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(54) Title: DISCOVERY TOOL WITH INTEGRATED MICROFLUIDIC BIOMARKER OPTICAL DETECTION ARRAY DEVICE AND METHODS FOR USE

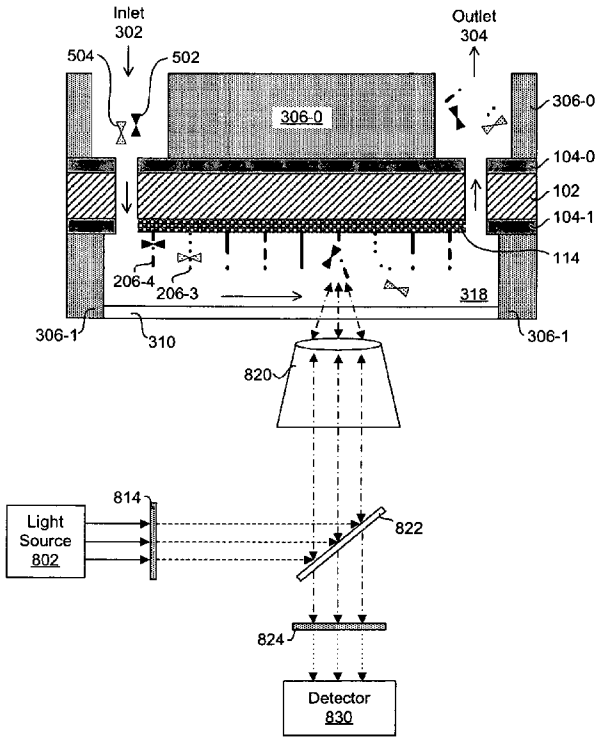

FIG. 8

(57) Abstract: The present disclosure relates to the fields of microchips with microfluidic optical chambers with enhanced Raman surfaces for multiplexed optical spectroscopy. Embodiments of the present invention allow for ultra small sample volume, as well as high detection speed and throughput, as compared to conventional cuvettes or devices used in optical spectroscopy. Particular embodiments relate to scientific and medical research, the diagnosis of diseases such as cancer, cardiovascular disease, diabetes, etc., and specifically to the detection of biomarkers and determination of protein activity with relevant scientific and medical applications.

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DISCOVERY TOOL WITH INTEGRATED MICROFLUIDIC BIOMARKER OPTICAL DETECTION ARRAY DEVICE AND METHODS FOR USE

TECHNICAL FIELD

[0001] Particular embodiments relate to scientific and medical research, the diagnosis of diseases such as cancer, cardiovascular disease, diabetes, renal disease, pulmonary diseases, infectious diseases of viral and microbial nature, as well as neurodegenerative, immunological, and metabolic diseases, *etc.* In particular, the detection of biomarkers and the measurement of protein and enzymatic activities, interactions, inhibition and activation with relevant scientific and medical applications are provided.

BACKGROUND

[0002] Recent, rapid increases in the scientific understanding of molecular physiology have been driven by, among many reasons, the completion of the sequence of the human genome and the advent of both highly sensitive and massively parallel systems for detection of biologically or medically interesting analytes. In particular, such detection systems for biological analytes of interest, or biomarkers, are of growing importance in scientific research and, increasingly, for patients in clinical settings. Analytical methods that employ spectroscopic detection systems are frequently used in the detection and quantification of biomarkers, often providing information about the interaction of biomarkers with various test molecules. Such assay methods may be employed initially during the identification, characterization, and development of molecular diagnostics, and may also be employed as molecular diagnostic tests used to assay biological samples. Thus, these assay methods may be employed to measure the health status of patients or to provide information that may support medical decisions.

[0003] Raman spectroscopy is a spectroscopic technique that measures the inelastic scattering of monochromatic light (known as Raman Scattering) commonly used to interrogate molecular vibrational or rotational aspects of a sample. Typically, a laser in the range of visible, near infrared or near ultraviolet light is used to excite the sample/system. The energy of laser photons is then shifted up or down (known as the Raman effect or Raman shift), and this shift in energy (wavelength, frequency or wave number) provides information about molecular vibrational or rotational aspects of the system. The Raman

effect occurs when light interacts with the electron cloud of the bonds of a molecule or a molecular complex with multiple molecules or atoms; the magnitude of deformation in the electron cloud caused by the incident light is a reflection of the polarizability of the molecule, which determines the intensity and frequency of the reflected energy and the characteristic, fingerprint-like Raman spectra.

