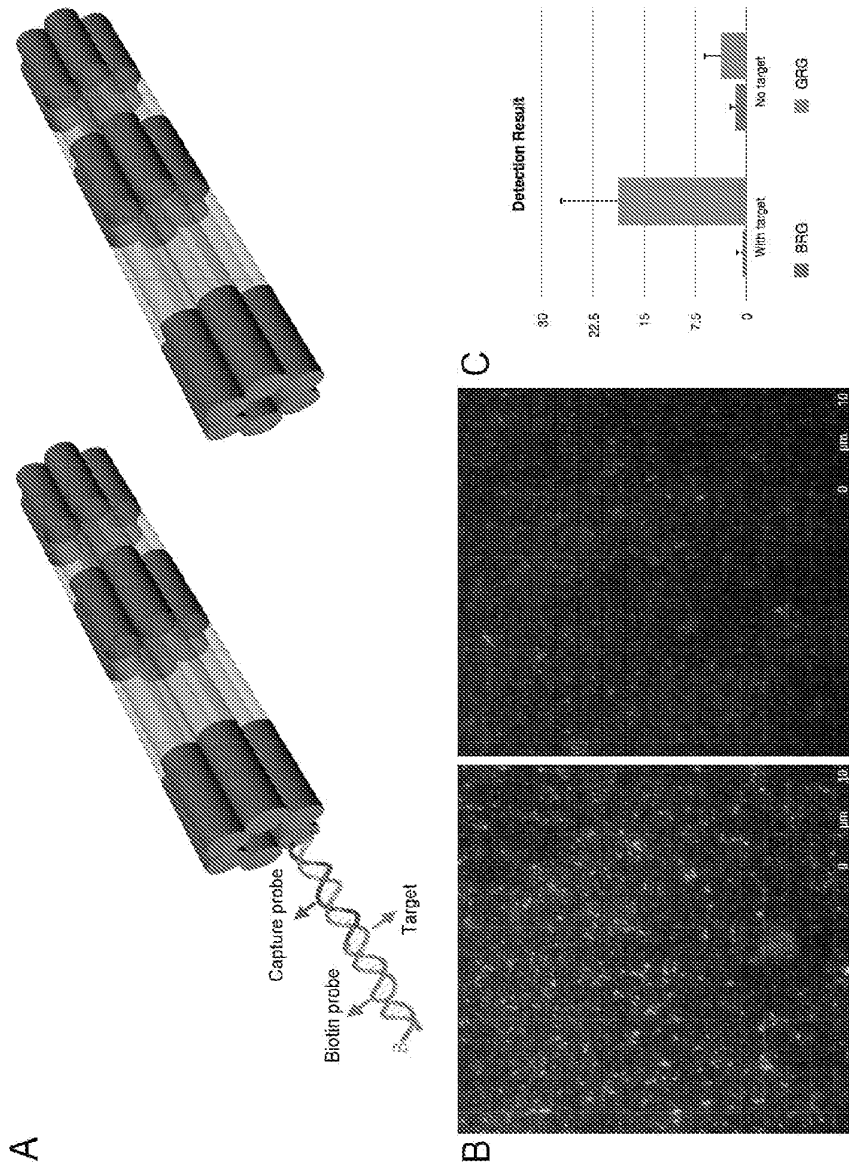


FIG. 5

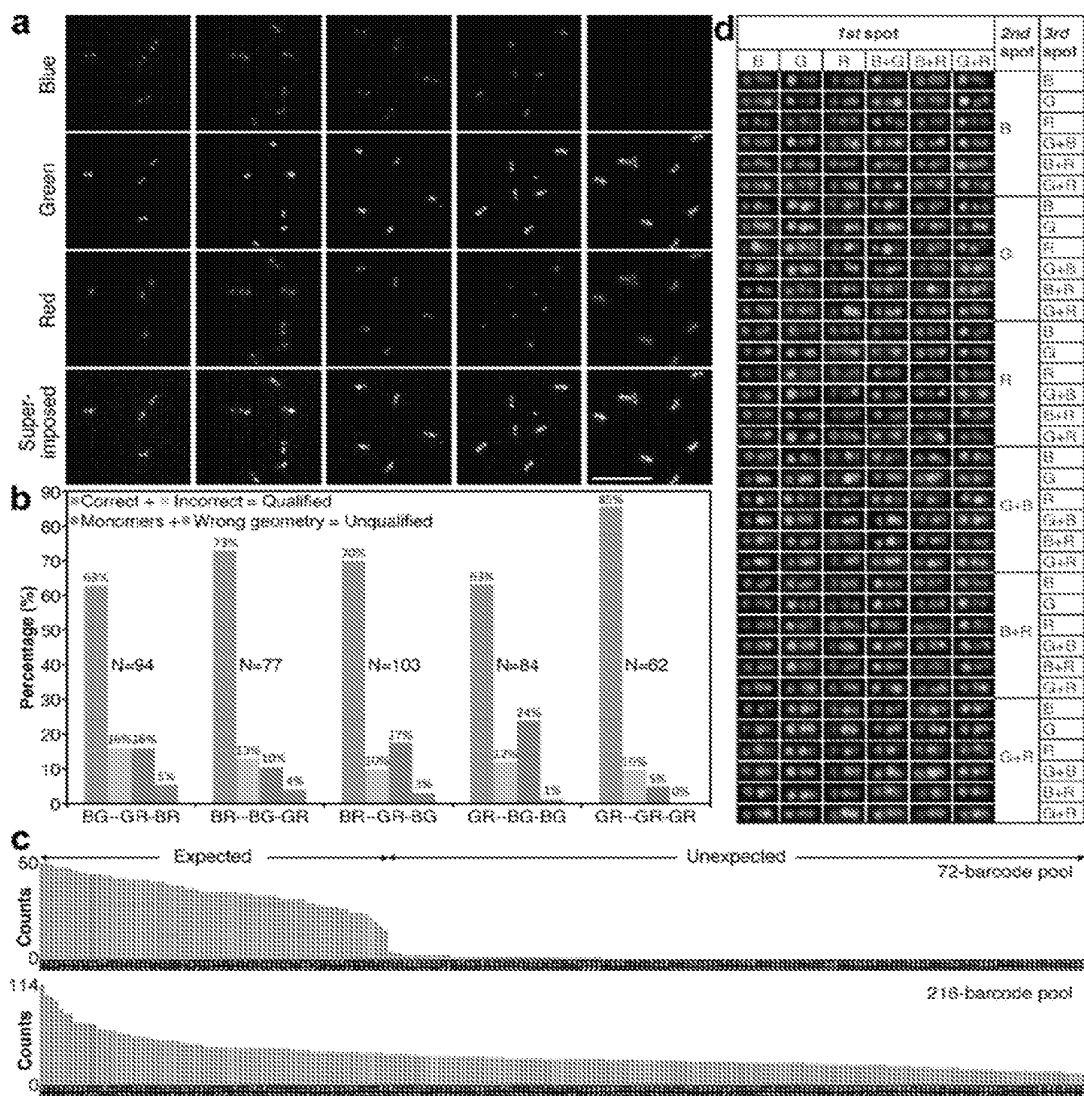


FIG. 6

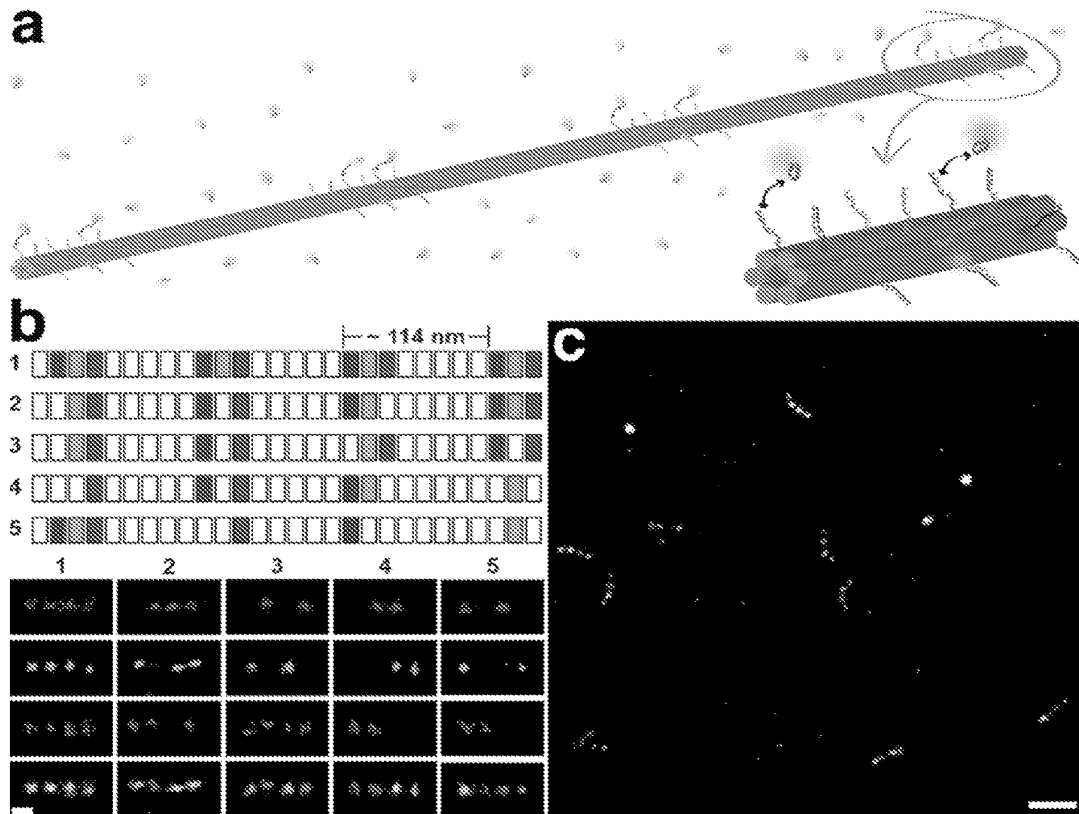


FIG. 7

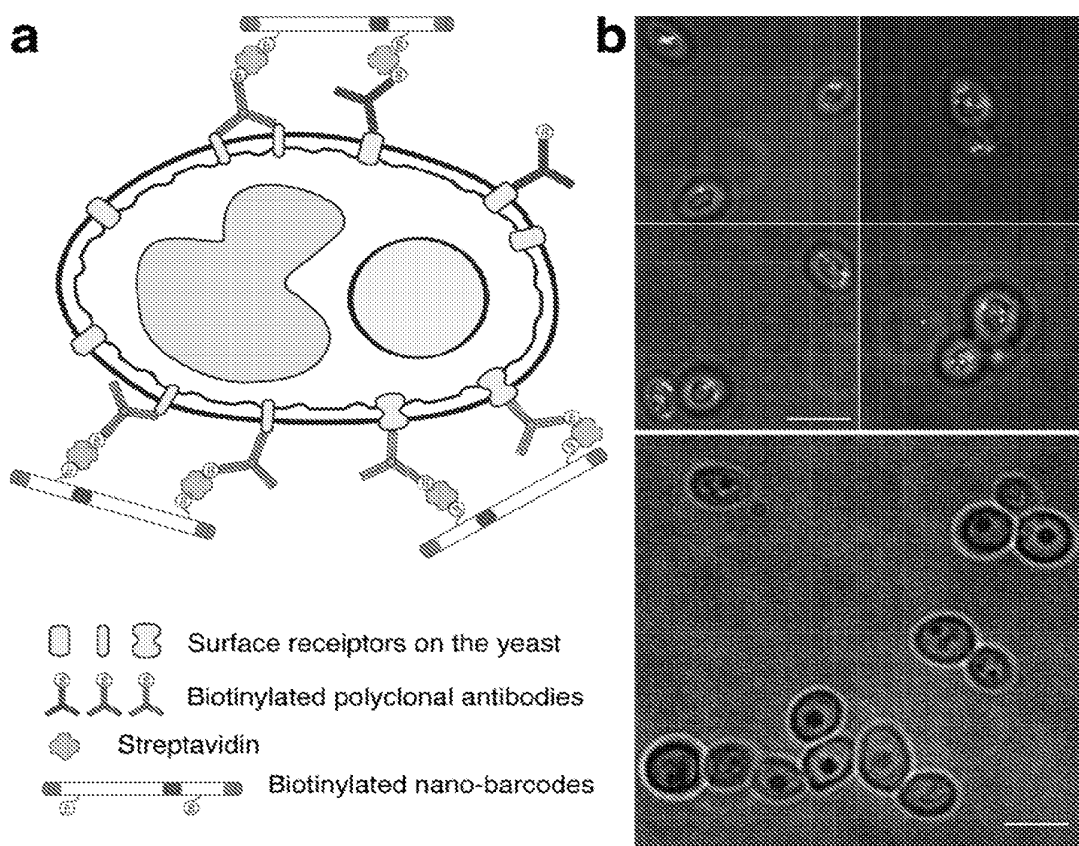
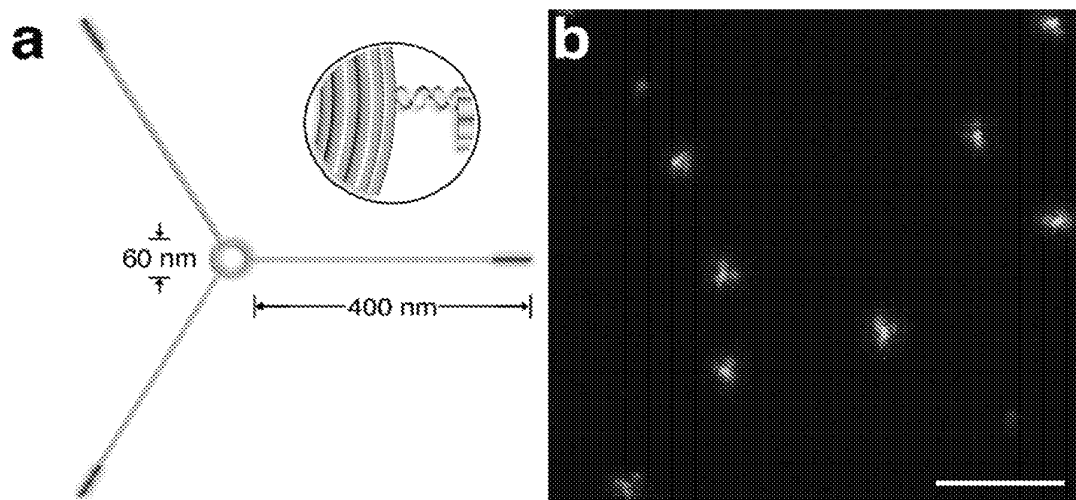


FIG. 8





(51) International Patent Classification:
C12Q 1/68 (2006.01) *B82Y 15/00* (2011.01)

(21) International Application Number:
PCT/US2011/058458

(22) International Filing Date:
28 October 2011 (28.10.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/408,358 29 October 2010 (29.10.2010) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))
- with information concerning authorization of rectification of an obvious mistake under Rule 91.3 (b) (Rule 48.2(i))

[Continued on next page]

(54) Title: NUCLEIC ACID NANOSTRUCTURE BARCODE PROBES



Fig. 1A

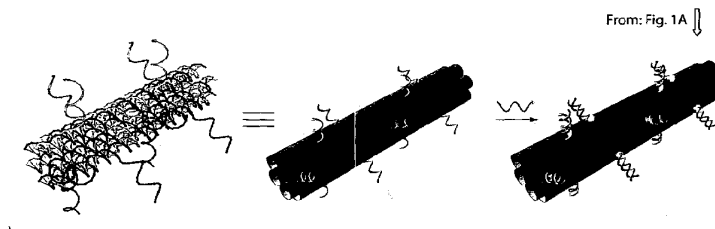


Fig. 1B

(57) Abstract: Provided herein are, inter alia, barcode probes comprised of transiently or stably fluorescently labeled nucleic acid nanostructures that are fully addressable and able to be read using standard fluorescent microscope and methods of use thereof including methods of use as detectable labels for probes, e.g. in the multiplex detection of targets, based on the pattern and orientation of the labels.