[0004] Surface Enhanced Raman Spectroscopy (SERS) is a highly sensitive method that can enhance the signal intensity of low-probability or weak Raman spectra emitted from a small sample. SERS, in fact has been demonstrated to detect the Raman spectra of single molecules. SERS systems for the detection of biologically or medically interesting analytes typically immobilize or fix the analyte, substrate, or complex of interest onto or adjacent to a solid, usually metal or metal alloy surface, or metal complexed with other non-metal materials with Raman enhancing, dampening or tuning capabilities. This is often referred to as a SERS-active structure. Interactions between the analyte, substrate, or complex of interest and the metal surface and the metal surface derivatives, result in an increase or a modulation in the intensity and specific profiles of the Raman-scattered radiation. Accordingly, different binding events and chemical reactions, such as phosphorylation and de-phosphorylation may be detected and compared based on the characteristic, fingerprint-like Raman spectra they create.

[0005] The use of SERS in biological and medical applications has tremendous potential for directly measuring medically and scientifically interesting molecular interactions and protein and enzymatic activity. In particular, SERS may be employed to measure protein-substrate binding events and reactions, such as those involving protein-protein, protein-small molecule, small molecule-small molecule, nucleic acid-protein, and riboprotein-nucleic acid interactions, for example. The sensitivity of such applications, perhaps enabling single-molecule detection, thus offers the potential to detect very low copy-number proteins and components of lysates from rare cells. While recent advances have been made in high-throughput measurement of DNA (sequencing), RNA (gene expression technologies) and proteins (proteomics); to date, high-throughput measurement of protein activity, in particular enzyme activity, has remained technically out of reach. Such information is clearly valuable both medically and scientifically. For example, while the value is clear in knowing a patient's complete DNA sequence or the expression levels of all genes or proteins in a cell, understanding the activity of all proteins in a cell is actually

more informative and represents a higher order of biological information. This is because proteomic-level information is directly tied to function and cell phenotype.

[0006] Microfluidic devices and systems of integrated microfluidics devices employ small capillaries or microchannels attached or integrated with a solid substrate to perform a variety of operations in a number of analytical, chemical and biochemical applications on a very small scale. For example, integrated microfluidic devices can first employ electrical fields to effectively separate nucleic acids, proteins or other macromolecules of interest and then use microscale detection systems for characterization and analysis of the separation products. Such microfluidic devices accomplish these operations using remarkably small reaction volumes that can be at least several orders of magnitude smaller than conventional methods. The small size of these systems allows for increased reaction rates that use less reagent volume and that take up far less laboratory, clinical, or industrial space. Microfluidic systems thus offer the potential for attractive efficiency gains, and consequently, substantial economic advantages.

[0007] Microfluidic devices are particularly well-suited to conduct analytical methods that employ spectroscopic detection systems. A variety of spectroscopic techniques can be employed in conjunction with microfluidic devices, including light scattering spectroscopy, such as Raman spectroscopy. In research or industrial settings, microfluidic devices are typically employed in biochemical or cell-based assays that use spectroscopic detection systems to quantify labeled or unlabeled molecules of interest. For example, such an assay measures the expression of green fluorescent protein in mammalian cells following treatment by a candidate small molecule or biologic drug of interest. Another example is the use of the quantitative polymer chain reaction technique (PCR) in microfluidics devices for gene amplification and analysis with intercalating fluorescence dye as the spectroscopic indicator. Other examples include, but are not limited to, enzymatic and biochemical reactions in general, chemical reactions, phase transition detections, *etc.*

[0008] Microfluidic devices typically employ networks of integrated microscale channels and reservoirs in which materials are transported, mixed, separated and detected, with various detectors and sensors embedded or externally arranged for quantification, as well as actuators and other accessories for manipulations of the fluidic samples. The development of sophisticated material transport systems has permitted the development of systems that are readily automatable and highly reproducible. Such operations are potentially automatable and can be incorporated into high-throughput systems with

tremendous advantages for numerous industrial and research applications. Microfluidic devices often use plastics as the substrate. While polymeric materials offer advantages of easy fabrication, low cost and availability, they tend to be fluorescent. For example, when irradiating a sample with excitation light, light scatter may result in a significant background signal, particularly when the excitation pathway and emission pathway are the same. Other materials, such as glass, silicon, metal, and metal oxides may be used as well.

[0009] Analysis of biomarkers is fast becoming the preferred method for early detection of disease, patient stratification and monitoring efficacy of treatment. Rapid and highly sensitive detection of changes in a biomarker is often technically impossible, or may require a cumbersome procedure involving multiple processing steps, necessitating large sample volumes and a prolonged diagnosis/prognosis timeline. The sample from a patient is often of a limited volume and not amenable to processing or to procedures requiring multiple steps that extend the processing time. The devices and methods of the current application provide considerable advantages that work to mitigate these problems, such that SERS spectral detection of biological and chemical samples may be performed in a real-time, microfluidic environment.