(88) Date of publication of the international search report:
20 December 2012

Previous Correction:
see Notice of 9 August 2012

(15) Information about Correction:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/058458

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12Q1/68 B82Y15/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12Q B82Y

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/076128 A2 (NANOSTRING TECHNOLOGIES INC [US]; INST SYSTEMS BIOLOGY [US]; GEISS GAR) 5 July 2007 (2007-07-05) cited in the application page 3, lines 25-31; figure 1 page 20 - pages 26-27 figure 3 figures 6-7 page 30, lines 16-17 page 94, lines 8-14 page 49 - page 50 page 120, lines 18-20 page 52	1-14,16, 18-34
X	US 2007/048759 A1 (LUO DAN [US] ET AL) 1 March 2007 (2007-03-01) claims 1-2,6,11-14,18; example 1; tables 1,9	1,2,4-6, 8
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Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

3 July 2012

Date of mailing of the international search report

12/07/2012

Name and mailing address of the ISA/

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Knudsen, Henrik

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/058458

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/058458

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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T	RALF JUNGMAHN ET AL: "Nanoscale imaging in DNA nanotechnology", WILEY INTERDISCIPLINARY REVIEWS: NANOMEDICINE AND NANOBIO TECHNOLOGY, vol. 4, no. 1, 1 January 2012 (2012-01-01) , pages 66-81, XP55031394, ISSN: 1939-5116, DOI: 10.1002/wnan.173 the whole document -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/058458

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Form PCT/ISA/210 (patent family annex) (April 2005)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization

International Bureau

(43) International Publication Date
9 August 2012 (09.08.2012)



(10) International Publication Number
WO 2012/106428 A2

- (51) **International Patent Classification:** Not classified
- (21) **International Application Number:**
PCT/US2012/023485
- (22) **International Filing Date:**
1 February 2012 (01.02.2012)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/439,363 3 February 2011 (03.02.2011) US
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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) **Title:** DETECTION METHODS FOR TARGET DNA

(57) **Abstract:** The invention pertains to a safe, quick and reliable method of detecting the presence of a target DNA sequence in a sample. The invention also pertains to a system for detecting presence of a target DNA sequence in a biological sample. The system includes an ITC template that includes a probe binding sequence that binds to a corresponding ITC probe and a first and second flanking primer recognizing sequence that binds to a first and second primer, respectively. The system also includes an ITC probe that binds to the ITC template probe binding sequence. The ITC probe includes a first marker molecule. The system also includes a first primer that binds to the first flanking primer sequence and a second primer that binds to said second primer sequence. The system further includes a target DNA sequence probe, wherein the target DNA sequence probe comprises a second marker molecule.

WO 2012/106428 A2

DETECTION METHODS FOR TARGET DNA

BACKGROUND

[001] The availability of simplified and controlled tests for detecting exogenous DNA molecules is of great demand in infectious disease diagnosis and evaluating the response to treatment, evaluating biodistribution of vectors used in legitimate gene therapy clinical trials, and detection of illicit gene doping. Real-time PCR can detect specific DNA signals, even at a very low concentration with reliability and specificity. In addition, real-time PCR is amenable to automation and remote data collection for high throughput screening. Taqman real-time PCR, using specific sequence probes, provides an efficient method to detect exogenous DNA accurately and quantitatively. However, to determine with confidence if the PCR signal is not a false positive or a false negative requires multiple controls. In addition, for quantitative determination of copy number, external copy number standard curves are required and pose a risk of contaminating the laboratory.

[002] Several viral-based and non-viral based gene transfer systems are being developed and evaluated in human clinical trials. These systems have demonstrated the ability to safely and efficiently deliver therapeutic transgenes to a variety of tissues of animals and humans, and examples of therapeutic benefit in humans are increasing [1,2,3,4,5,6,7]. Recombinant adeno-associated viral (rAAV) vectors and naked plasmid are two such gene transfer systems capable of gene delivery to skeletal muscle of animals [8],[9,10,11,12] and humans [13,14,15,16]. Recently, as an alternative to direct injection, regional vascular infusion of vector to achieve skeletal muscle transduction has been reported for plasmid DNA [17,18] and for rAAV vectors [19,20].

[003] When developing legitimate gene transfer modalities for gene therapy and vaccination, the evaluation of the distribution of vector sequences

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in pre-clinical animal studies and human clinical trials is required by regulatory agencies to determine the level of gene delivery to the target tissue and non-target tissues transduced collaterally, and to evaluate vector shedding into the environment. The type of vector, the delivery method, injection schedule, route of administration, and administered dose are the main variables to impact biodistribution and shedding [20,21,22,23,24]. To date, traditional real-time PCR assays have been used to analyze rAAV vector distribution after administration in human trials [25] or animal models [9] [26] [27,28,29]. To control for the presence of different potential inhibitors for each tissue source (eg. matrix effects), a common practice is to analyze each sample in duplicate with one of the duplicates spiked with a known number of copies of a plasmid harboring the PCR target sequences.

[004] Sports organizations have increased their focus on developing efficient ways to curtail the illegitimate use of genes or genetic elements that have the capacity to enhance athletic performance, also referred to as gene doping [30]. These organizations recognize that gene doping has the potential to threaten the integrity of sport, undermine principles of fair play in sport, imposes potential harm to non-doping athletes, and involves major health risks to athletes [31].

SUMMARY

[005] One of the major challenges in standard real-time PCR analysis is how to eliminate the false negative signals which can be caused by inhibitors [33] or inefficient PCR conditions. Although multiplex Taqman PCR assays have been applied in an effort to address problems of reliability, such as by adding an extra primer-probe sets targeted to other endogenous DNA sequences (housekeeping genes), however, the sequence and secondary structure differences between primers and probe binding sites, and amplified

sequences contribute to different detection efficiencies. Competitive PCR methods can be used to quantify DNA copy number, however, the method is limited by the necessity of assembling multiple competitive reactions for a single determination and, most notably, the need for a post-PCR electrophoresis-based detection and analysis step. In realizing these problems and difficulties of utilizing real-time PCR to detect exogenous DNA sequences, different Taqman PCR assays which use internal controls have been applied in an effort to address problems of reliability, such as by adding an extra primer-probe set targeted to other endogenous DNA sequences [34] or exogenous targets [34,35,36,37,38,39,40,41]. These previous approaches were primarily aimed at controlling sample adequacy, eliminating false negative results, performed in separate reactions, did not share the same primers, or preferentially amplified the target.

[006] In realizing these problems and difficulties of utilizing real-time PCR to detect exogenous DNA sequences, the inventors have developed a more efficient and simple detection system. According to one embodiment, the system includes the use of an internal threshold control (ITC) template and corresponding ITC probe. Sample DNA, a prescribed number of ITC template molecules, a single pair of primers, target probe, and ITC probe are added to one reaction. Marker signals, such as fluorescence emission signals are obtained simultaneously to determine the cycle thresholds (Ct) for amplification of the target and ITC sequences. Comparison of the Ct from the ITC and the Ct of the target is the parameter used to determine if a test sample is positive or negative for the presence of a homologous or nonhomologous exogenous DNA sequence.

[007] As will be discussed in more detail herein, such in reference to FIG. 3, for the ITC assays, if the Ct of the Target probe is less than or equal to the Ct of the ITC probe, then the sample is considered positive (meaning that

there is the same or more copies of the target sequence of interest relative to the ITC template). Additionally, if the Ct of the Target probe is greater than the Ct of the ITC probe, then the sample is considered negative. In a typical embodiment, the primers recognize both the target sequence and ITC template.