SUMMARY

[0010] In one embodiment, the invention involves the integration of SERS substrates into microfluidics systems. The SERS substrates include various nanoscale structures such as nanopillars, nanorings, nanotriangles, nanobowties, nanospheres, nanorods, and/or nanospirrals.

[0011] In one embodiment, the invention provides a method for determining the activity of a target biomolecule using a surface enhanced Raman spectroscopy (SERS) system. The method comprises introducing a fluid sample into a microfluidic optical chamber wherein the optical chamber comprises a Raman active surface with a plurality of substrates extending therefrom. Passage of the fluid sample through the microfluidic optical chamber allows for specific binding and/or interaction between a biomolecule in the fluid sample and a plurality of said substrates. The enzymes or proteins in the fluidic sample exert an effect on the surface-immobilized biomolecule, either by cleavage or addition of chemical groups. These alteration effects can be detected by reading the Raman signal on the surface with SERS.

[0012] In one embodiment, the invention has minimal to no requirement for washing of the fluid sample. The change to the surface-bound biomolecules can be measured without significant interference from the molecules in the fluidic sample.

[0013] In some embodiments, a laser is directed at the fluid sample in the microfluidic optical chamber, wherein the interaction of the laser with the fluid sample produces a SERS signal that is specific for the interaction between the biomolecule and the substrate.

[0014] In some embodiments, the presence, quantity and/or activity of a biomolecule may be detected by recording a change in the Raman scattering spectrum of the biomolecule upon binding to the plurality of substrates.

[0015] In one embodiment, cells are lysed and the lysates are applied to target molecules on a SERS surface, without purification of enzymes from the lysates. The absence of the enzyme purification steps allows for direct and quick measurement of enzyme activity, and reduction of result variation due to sample manipulation.

[0016] In one embodiment, the labeling of target proteins with additional labels is not required.

[0017] In a further embodiment, a set of protease substrate peptides are immobilized on the surface in a microarray format, or in a linear row, or in a folded channel such as a serpentined channel, for example.

[0018] In another embodiment, Raman label molecules, metal ions, and/or nanocomposite are conjugated to the enzyme substrate to enhance the Raman signal. Organic solvents may also be added in the sample to enhance the Raman signal.

[0019] In one embodiment, a set of kinase substrate peptides are immobilized on the surface in a microarray format, or in a linear row, or a folded channel such as a serpentined channel, for example.

[0020] In one embodiment, the sample volume is 10 microliters or less, and in a preferred embodiment, the sample volume is less than 1 microliter. The concentration range required for detection may be 1 micromolar or less.

[0021] In one embodiment, the reaction dynamics and kinetics measurements may be detected in real-time, rather than in end-point fashion, as labeling methods in the art require. Multiple data points may be obtained from the reaction at a data rate of between about 1 millisecond to 1 minute per measurement, and at a time duration from between about 1 minute to 24 hours.

[0022] In a further embodiment, a washing step is not required in the real time measurement as the SERS detection is a near field optical detection method, and thus only molecular reaction events at the SERS substrate surface can be detected. Reactions taking place at roughly100 nanometers distant from the surface will not contribute significantly to the signal. In this embodiment, the removal of noise generated from background compounds is realized by the natural or facilitated diffusion of the background compounds from the SERS substrate surface.

[0023] In another embodiment, multi-channel measurement can be performed by employing a multichannel microfluidic system. These measurements can be completed simultaneously without interfering with each other.

[0024] In one embodiment, a high speed optical scanning system can be used for scanning multiple channels in a timely manner. In a particular embodiment, the high speed optical system involves using a motorized galvo mirror to scan multiple samples.

[0025] In one embodiment, the microfluidic operation is fully automated including sample loading, sample mixing, reagent exchange, sample heating and temperature control, *etc.* The fluidic actuation methods include, but are not limited to, mechanical pumping, optical pumping, and thermal pumping.

[0026] In one embodiment, the liquid flow can be controlled during the optical measurement to facilitate reagent mixing, to increase diffusion of lytic reaction end products from the surface, and to prevent molecule precipitation, and so forth.

[0027] In a further embodiment, a polarized laser may be used as the excitation source, and molecular chirality may be measured with increased signal-to-noise ratio.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Particular embodiments are best understood from the following detailed description when read in conjunction with the accompanying drawings. It is emphasized that, according to common practice, the various features of the drawings may not necessarily be to-scale. In some cases, the dimensions of various features may be arbitrarily expanded or reduced for clarity.