[008] The inventors have developed different ITC assay methodologies, which have validated the effectiveness of technology. For example, real-time PCR assays were developed to detect a performance enhancing transgene (erythropoietin, EPO) or vector backbone sequences in the presence of endogenous cellular sequences. EPO is a therapeutic gene that has been clinically evaluated and can potentially be illicitly used for gene doping. Two different ITC^{EPO} duplex assays target macaque and human EPO cDNA. These ITC^{EPO} duplex assays are performed in the presence of the cellular homologous genomic DNA locus, thus the ITC assay format is capable of distinguishing the cDNA carried in a gene transfer vector from the cellular host genomic DNA. By real-time PCR, the vector transgene is distinguishable from the genomic DNA sequence due to the absence of introns, and the vector backbone can be identified by heterologous gene expression control elements. In addition to developing the real-time PCR assays and ITC assay format, the steps involved in specimen collection, DNA extraction, DNA storage and DNA transport were validated. Bio-distribution of gene transfer vectors in legitimate gene therapy clinical trials is an important parameter to evaluate biosafety in humans. Thus, ITC assays might be applied to legitimate pre-clinical studies and clinical gene therapeutic trials to determine the presence or absence of gene transfer vector sequences in different tissues.

[009] Embodiments of the technology are also capable of being used for detection of human infectious agents such as viruses or bacteria that have

sequences that are nonhomologous to human genomic DNA. Those skilled in the art will appreciate in view of the teachings herein that certain embodiments of the invention can be used to determine the presence of a target sequence of interest in a sample.

BRIEF DESCRIPTION OF THE DRAWINGS

[010] Figure 1. Internal Threshold Control (ITC) assay format.

Panel (A) ITC^{EPO} duplex assay format. The EPO probe specifically detects the EPO cDNA harbored in rAAV vectors. The EPO ITC probe recognizes only the synthetic ITC^{EPO} template. The EPO primers recognize the EPO cDNA, the ITC^{EPO} template, and the genomic EPO locus. **Panel (B)** ITC^{CMV} duplex assay format. The CMV probe specifically detects the CMV immediate early promoter region in the pSSV9-MD2-cmEPO plasmid. The CMV ITC probe recognizes only the synthetic ITC^{CMV} template. The CMV primers recognize the CMV promoter and the ITC^{CMV} template.

[011] Figure 2. ITC duplex assay equivalence testing. All three ITC duplex assays were tested in the presence of same amount of target and ITC template and 500ng naïve gDNA. Five copies of pSSV9-MD2-cmEPO plasmid and ITC^{cmEPO} template were amplified using the ITC^{cmEPO} duplex assay. 10 copies of pShuttle-CAG-hEPO-pA plasmid and ITC^{hEPO} template were amplified using the ITC^{hEPO} duplex assay. 10 copies of pSSV9-MD2-cmEPO plasmid and ITC^{CMV} template were amplified using the ITC^{CMV} duplex assay. Each reaction was repeated 15 times. Similarities in mean Ct values were analyzed by SAS9.2.

[012] Figure 3. ITC duplex assay competition testing. The copy number of the ITC template was held at 5 copies (cmEPO ITC) or 10 copies (hEPO or CMV ITC) in each reaction, while the target template was titrated from 5 or 10 copies to 100 copies. Each reaction was repeated 5 times in the

presence of 500ng naïve gDNA to obtain the mean Ct value. **Panel (A)** ITC^{cmEPO} duplex assay, **Panel (B)** ITC^{hEPO} duplex assay and **Panel (C)** ITC^{CMV} duplex assay.

[013] Figure 4. ITC duplex assay interference testing. Target plasmid (◆) and ITC template (○) were amplified in one reaction in the presence of 500ng naïve gDNA to test the influence on the Ct between the two DNA targets. The total copy number of the plasmid and ITC template was maintained at 100. The target plasmid copy number is 10, 25, 50, 75, 90 and the ITC template copy number is 90, 75, 50, 25, 10 from left to right. Each reaction was repeated 5 times to obtain the mean. **Panel (A)** ITC^{cmEPO} duplex assay **Panel (B)** ITC^{hEPO} duplex assay and **Panel (C)** ITC^{CMV} duplex assay.

[014] Figure 5. Alignment between the macaque and human Epo genes. The location of the macaque assay (across the exon 2-3 boundary) is similar to the homologous location of the human assay (across the exon 3-4 boundary).

DETAILED DESCRIPTION

[015] The inventors have developed a system that enables the straightforward, accurate and efficient detection of exogenous sequences in a biological sample. Embodiments of the invention include the detection of genes that can be used in gene doping and may also be implemented to detect and monitor the efficacy, safety and spread of vectors and other constructs utilized for legitimate gene therapy. In certain specific embodiments, the invention pertains to methods, genetic constructs, and systems that are engineered to identify transfected or transduced cDNA sequences that pertain and can be homologous to endogenous genomic DNA. In alternative embodiments, such as, but not limited to, those related to monitoring the use of viral vectors for gene transfer or detection of infectious

agents, the invention pertains to detection of any foreign DNA material including, but not limited to, transfected, transduced or infected exogenous DNA material.

[016] In one embodiment, the invention pertains to a method of detecting exogenous DNA material in a subject. The term “exogenous DNA” means DNA that would not otherwise be in a subject but for the intentional transfection or transduction of exogenous DNA into the subject or infection. The method includes obtaining a specimen and preparing a DNA-containing sample from said subject and conducting real-time PCR on the DNA sample in the presence of a prescribed amount of an ITC template, primers for a target DNA sequence; a target probe that binds to the target DNA sequence and an ITC probe. Examples of a sample include, but are not limited to, blood, urine, mucous, hair, semen, or tissue sample. The method involves then determining whether the target DNA sequence amount is equal to or greater than the ITC template amount. In the case of determining Ct, the lower the Ct the higher the amount of copies are present in the sample.

[017] In a specific embodiment, the target DNA sequence pertains to an exon-exon junction of a cDNA that is homologous to an endogenous gene. In a more specific embodiment, the endogenous gene is erythropoetin.

[018] In a typical embodiment, the ITC template and the target DNA sequence comprise primer binding sequences that are homologous. In the context of the primer binding sequences, the term “homologous” means that sequences are sufficiently the same so as to each be recognized by the same primers.

[019] The inventors have determined that the sensitivity of their method is exceptional and can reliably detect the presence of approximately 5 copies of the target or ITC template in the presence of 500ng of genomic DNA (equivalent to 75,000 diploid genomes). This means that the ITC assay

format can determine whether there are approximately 5 or more copies of illicit genes in a sample from a subject. In a more specific embodiment, approximately in the context of copy number means 1-3 copies more or less. Thus, approximately 5 or more copies may be 2 or more, 3 or more, 4 or more, 6 or more 7 or more copies, etc. This level of sensitivity dramatically increases the ability of determining whether someone has undergone prohibited gene doping, or the presence of vector sequences in legitimate gene transfer, or presence of infectious agents.

[020] In most cases, the method embodiments are utilized to detect foreign DNA in a human, but can be used for non-human animals as well. In other words, this can be used to monitor gene doping in race horses or other race animals, and the presence of vector sequences in tissues analyzed in pre-clinical studies used to support human clinical trials. It also could be used by the USDA to monitor whether meat or plant based materials have been genetically modified.

[021] In a more specific embodiment, the ITC probe includes a fluorophore that generates a first color signal and the target probe comprises a fluorophore that generates a second color signal. Detection can be conducted by determining whether the Ct of the target is less than or equal to the Ct of the ITC template (positive), or greater than the Ct of the ITC (negative).

[022] In yet another embodiment, the invention pertains to a system for detecting foreign DNA material in a subject. The system includes a real-time PCR instrument that includes a receptacle for holding a PCR reaction containing the DNA sample; and a known amount of copies of an ITC template, primers for a target DNA sequence; target probe specific to said target DNA sequence and an ITC probe disposed in said receptacle.

[023] Another embodiment of the invention pertains to an ITC template. The template comprises a probe binding sequence that binds to a corresponding ITC probe and flanking sequences that hybridize to the primers. The ITC template's flanking primer recognizing sequences are homologous to primer sites of a separate target DNA sequence, however, the target DNA sequence lacks the ITC probe binding sequence. This prevents cross-interaction between the ITC probe and the target DNA sequence.