[0029] FIGS. 1A-1F show an example fabrication process for a silicon based surface enhanced Raman scattering (SERS) substrate device in accordance with embodiments of the present invention.

[0030] FIGS. 2A-2F show process diagrams of printing various molecular probes on a SERS chip in accordance with embodiments of the present invention.

[0031] FIGS. 3A-3B show an example assembly process with a completed assembly of an example microfluidic molecular diagnostic device in accordance with embodiments of the present invention.

[0032] FIGS. 4A-4B show an example of use of microfabrication masks for making two-channel devices in accordance with embodiments of the present invention.

[0033] FIGS. 5A-5B show principles of protease and/or nuclease biomarker detections in an example microfluidic SERS chip in accordance with embodiments of the present invention.

[0034] FIGS. 6A-6B show principles of a phosphorylation event. Alterations in biomarkers are detected in an example microfluidic SERS chip in accordance with embodiments of the present invention.

[0035] FIGS. 7A-7B show example views of an integrated well plate and silicon microfluidic device structure in accordance with embodiments of the present invention.

[0036] FIG. 8 shows an example configuration of a fluorescence detection system for a microfluidic protease/nuclease biomarker diagnostic device in accordance with embodiments of the present invention.

[0037] FIG. 9 shows an example configuration of a Raman detection system for the microfluidic protease/nuclease biomarker diagnostic device in accordance with embodiments of the present invention.

[0038] FIG. 10 shows an example configuration of a high throughput Raman detection system for a microfluidic protease/nuclease biomarker diagnostic device in accordance with embodiments of the present invention.

[0039] FIG. 11 shows an example Raman signal enhancement of peptide probes in kinase biomarker detections in accordance with embodiments of the present invention.

[0040] FIG. 12 shows a flow diagram of an example method of fabricating a structure for a microfluidic optical device in accordance with embodiments of the present invention.

[0041] FIG. 13 shows a flow diagram of an example method of making a device for discovery of characteristics of a fluid sample in accordance with embodiments of the present invention.

[0042] FIG. 14 shows a flow diagram of an example method of using a discovery device for fluid sample analysis in accordance with embodiments of the present invention.

[0043] FIG. 15. shows a galvo mirror drawing. The motorized galvo mirror allows for the quick scan of multiple substrate coordinates.

DETAILED DESCRIPTION

[0044] Before the methods and devices of embodiments of the present invention are described, it is to be understood that the invention is not limited to any particular embodiment described, as such may, of course, vary. It is also to be understood that the terminology used herein is with the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[0045] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0046] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The present disclosure is controlling to the extent there is a contradiction between the present disclosure and a publication incorporated by reference.

[0047] It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a peptide" includes a plurality of such peptides and

reference to "the method" includes reference to one or more methods and equivalents thereof known to those skilled in the art, and so forth.

[0048] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

DEFINITIONS

[0049] The terms "nucleic acid" and "polynucleotide" are used interchangeably herein to refer to deoxyribonucleotides or ribonucleotides, and polymers thereof, in either single- or double-stranded form. The terms generally encompass nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

[0050] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, *e.g.*, an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0051] "Biological sample" as used herein is a sample of biological tissue or chemical fluid that is suspected of containing an analyte of interest. Samples include, for example, body

fluids such as whole blood, serum, plasma, cerebrospinal fluid, urine, lymph fluids, and various external secretions of the respiratory, intestinal and genitourinary tracts such as tears, saliva, semen, milk, and the like; and other biological fluids such as cell culture suspensions, cell extracts, cell culture supernatants. Samples may also include tissue biopsies, *e.g.*, from the lung, liver, brain, eye, tongue, colon, kidney, muscle, heart, breast, skin, pancreas, uterus, cervix, prostate, salivary gland, and the like. Samples may also be microbiopsies, small samples or even single cells extracted from patients and subsequently processed, for example, using laser capture microdisecction. A sample may be suspended or dissolved in, *e.g.*, buffers, extractants, solvents, and the like. A sample can be from any naturally occurring organism or a recombinant organism including, *e.g.*, viruses, prokaryotes or eukaryotes, and mammals (*e.g.*, rodents, felines, canines, and primates). The organism may be a nondiseased organism, an organism suspected of being diseased, or a diseased organism. A mammalian subject from whom a sample is taken may have, be suspected of having, or have a disease such as, for example, cancer, autoimmune disease, or cardiovascular disease, pulmonary disease, gastrointestinal disease, musculoskeletal, disorders, central nervous system disorders, infectious disease (*e.g.*, viral, fungal, or bacterial infection). The term biological sample also refers to research samples which have been deliberately created for the study of biological processes or discovery or screening of drug candidates. Such examples include, but are not limited to, aqueous samples that have been doped with bacteria, viruses, DNA, polypeptides, natural or recombinant proteins, metal ions, or drug candidates and their mixtures.

[0052] The terms "peptide" and "peptidic compound" are used interchangeably herein to refer to a polymeric form of amino acids of from about 10 to about 50 amino acids (may consist of at least 10 and not more than 50 amino acids), which can comprise coded and non-coded amino acids, chemically or biochemically modified or derivatized amino acids, L- or D- amino acids, peptides having modified peptide backbones, and peptides comprising amino acid analogs. The amino acid may be limited to only amino acids naturally occurring in humans. The peptidic compounds may be polymers of: (a) naturally occurring amino acid residues; (b) non-naturally occurring amino acid residues, *e.g.*, N-substituted glycines, amino acid substitutes, *etc.*; or (c) both naturally occurring and non-naturally occurring amino acid residues/substitutes. In other words, the subject peptidic compounds may be peptides or peptoids. Peptoid compounds and methods for their preparation are described in WO 91/19735, the disclosure of which is hereby incorporated

in its entirety by reference herein. A peptide compound of the invention may comprise or consist of 23 amino acids or from 18 to 28 amino acids or from 20 to 26 amino acids. The active amino acid sequence of the invention comprises or consists of three motifs which may be overlapping, which are: an integrin binding motif sequence, a glycosaminoglycan binding motif sequence, and a calcium-binding motif.

[0053] By "protein" is meant a sequence of amino acids for which the chain length is sufficient to produce the higher levels of tertiary and/or quaternary structure. This is to distinguish from "peptides" or other small molecular weight drugs that do not have such structure. Typically, a protein will have a molecular weight of about 15-20 kD to about 20 kD.

[0054] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

[0055] The term "substrate" when used in context of biochemistry, means a molecule upon which an enzyme acts. Enzymes catalyze chemical reactions involving substrates. A substrate binds to an enzyme's active site, and an enzyme-substrate complex is formed. The substrate is broken down into a product and is released from the active site.

[0056] The term "substrate" when used in context of material science, is used to describe the base material or surface on which processing is conducted to produce new film or layers of material such as deposited coatings, attachment of nucleic acids, peptides, sugars, and fatty acids, *etc.*

[0057] A "kinase" is an enzyme that catalyzes the transfer of a phosphate group (*e.g.*, from ATP or GTP) to a target molecule such as a kinase substrate, leading to phosphorylation of the substrate.

[0058] A "kinase substrate" refers to a molecule that can be partially or completely phosphorylated by a kinase.

[0059] A "phosphatase" is an enzyme that catalyzes the removal of a phosphate group from a phosphatase substrate thereby resulting in the partial or complete dephosphorylation of that substrate.

[0060] A "phosphatase substrate" refers to a molecule that can be partially or completely dephosphorylated by a phosphate.

[0061] The terms "treatment," "treating" and the like are used herein to refer to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented. In general, this encompasses obtaining a desired pharmacologic and/or physiologic effect, *e.g.*, stimulation of angiogenesis. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. The terms as used herein cover any treatment of a disease in a mammal, particularly a human, and include: (a) preventing a disease or condition (*e.g.*, preventing the loss of cartilage) from occurring in a subject who may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, *e.g.*, arresting loss of cartilage; or (c) relieving the disease (*e.g.*, enhancing the development of cartilage).

[0062] The terms "subject," "individual," "patient," and "host" are used interchangeably herein and refer to any vertebrate, particularly any mammal and most particularly including human subjects, farm animals, and mammalian pets. The subject may be, but is not necessarily under the care of a health care professional such as a doctor.

[0063] "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, *etc.* Preferably, the mammal is human.

[0064] A "disorder" is any condition that would benefit from treatment with the peptide. This includes chronic and acute disorders or diseases including those pathological conditions which predispose the mammal to the disorder in question. Non-limiting examples of disorders to be treated herein include skeletal loss or weakness and bone defects or breakage.

[0065] "Surface Enhanced Raman Spectroscopy", or "Surface Enhanced Raman Scattering", often abbreviated SERS, is a surface sensitive technique that results in the enhancement of Raman scattering by molecules adsorbed on rough metal surfaces. The enhancement factor can be as much as 10^{14}-10^{15}, which allows the technique to be sensitive enough to detect single molecules.