[024] *General Features of one ITC embodiment*

- a. Primers are the same for ITC template and target sequence
- b. Primers are separated by a similar distance in ITC template and target sequence
- c. The ITC probe and Target Probe have similar T_m 's.
- d. Two different probes (dyes) are detected
- e. Readout is simple

[025] A further embodiment of the invention pertains to a system for detecting presence of a target DNA sequence in a biological sample. The system includes an ITC template that includes a probe binding sequence that binds to a corresponding ITC probe and a first and second flanking primer recognizing sequence that bind to a first and second primer, respectively. The system also includes an ITC probe that binds to the ITC template probe binding sequence. The ITC probe includes a first marker molecule. The system also includes a first primer that binds to the first flanking primer sequence and a second primer that binds to said second primer sequence. The system further includes a target DNA sequence probe, wherein the target DNA sequence probe comprises a second marker molecule.

[026] *General features/advantages of a method embodiment:*

- Single tube: DNA sample + master mix (including primers, ITC probe, Target probe, and ITC template)
- Specific and sensitive, all samples INTERNALLY controlled
- Fast: 2 to 3 hours (including set up and analysis)
- No standard curve titration tubes (NO EXTERNAL STDS) needed
- High throughput: many samples analyzed at once
- Automated: data captured by PCR machine
- Can Transfer results to centralized database(s). Database(s) can be accessible by multiple remote users.
- No cumbersome manipulations
(such as 2 PCR reactions for nested PCR or Gel electrophoresis analysis)
- Reduced risk of contamination (false positives)
 - No positive control plasmid needed
 - uracil-N-glycosylase (UNG) can be used in specific embodiments which acts to prevent the reamplification of carryover PCR products in subsequent analyses

[027] Examples

[028] Detection of EPO

[029] A. Materials and Methods

[030] *Recombinant human and macaque EPO plasmid*

[031] The pShuttle-CAG-hEPO-pA plasmid contains the human erythropoietin (hEPO) cDNA under the control of the CAG promoter and the SV40 polyA (pA) sequence. The pSSV9-MD2-cmEPO rAAV vector plasmid harbors the macaque Epo (cmEPO) transgene under the control of the CMV

promoter and SV40 pA. The integrity of the plasmids was verified by complete sequencing.

[032] *rAAV Vector Production*

[033] The rAAV1 and rAAV8: rAAV-MD2-cmEPO vectors were made by transient transfection of 293 cells and purified by cesium chloride density gradients followed by extensive dialysis against phosphate-buffered saline. Appropriate quality control was performed to evaluate viral vector purity, vector genome titer, and infectious titer.

[034] *rAAV vector administration to macaque skeletal muscle*

[035] Experiments were conducted on captive-bred cynomolgus macaques purchased from BioPrim (Baziège, France). Animals were prescreened for the presence of anti-AAV1 or 8 antibodies, SV40, and other pathogens. For direct rAAV IM injections, the total dose was split over one or two pre-tattooed injection sites along the Tibialis Anterior muscle in a maximal volume of 600µl. Mac 3 was injected with 2.5E10 vg/kg rAAV1-MD2-cmEPO vector. Mac 4 was injected with 2.5E11 vg/kg rAAV1-MD2-cmEPO vector. Mac 5 was injected with 5E9 vg/kg rAAV8-MD2-cmEPO vector. Mac 6 was injected with 2.5E10 vg/kg rAAV8-MD2-cmEPO vector. All injections and blood samples were collected under ketamine-induced anesthesia (10mg/kg).

[036] *DNA extraction from macaque and human white blood cells*

[037] Human (naïve) and macaque (naïve and rAAV transduced) whole blood was collected and DNA extracted from the WBC pellet using the Gentra Puregene kit (cat # 158467) from Qiagen. Concentration and purity of the gDNA was determined using a nano-spectrophotometer from Implen. Integrity of the DNA was verified by migration of 3µg of total DNA on a 0.8% agarose gel, followed by Ethidium Bromide staining, and for macaque DNA by real-time PCR of the endogenous macaque ϵ -globin gene.

[038] ITC assay Development**[039] Primer-Probe design**

[040] Primers and probes were designed using ABI Primer Express 3.0 based on the cytomegalovirus (CMV) immediate early promoter in the pSSV9-MD2-cmEPO plasmid, the human EPO gene (NC_000007.13), or macaque EPO gene (NC_007860.1). Because of the constraints of the EPO Exon-Exon junction sequences and the required T_m, screening of multiple primer-probes combinations was required. Primer and probe sequences were screened *in silico* against the human genome and the macaque genome (<http://genome.ucsc.edu/cgi-bin/hgPcr?command=start>). Primers, probes and ITC templates were quantified using a nano- spectrophotometer from Implen.

[041] a. ITC^{cmEPO} duplex assay

[042] The cmEPO primer-probe assay targets the cmEPO Exon2-3 junction, harbored in pSSV9-MD2-cmEPO plasmid. The ITC^{cmEPO} duplex assay was designed with forward primer 5'AATGAGAATATCACCGTCCCAGAC3', reverse primer 5'AGCTTCTGAGAGCAGGGCC3', cmEPO probe 6FAM-AAGAGGATGGAGG TCGG-MGBNFQ and ITC probe 6VIC-CGGCCATTTTCCA-MGBNFQ. The ITC probe targets ITC^{cmEPO} template of two complimentary synthetic single strand DNAs that were annealed. The sequence of the forward ITC template sequence is

5'GAATGAGAATATCACCGTCCCAGACACCAAAGTTAACTT
CTATGCCTGGAAGACGGCCATTTTCCAAGCAGGCTGTAGAAGTCTGGCA
GGGCCTGGCCCTGCTCTCAGAAGCTGACGT3' and the sequence of the complementary sequence is

5'CAGCTTCTGAGAGCAGGGCCAGGCCCTGCCAGACTTCTACA

GCCTGCTTGGAAAATGGCCGTCTTCCAGGCATAGAAGTTAACTTTGGTG
TCTGGGACGGTGATATTCTCATTCTGCA.3'.

[043] b. ITC^{hEPO} duplex assay

[044] The hEPO primer-probe assay targets the hEPO Exon3-4 junction, harbored in pShuttle-CAG-hEPO-pA plasmid. The ITC^{hEPO} duplex assay was designed with forward primer

5'TGAATGAGAATATCACTGTCCCAGAC3', reverse primer

5'CTTCCGACAGCAGGGCC3', hEPO probe 6FAM-AAGAGGATG

GAGGTCCG-MGBNFQ and ITC probe VIC-CGGCC ATTTTCCA-MGBNFQ.

The ITC probe targets ITC^{hEPO} template of two complementary synthetic single strand DNAs that were annealed. The sequence of the forward ITC template is

5'GTGAATGAGAATATCACTGTCCCAGACACCAAAGTTAACTTC

TATGCCTGGAAGACGGCCATTTTCCAAGCAGGCTGTAGAAGTCTGGCAG

GGCCTGGCCCTGCTGTC GGAAGGACGT3' and the sequence of the complementary ITC sequence is

5'CCTTCCGACAGCAGGGCCAGGCCCTGCCAGACTTCTACAGC

CTGCTTGGAAAATGGCCGTCTTCCAGGCATAGAAGTTAACTTTGGTGTCT

GGGACAGTGATATTCTC ATTCAGTCA3'.

[045] c. ITC^{CMV} duplex assay

[046] The CMV primer-probe assay targets the CMV immediate early promoter junction, harbored in pSSV9-MD2-cmEPO plasmid. The ITC^{CMV} duplex assay was designed with forward primer

5'AATGGGCGGTAGGCGTGTAA3', reverse primer

5'CGATCTGACGGTTCATAAAG3', CMV probe 6FAM-TGGGAGGT

CTATATAAGC-MGBNFQ and ITC probe VIC-CG GCCATTTTCCA-

MGBNFQ. The CMV ITC probe targets ITC^{CMV} template of two

complementary synthesized single strand DNAs that were annealed. The

sequence of the forward ITC template is

5'CCGATCTGACGGTTCACATAACGAGCTCTTGGAAAATGGCCGCCGTAC
ACGCCTACCGCCCATTCTGCA3' and the sequence of the complementary
sequence is

5'GAATGGGCGGTAGGCGTGTACGGCGGCCATTTTCCAAGAGCTCGTTTA
G TGAA CCGTCAGATCGGACGT3'.