[0066] "Raman scattering" or "Raman effect" is the inelastic scattering of a photon. When light is scattered from an atom or molecule, most photons are elastically scattered. The scattered photons have the same energy (frequency) and wavelength as the incident photons. However, a small fraction of the scattered light is scattered by an excitation, with

the scattered photons having a frequency different from, and usually lower than, the frequency of the incident photons.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0067] Certain embodiments of the invention include microchips with microfluidic sample flow channels, active nanostructured surfaces, optical windows, and attached molecular probe arrays for multiplexed optical detection. Advantages include ultra small sample volume, high detection speed, throughput, sensitivity, reliability and completeness over the conventional molecular diagnostic method and devices, as well as two to three orders of magnitude lower cost. This may be applied to the molecular-level disease diagnosis in laboratory and clinical environments with unprecedented sensitivity, accuracy and affordability.

[0068] Methods and devices are provided for a device for surface enhanced Raman scattering (SERS) detection from microchannels in silicon or plastic substrates. The silicon device can be formed by separately etching and machining different microstructures with appropriate masking and different protective coatings and layers, which may be individually removed prior to final etching to provide deep microstructures, and by chemical and physical surface roughening to generate unique nanostructures as SERS substrate. The device can accommodate parallel fluid streams, and allow focused laser light to illuminate the SERS substrate surface. For molding with polymeric materials, the silicon device may be replicated twice and used with polymers to obtain a desired result.

[0069] The present invention demonstrates an integrated microscale fluidic chamber with sub-micro liter volume and a nanostructured surface for SERS spectroscopy. The microscale optical chamber has one transparent surface which allows for light to be transmitted in the chamber and illuminated onto a SERS substrate surface. This also allows Raman scattering light to be transmitted out of the chamber and collected. Compared to the conventional optical chamber or cuvette used for Raman measurements, the volume of this Raman detection fluidic chamber may be smaller than 1 μL. The shorter or shallower microchannel can allow for further miniaturization of the detection module in the chip. The SERS signal can be detected by a spectrometer camera but the required volume can be more than 1000 times smaller than that used in conventional Raman spectroscopy. The microscale dimensions of the optical chamber can enable integration of multiple individual optical chambers in one chip, such that multiplexed SERS spectroscopy

of 2, 3, 8, 16, 32, 48, 96, 192, 384, 768, and even 1536 samples can be accomplished using a single device which holds all the samples at once.

[0070] Accordingly, certain embodiments present high sensitivity biomolecule detection on a chip with simultaneous detection of SERS spectra. The fluidic sample flow and reaction temperature in the microscale chamber may be controlled by external electronics, and/or mechanical micro-pumps. Due to the relatively small volume of the microchip and the fluidic sample, the flow rate and heating/cooling rate can be orders of magnitude higher than bulk scale counterparts, which enable many special applications, such as on-chip PCR and fast fluidic exchange.

[0071] Particular embodiments include a monolithically fabricated nanostructured SERS substrate, also enclosed in a microfluidic chamber such that SERS spectral detection of a biological/chemical sample can be implemented in the microfluidic environment. The unique microfabrication, nanofabrication and packaging as described herein allows for the detection of SERS spectra in a simulated aqueous biological environment.

[0072] Multiple biological or enzymatic substrate extensions, such as small peptides and nucleotides may be attached on the SERS substrate in the microfluidics chamber, and may also be specific to multiple kinds of biomarkers, such as enzymes, for example, which are related to cancer, cardiovascular disease, diabetes and neurological diseases. Human and animal fluidic samples can be introduced into the microfluidic chamber and reacted with the attached probes. The chemical change of the probes can be detected by SERS spectral detection.

[0073] Conventionally, a chemical or biological sample is dropped on the SERS substrate and dried for Raman spectroscopic analysis. However, real time biological events may only occur in aqueous solutions. Particular embodiments of the present invention allow for the detection of biomolecule Raman signals in a simulated biofluidic environment for both static and dynamic biochemical reactions.

[0074] Nanostructures may be on the surface of the microfluidics channel to provide enhancement of optical signals or to anchor enzymatic substrate extensions to capture target molecules or particulates for detection. Substrate extensions, such as antibodies, aptamers, DNA or RNA oligonucleotides and longer extensions, including peptides, polysaccharides, polymers, small molecules, *etc.*, can be chemically linked to the surfaces of the microfluidic chamber in the chip. Enzymatic substrate extensions may also be

tethered to physically fabricated nanostructures to create nanobio-hybrid probes in the microfluidic chamber.