[047] Traditional real-time PCR program

[048] Taqman Real-time PCR conditions were optimized with primers and their corresponding fluorescent probes. The concentrations of 250nM probe and 900nM primers were found to be optimal. 500ng of each DNA sample was amplified in a final volume of 25μL containing 1x TaqMan® Universal PCR Master Mix (Applied Biosystems cat# 4304437). Amplification was performed using an ABI StepOnePlus PCR machine with an initial incubation at 50 °C for 2min, a denaturation at 95 °C for 10min, then 40 cycles of denaturation at 94 °C for 15s and an annealing/extension step at 60 °C for 1min. During thermal cycling, emission from each sample was recorded and ABI StepOne software v2.0 processed the raw fluorescence data to produce threshold cycle (Ct) values for each sample.

[049] ITC duplex assay real-time PCR program

[050] 500ng of macaque gDNA sample (for ITC^{cmEPO} duplex assay) or human gDNA (for ITC^{hEPO} and ITC^{CMV} duplex assays) was amplified in a final volume of 30μL containing 1x TaqMan® Universal PCR Master Mix (Applied Biosystems cat# 4304437) or 1x TaqMan® Fast Virus 1-Step Master Mix with reverse transcriptase (Applied Biosystems cat# 4444432). 5 copies or 10 copies of the corresponding ITC template were added in each reaction system. DMSO (Sigma D2650) was added in the final master mix to increase the assay sensitivity. Amplification was performed using an ABI StepOnePlus PCR machine with an initial incubation at 50 °C for 2min, a denaturation at

95°C for 10min, then 40 cycles of denaturation at 94°C for 15s and an annealing/extension step at 60°C for 1min. During thermal cycling, 6FAM and VIC fluorescence emissions were recorded and ABI StepOne software v2.0 processed the raw 6FAM fluorescence data to produce threshold cycle (Ct) values for testing samples and VIC fluorescence data for ITC templates.

[051] Statistical Analyses

[052] a. SAS Analyses

SAS 9.2 software was utilized to analyze data from ITC assays. SAS T-Test procedure was applied to compare the Ct values from each ITC assays. SAS GLM procedure was used to perform One-Way ANOVA and Two-Way ANOVA analyses.

b. Equivalence Testing

Independent sample equivalence testing was performed [42]. The null hypothesis (H_0) is $Ct_{Target} > Ct_{ITC}$ and $Ct_{Target} < Ct_{ITC}$; The alternative hypothesis (H_A) is $Ct_{Target} = Ct_{ITC}$. The tolerance limit (Δ) was set to 0.5 Ct to evaluate the parity of the Ct's from the two different real-time PCR reactions in the duplex assay. The confidence level (α) was set to 0.10. The critical t-value is $t_{\alpha, 2^{*}n-2}$ which is obtained from the Student's t-test distribution table. The observed t-values are calculated:

$$t_{ci} = \frac{d - (-\Delta)}{S_d}$$

$$t_{cs} = \frac{\Delta - d}{S_d}$$

d is the difference in the mean Ct between the target sequence and corresponding ITC template. S_d is the pooled standard deviation of the two

independent samples:

$$S_d = \sqrt{\frac{(n-1)s_1^2 + (n-1)s_2^2}{(2n-2)}} * \sqrt{\frac{2n}{(n*n)}}$$

n : Number of replicates

S_1 : Standard deviation of $C_{t_{\text{target}}}$.

S_2 : Standard deviation of $C_{t_{\text{ITC}}}$.

The rejection rule is: if t_{ci} and $t_{cs} > t_{\alpha, 2 \cdot n - 2}$, then reject H_0 .

[053] B. Results

[054] A novel real-time PCR-based approach for detecting exogenous DNA sequences has been developed. The system includes the use of an internal threshold control (ITC) template and corresponding ITC probe. The implementation of the ITC involves maintaining the melting temperature (T_m) of the ITC probe similar to the T_m of the probe used for the target, having the distance between the primer hybridization sites on the ITC template similar to the distance in the target, and labeling the ITC probe with a fluorescent dye different than the target probe. In this duplex assay format, the target and ITC template are co-amplified by the same primers, but are detected by two different probes each with a different fluorescent dye. Sample DNA, a prescribed number of ITC template molecules set near the limit of sensitivity, target primers, target probe and ITC probe are amplified in one reaction. Fluorescence emission signals are obtained by the real-time PCR machine simultaneously to determine the cycle thresholds (C_t) for amplification of the target and ITC sequences. Comparison of C_t from the ITC and C_t of the target is the parameter used to determine if test samples are positive or negative for the targeted DNA sequence. For the ITC duplex assays, if the C_t of the target probe is less than or equal to the C_t of the ITC probe, then the sample is

considered a true positive (meaning that there is the same or more copies of the gene of interest relative to the ITC template). Additionally, if the Ct of the Target probe is greater than the Ct of the ITC probe, then the sample is considered negative.

[055] **Figure 1** represents the features and rationale of applying the ITC to detect exogenous sequences that are either homologous or non-homologous with genomic DNA. Two different ITC^{EPO} duplex assays were developed that target macaque or human EPO cDNA. These ITC^{EPO} duplex assays are performed in the presence of the endogenous homologous genomic locus, thus the ITC assay needs to distinguish the cDNA carried in a gene transfer vector from the cellular host genomic DNA. For this, the EPO primer-probe assays were designed to target an EPO Exon-Exon junction (Exon 2-3 junction for cmEPO and Exon 3-4 junction for hEPO). The synthetic ITC^{EPO} template includes a different probe binding site and maintains the flanking EPO sequences including the EPO primer binding sites. As a consequence, the EPO primers recognize the EPO cDNA in the viral vector, along with the ITC^{EPO} template, and macaque or human gDNA. However, the EPO probe (6FAM dye) specifically detects the EPO cDNA, and the EPO ITC probe (VIC dye) specifically detects the EPO ITC template and neither can detect genomic DNA (**Figure 1A**).

[056] To demonstrate the applicability of the ITC duplex assay approach to address infectious agent detection, we also developed an ITC duplex assay in which the cytomegalovirus (CMV) promoter, used in the pSSV9-MD2-cmEPO plasmid, was targeted. The CMV promoter PCR target developed here is homologous to the promoter found in most CMV strains, including: the Towne strain (Genbank AY315197) that is the basis of the National Institute of Standards and Technology (NIST) Reference plasmid, the Merlin strain (Genbank AY446894) used in the World Health Organization

(WHO) reference standard (National Institute for Biological Standards and Control (NIBSC) product # 09/162), the JP strain (Genbank GQ221975) from a clinical specimen, and cell culture strains HAN38 (Genbank GQ396662) and VR1814 (Genbank GU179289). Since the heterologous CMV sequences are targeted, there is no competition with the host genomic DNA (**Figure 1B**).

[057] Traditional real-time PCR assays to detect the hEPO cDNA and CMV promoter were first developed using an approach similar to our previously published assay for cmEPO cDNA [32]. Design of the corresponding synthetic ITC template for each of these targets requires that (1) the distance between the primers is similar to the distance between the same primer sites on the target; (2) the target probe and ITC probe have similar T_m ; (3) the PCR products have similar T_m ; (4) there is no homology between the target probe and ITC template nor between ITC probe and target sequences. For each assay the primers and probes were verified *in silico* to ensure that there was no cross hybridization between primers, primers and probes, primers/probe sets and EPO cDNA or genomic DNA or ITC template. The PCR products of each individual PCR assay were analyzed by agarose gel electrophoresis and demonstrated a single band (data not shown). The performance of each individual assay was evaluated.

[058] Performance and detection limits of individual assays

[059] Traditional real-time PCR was performed to evaluate the lower limit of quantitation and linearity of the six individual assays. A titration of the pSSV9-MD2-cmEpo plasmid in the presence of naïve macaque genomic DNA illustrates that the cmEPO assay is capable of detecting 5 copies. Likewise, a titration of the ITC^{cmEPO} template illustrates that the ITC^{cmEPO} assay is capable of detecting 5 copies in the presence of naïve macaque genomic DNA. The sensitivities of the individual hEPO, ITC^{hEPO}, CMV, ITC^{CMV} assays in the presence of naïve human genomic DNA is 10 copies. The linearity of all the

six assays is above 0.98 over an 8 log dynamic range from 10 to 1E9 copies (**Table 1**). The reduction in efficiencies seen in the presence of gDNA most likely reflects competition for primers. To evaluate the accuracy of detecting the sequences at the lower limit of quantitation, 15 replicates were performed for cmEPO and ITC^{cmEPO} assays at 5 copies and at 10 copies for the other four assays and the means and standard errors of copy number and Ct were calculated (**Table 2**).

[060] Specificity of the individual assays

[061] The specificity of the individual assays was tested (**Table 3**). A lack of signal at 40 cycles was defined as "negative" and a Ct signal before 40 cycles of amplification was considered "positive". 500ng of naïve macaque or human gDNA were used as samples. **Table 3** demonstrates that no false positive signals were detected in 20 replicates of each of the six individual assays caused by either non-targeted exogenous or endogenous DNA sequences, or laboratory contamination. To confirm that we are detecting the vector genome harboring the EPO cDNA and not residual endogenous mRNA, we obtained the copy number signal with our standard master mix and this signal was not influenced by RNase. Furthermore, when a master mix that utilizes a reverse transcriptase step was used, endogenous mRNA was detected and this RT-dependent signal was reduced with an RNase A pre-treatment (data not shown).

[062] Equivalence testing of ITC duplex assays

[063] Each of the three individual target assays was paired with the corresponding ITC assay to create the three ITC duplex assays. The ITC duplex assay format includes the requirement that same copy number of target sequences and corresponding ITC templates give similar Ct's. In cases where the P-value shows a statistically significant difference, such as when the Ct of the target is significantly higher or lower than the Ct of the ITC, then

the Student's t-test can be used. However, when the Ct of the target is equal to the Ct of the ITC, the equivalency needs to be confirmed statistically to be able to designate the sample as a true positive. Equivalence testing of our three ITC duplex assays was performed. Each assay was used to detect target DNA sequences near their limit of sensitivity in the presence of an equal amount of ITC template and 500ng of naïve gDNA (**Figure 2**). Fifteen replicates were performed and the Ct's were recorded and analyzed. First, large P-values (cmEPO $P=0.5816$, hEPO $P=0.6783$, CMV $P=0.4819$) were obtained by the Student's t-test suggesting that no significant differences exist between each target Ct and the corresponding ITC Ct from all three duplex assays. To determine if the Ct values were statistically equivalent, equivalence testing was conducted (see Materials and Methods), where the tolerance limit was set as 0.5 Ct (equal to 1.5% of the max Ct of 37), the confidence level (α) was set to 0.10, and the critical t-value is $t_{0.10, 28}=1.31$. The calculated t_{ci} and t_{cs} of the three assays are 2.8 and 1.7 for cmEPO, 2.7 and 2.1 for hEPO, and 1.6 and 3.0 for CMV. All of these t-values are greater than the critical t-value of 1.31, demonstrating that the Ct from a target DNA and the Ct from an equal amount of corresponding ITC template in each duplex assay are statistically equivalent.

[064] Assay Precision

[065] As shown in **Table 2**, the reproducibility of the assays was evaluated. Coefficients of variation (CV) from all six assays are within 3.2%. Furthermore, to determine the precision of the ITC^{hEPO} duplex assay, an additional experiment was conducted where eight replicates of the ITC^{hEPO} duplex assay were performed on three consecutive days using hEPO plasmid DNA in the presence of naïve human gDNA. The intra-assay CV is 1.3% and the inter-assay CV is 2.8%. These CVs of less than 3% demonstrate that the ITC^{hEPO} assay is highly reproducible. Moreover, one-way ANOVA was

performed to determine the relationship between testing days and Ct from the individual hEPO and ITC^{hEPO} PCR reactions, and shows that each Ct does not vary significantly over the testing days (data not shown).

[066] Evaluation of assay interference

[067] The target probe and its corresponding ITC probe are designed to detect two unique DNA sequences in one reaction. However, the two amplification systems share the same pair of primers, thus, possible competition between the target PCR reaction and the ITC PCR reaction was analyzed for each of the three ITC duplex assays. Experiments were performed where the copy number of the ITC template was held at 5 copies (cmEPO ITC) or 10 copies (hEPO or CMV ITC) in each reaction, while the target template was titrated from 5 or 10 copies to 100 copies, which is at the upper range of rAAV copies seen in 500ng of macaque WBC gDNA at late timepoints following intramuscular injection [32]. As shown in **Figure 3**, the observed Ct from the ITC probe is stable while the Ct from the corresponding target probe increases according to the decrease in target copy number in the presence of 500ng naïve gDNA. All three assays show the same pattern, which demonstrates that the target template does not interfere with the ITC detection in this copy number range. In the cases where the target copy number is over 100 copies, then an unequivocal signal will be detected by the target probe, even if an ITC signal is not detected, and will warrant further analysis of the sample.

[068] In addition, testing was performed to evaluate the dynamic range of all the three ITC duplex assays (**Figure 4**). The total number of the two templates was maintained at 100 copies. For each duplex assay, a plasmid harboring the target was titrated reciprocally with the ITC template in the presence of 500ng naïve gDNA. The Ct of both probes illustrates that the Ct values for each template changed only with the template amount, without

interference from the other template. As a result, if no signal is obtained from the ITC template it is most likely due to an inhibitor present in the sample, and the test will be invalid and require further analysis.

[069] Transduced Macaque blood sample testing

[070] The performance of the ITC assay format was evaluated on the WBC DNA samples taken from macaques transduced *in vivo* with rAAV vectors and previously analyzed by traditional real-time PCR, where the actual copy number was determined at each timepoint [32]. The ITC^{cmEPO} duplex assay was conducted on both rAAV1 and rAAV8 *in vivo* samples. For the ITC testing, a 500ng DNA sample and 5 copies of ITC^{cmEPO} template were amplified simultaneously in the presence of the cmEPO primers, the cmEPO probe, and the cmEPO ITC probe, and both fluorescence signals were recorded to obtain the Ct's. Each sample was tested repeatedly 5 times in order to acquire the mean and standard error for statistical analysis. Comparing the mean of cmEPO Ct and ITC^{cmEpo} Ct, the tested samples are defined to be positive (cmEPO Ct is less than or equal to the ITC^{cmEpo} Ct) or negative (cmEPO Ct is greater than ITC^{cmEpo} Ct with P-Value < 0.05). As shown in **Table 4**, the ITC^{cmEPO} duplex assay results from both rAAV1 and rAAV8 injected animals are consistent with the previous absolute copy number data. Samples having more than two copies per 500ng DNA are positive in the ITC duplex assay, meanwhile, the pre-injected samples test negative. The Student's t-test was applied and P-values of <0.001 were obtained when the absolute value of the difference between cmEPO cDNA and ITC^{cmEPO} template copy numbers is larger than five, demonstrating that this Ct difference is statistically significant. In addition, there is little to no competition of the target with the ITC, since the Ct's of the ITC for both animals at all vector copy numbers is ~37 (CV=1.5%). Furthermore, the

samples do not appear to contain inhibitors since the Ct=37 is similar to the Ct seen in TE (in the absence of gDNA, **Table 2**).

[071] Testing of human WBC gDNA spiked with plasmid DNA

[072] The plasmid pShuttle-CAG-hEPO-pA harboring the hEPO cDNA was spiked into 500ng naïve human gDNA at the same copy numbers detected in the rAAV1 injected macaque shown in **Table 4**, and ten copies of ITC^{hEPO} template was added to each reaction. **Table 5** shows that spiking with 188, 13 and 8 copies of pShuttle-CAG-hEPO-pA were designated as positive, meanwhile 0 and 2 copies were designated negative when compared to the ITC^{hEPO} Ct.