[0075] Particular embodiments as described herein have applications in, *inter alia*, diagnostic tests and molecular diagnostics. For example, molecular diagnostics, and in particular molecular diagnostics that detect biomarkers related to cancer, measure biomarkers including small molecule metabolites or metabolic intermediates, nucleic acids, carbohydrates, proteins, protein fragments, protein complexes and/or derivatives or combinations thereof. Chemical assays such as analytical methods that employ spectroscopic detection systems may be used in the detection and quantification of such biomarkers, and may provide information about the interaction of biomarkers with test molecules such as small molecules, enzymes, carbohydrates, nucleic acid probes, nucleic acid or protein aptamers, peptide nucleic acids, peptides, or polyclonal or monoclonal antibodies. Such assay methods may be employed initially during the identification, characterization, and development of molecular diagnostics, and may also be employed as molecular diagnostic tests used to assay biological samples and thus measure the health status of patients or to provide information that may support medical decisions.

[0076] Particular embodiments also have applications in, *inter alia*, molecular therapeutics. For example, identification and characterization of drug targets may involve detection and quantification of such drug targets in biological samples. Chemical assays and analytical methods that employ spectroscopic detection systems may be used to detect and quantify potential drug targets including proteins such as cell surface proteins, extracellular proteins, peptide hormones, transmembrane proteins, receptor proteins, signaling proteins, cytosolic proteins or enzymes, nuclear proteins, DNA-binding proteins, RNA molecules including messenger RNA or micro-RNAs, and/or DNA. Such assays and methods may also provide information about the interaction of drug targets with drugs such as small molecules, polyclonal or monoclonal antibodies, therapeutic proteins or therapeutic enzymes, antisense nucleic acids, small-interfering RNAs, nucleic acid or protein aptamers, peptide nucleic acids, or other drugs and potential drugs. Such assay methods may be employed initially during the identification, characterization, and development of molecular therapeutics, and may also be employed in tests to identify individual patients' responsiveness to treatment with drugs or potential drugs, and thus provide valuable information that may support medical decisions.

[0077] Silicon wafers are preferable to conventional antibody affinity binding assay substrates that can only detect concentration. Other semiconductor wafers (*e.g.*, GaAs, InP, GaP, GaSb, InSb, InAs, CaF_2, LaAl2O3, LiGaO2, MgO, SrTiOq, YSZ and ZnO) can also be used in certain embodiments. Suitable semiconductor materials for the wafer include, but are not limited to, elements of Groups II-VI (ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, *etc.*) and III-V (GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, *etc.*) and IV (Ge, Si, *etc.*) groups on the periodic table, and alloys or mixtures thereof. Suitable metals and metal oxides for the surface coating include, but are not limited to, Au, Ag, Co, Ni, Fe_2O_3, TiO_2, and the like. Suitable carbon nanoparticles for surface coating include, *e.g.*, carbon nanospheres, carbon nano-onions, carbon nanotubes, and fullerene.

[0078] In particular embodiments, enzymatic activity, in addition to protein concentration may be detected. In the context of prostate tumors, for example, whereas prostate-specific antigen (PSA) concentration can now be detected, such assays do not necessarily clarify whether the antigen is active or not, and may provide a misleading measurement. An aspect of certain embodiments of the invention includes generating information regarding not only concentration, but also activity. Further, particular embodiments also include a detection system in lieu of a chip scanner.

[0079] A system for liquid sample microspectroscopy in certain embodiments may generally include a detection apparatus (*e.g.*, instrumentation portion) coupled to a microfluidics optical device (*e.g.*, a chip or integrated circuit (IC) portion). The detection apparatus can include a light source for sending light through a liquid sample to be characterized, and a spectrograph and/or analysis unit to analyze the light (*e.g.*, fluorescence, absorbance, *etc.*), which is affected by the molecules of the sample. The microfluidic optical device can be fabricated using semiconductor processing techniques, and may be packaged to protect the semiconductor therein and to accommodate inlet/outlet ports for the liquid sample.

[0080] Referring now to FIGS. 1A-1F, shown is an example fabrication process for a silicon based surface enhanced Raman scattering (SERS) substrate device in accordance with embodiments of the present invention.

[0081] FIG. 1A shows thermal deposition of relatively thin layers of polycrystalline silicon 104-0 and 104-1 on top and bottom surfaces of single crystal wafer 102. For example,

polycrystalline silicon layers 104-0 and 104-1 can be in a range of from about 100 nm to about 500 nm thick, such as from about 200 nm to about 400 nm, and more specifically about 300 nm.

[0082] FIG. 1B shows laser drilling or chemical etching of via-holes 116 through wafer 102 and polycrystalline silicon 104-0/104-1. The etchant may be hot potassium hydroxide and a 30W carbon dioxide laser may be employed. In one embodiment, via-holes 116 may have a diameter/width of about 100 μm. Of course, any suitable width for these via-holes (*e.g.*, within ranges of from about 80 μm to about 120 μm, or from about 50 μm to about 150 μm) can be utilized in particular embodiments. For example, these via-hole widths may also be configured to form a filtering function, such as by disallowing larger molecules from flowing into the microfluidic optical chamber, as will be discussed in more detail below.