[073] The ITC duplex assay format is also capable of being used to detect human infectious agents such as viruses or bacteria that have sequences that are non-homologous to human genomic DNA. Cytomegalovirus causes many human infections [43], and the viral load in blood is very important for clinicians to evaluate patients' prognosis. As a proof of concept, The CMV immediate early promoter in plasmid pSSV9-MD2-cmEPO was used as a PCR target for two reasons. The first is to compare the sensitivity of the EPO intron-spanning PCR to a target that has no competition with human genomic DNA, and the second is to demonstrate the applicability to using the ITC approach for infectious disease diagnosis and treatment monitoring. As can be seen in **Tables 1 and 2**, the CMV and hEPO assays had similar 10 copy sensitivities.

[074] For the ITC^{hEPO} and ITC^{CMV} duplex assays, we determined the difference in the Ct's between the target sequence and corresponding ITC template at the 95% confidence interval. For this purpose, the ITC templates were held constant at 10 copies and a titration of 5, 10 and 20 copies of target plasmid were added to evaluate the ability to determine positive (10 and 20 copies) from negative (5 copies) samples. Four different naïve human gDNA

samples spiked with 5, 10 and 20 copies of hEPO or CMV target plasmid were amplified in the presence of 10 copies of their corresponding ITC template. The Ct's were analyzed by Student's t-test and One-Way ANOVA. **Table 6** shows that, with all four human gDNA sources, the Ct from 5 copies of hEPO or CMV target sequence is significantly larger than 10 copies of corresponding ITC template, the Ct from 20 copies is significantly smaller than 10 copies of ITC template, and no statistical difference (evaluated by equivalence testing – data not shown) was seen when the target and ITC copy numbers were equal at 10 copies each. Two-Way ANOVA analysis was performed and showed that the copy number detected was independent of the different gDNA samples (data not shown).

[075] The human Epo PCR assay was designed in a homologous region as the macaque Epo PCR assay (Figure 5). The human Epo ITC assay format was also tested by titrating the two DNA molecules (plasmid target and ITC^{hEPO} template, Figure 4B). The Ct of both amplifications illustrated that Ct values changed only with the target template amount but was not affected by the other template, demonstrating that no obvious interference exists. As a result, there is a high confidence that an absence of ITC signal would indicate the presence of an inhibitor in the sample.

[076] Discussion

[077] Reported herein is the development of a real-time PCR assay format for detecting homologous and non-homologous exogenous DNA. These tests are useful for infectious disease diagnosis, gene therapy clinical trial safety, and gene doping surveillance where the control of false negative and false positive results, and the assurance of true positive results is required. These procedures facilitate the procurement, preparation, and testing of samples to detect exogenous DNA sequences in a user-friendly

format. Furthermore, the ITC assay format described here is ideal for clinical testing labs since 1) it is a "single tube" assay [sample DNA + master mix (2 primers, 2 probes and ITC template)], 2) it is specific and sensitive with samples internally controlled, 3) it is fast: 2 to 3 hours (including set up and analysis), 4) it requires no standard curve titration tubes (no external standards), 5) it is high throughput, capable of analyzing many samples at once, 6) it is automated: data captured by PCR machine and results can be transferred to centralized database(s), 7) no additional manipulations are needed for analysis such as gel electrophoresis, and 8) it reduces risk of laboratory contamination (a source of false positives) since no positive control plasmid is needed and uracil-N-glycosylase (UNG) prevents the re-amplification of carryover PCR products in subsequent analyses.

[078] When designing and validating an ITC duplex assay, in addition to considering GC content, primer and probe T_m , and amplicon length, additionally, lack of cross complementarity of the primers and two probes, the targets or amplicons, or any combination of these is needed [44]. Moreover, since both assays are amplified in a single tube, amplification competes for the same dNTPs and polymerase. One more challenge in the detection of cDNAs in the presence of gDNA is that the assay must detect the exon-exon junction of the cDNA, which greatly restricts the choice of primers and probes.

[079] The individual assays described here have a sensitivity of 10 copies or better in the presence of 1.5×10^5 cellular genome copies and maintain linearity over 8 logs. The two probes in each duplex assay give similar C_t values when detecting the same amount of their respective sequences, and this was supported statistically using equivalence testing. Interference and competition testing has shown that target probe, ITC probe, target template and ITC template will not inhibit each other in the range of 10-100 copies.

Furthermore, similar amplification of the PCR targets was achieved in individual PCR reactions compared with the duplex PCR reactions.

[080] The maintenance of rAAV sequences in WBC of nonhuman primates [32] and humans [25] provides an easily accessible target for the surveillance of gene doping. Our previous experiments in the nonhuman primate were designed to test the feasibility of detecting vector sequences in blood long-term following IM injection and to gain insight into testing humans. We have designed the ITC duplex PCR format described in this paper with the expectation that athlete samples will be sent to testing laboratories for preparation and PCR analysis, and then the test results will then be sent to central databases for analysis and trending. The methods developed to detect EPO also provide the basis to detect other prohibited gene doping targets.

[081] Previous studies have introduced internal controls using cellular housekeeping genes to control for possible PCR inhibitory factors, but they were not used to set a copy number threshold of the exogenous sequence target [45] [46]. Moreover, competitive PCR methods are used to quantify DNA copy number, however, this approach is limited by the necessity of assembling multiple competitive reactions for a single determination and, most notably, the need for a post-PCR detection and analysis step [47]. On the other hand, each ITC duplex assay detects two different DNA sequences in one reaction by real-time PCR, with the Ct from the ITC probe being a threshold to evaluate if the samples are positive or negative. The ITC^{cmEPO} duplex assay testing on blood samples from macaques transduced *in vivo* with rAAV vectors shows consistent results with our previous quantitative data [32]. Furthermore, to simulate the testing of human samples, the ITC templates were held constant and the corresponding hEPO or CMV target plasmid was titrated in the presence of naïve human genomic DNA to evaluate the ability to determine positive from negative samples.

[082] ITC assays can be used to detect heterologous sequences (infectious agents) or exogenously added homologous cDNA sequences (gene transfer vectors). Thus, ITC assays can be applied to pre-clinical animal biodistribution studies and legitimate human gene therapy clinical trials to determine the presence or absence of gene transfer vector sequences in different tissues, where the ITC can control for different types of inhibitors potentially present in different tissue samples. Likewise, molecular tests for infectious disease diagnosis, prognosis, and evaluation of response to therapy could benefit from an ITC assay approach. The ITC assay format is also applicable to gene doping surveillance testing as a means to deter the illegitimate use of gene transfer vectors for athletic performance. Compared to traditional real-time PCR, the ITC assay format has advantages for detecting exogenous DNA.

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[0131] It should be borne in mind that all patents, patent applications, patent publications, technical publications, scientific publications, and other references referenced herein are hereby incorporated by reference in this application in order to more fully describe the state of the art to which the present invention pertains.

[0132] It is important to an understanding of the present invention to note that all technical and scientific terms used herein, unless defined herein, are intended to have the same meaning as commonly understood by one of ordinary skill in the art. The techniques employed herein are also those that are known to one of ordinary skill in the art, unless stated otherwise. For purposes of more clearly facilitating an understanding the invention as disclosed and claimed herein, the following definitions are provided.

[0133] While a number of embodiments of the present invention have been shown and described herein in the present context, such embodiments are provided by way of example only, and not of limitation. Numerous variations, changes and substitutions will occur to those of skilled in the art without materially departing from the invention herein. For example, the present invention need not be limited to best mode disclosed herein, since

other applications can equally benefit from the teachings of the present invention. Also, in the claims, means-plus-function and step-plus-function clauses are intended to cover the structures and acts, respectively, described herein as performing the recited function and not only structural equivalents or act equivalents, but also equivalent structures or equivalent acts, respectively. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the following claims, in accordance with relevant law as to their interpretation.