[0083] FIG. 1C shows photoresist 106 applied on portions of polycrystalline silicon 104-0 to allow for photolithography patterning of to-be-etched areas.

[0084] FIG. 1D shows plasma etching 108 of polycrystalline layer 104-0 to form silicon nanostructures 110. Plasma etching 108 can include multiple steps in order to form geometric shapes or other suitable "roughness" on a surface of silicon nanostructure 110. For example, a nanopyramid array can be formed by application of a plasma treatment that includes $HBr + O_2$ for less than about 10 seconds. Plasma etching with HBr for from about 10 seconds to about 20 seconds can form nanopillar arrays. Oxide portions can then be removed from the pillars by plasma etching that includes, *e.g.*, SF_6. Next, the surface can be plasma etched for from about 1 minute to about 2 minutes with HBr plasma. Such an approach can produce nanopyramids having a height of from about 50 nm to about 200 nm, and more specifically about 100 nm.

[0085] Any suitable type of nanostructures can be implemented in certain embodiments. Any shape that accommodates an enhancement of certain frequencies inherent or appearing after modification of the substrate, such as by enzymatic substrate accommodation discussed below in further detail, can be utilized. Other example nanostructure may include different geometries with enhancement properties, nano rings, nano squares, nano wires, parallel wires, nano grooves, *etc.*, and these structures can be formed using e-beam, lithography, or any suitable processing method.

[0086] FIG. 1E shows metal deposition 112 of a thin film 114. For example, the deposited metal 114 can include gold, silver, platinum, palladium, or copper, *etc.*, and the thickness

of the thin film 114 can be from about 10 nm to about 80 nm, such as from about 20 nm to about 60 nm, and more specifically about 40 nm.

[0087] FIG. 1F shows the removal of photoresist 106 and annealing of thin metal nanoparticles 114 to form a smoothed metallic coating surface of layer 114. Suitable annealing temperatures may be from about 200-300°C, and more preferably 250°C.

[0088] A surface of layer 114 in particular embodiments may be relatively rough, or may contain other geometrical properties, *e.g.*, of sharp edges/points to make enhanced electromagnetic fields around such edges.

[0089] Referring now to FIGS. 2A-2F, shown are process diagrams of printing various molecular probes on a SERS chip in accordance with embodiments of the present invention. Different types of peptides or nucleotides may be dropped on a metallized nanostructure SERS substrate using microscale contact pins or injectors. Formed enzymatic substrate extensions can covalently bond to the SERS substrate surface.

[0090] FIG. 2A shows polycrystalline silicon 104-0 and 104-1 on either surface of single crystal wafer 102, with metal nanoparticles 114, and via-holes 116. Probe 204 can be positioned to apply a drop 202-0 of peptides or nucleotides. FIG. 2B shows enzymatic substrate extension 206-0 that is formed from a covalent bond between metal nanoparticles 114 and drop 202-0 of peptides/nucleotides.

[0091] FIG. 2C shows a repositioning of probe 204 with a different drop 202-1, and FIG. 2D shows a corresponding enzymatic substrate extension 206-1. Probe 204 can be repositioned a number of times to create a plurality of enzymatic substrate extensions bonded to metal nanoparticles 114.

[0092] FIG. 2E shows enzymatic substrate extensions 206-0, 206-1, 206-2, and 206-3. Probe 204 can then be repositioned to release drop 202-4 as shown. FIG. 2F shows a completed group of enzymatic substrate extensions in SERS substrate chip 210, including extension 206-4 corresponding to drop 202-4. In addition, an electromagnetic field around each enzymatic substrate extension may be altered, and metal 114 may serve as an enhancer for electromagnetic or photonic excitation of certain frequencies.

[0093] Referring now to FIGS. 3A and 3B, shown is an example assembly process with a completed assembly of an example microfluidic molecular diagnostic device in accordance with embodiments of the present invention. Generally, three separated units can be included in the assembly process. A top layer can be formed with polydimethylsiloxane (PDMS) portions 306-0 and liquid sample inlet 302 and outlet 304. Because the optical

apparatus or instrumentation portion may be placed on an opposite chip side (*e.g.*, the bottom side) relative to inlet/outlet channels (*e.g.*, the top side), there is substantial leeway as to placing the inlet and outlet channels without interfering with the optical analysis aspects. A middle unit can include SERS substrate chip 210 with enzymatic substrate extensions. A bottom layer can include PDMS portions 306-1 and transparent window 310 to accommodate microfluidic channels therein.

[0094] In particular embodiments, transparent window 310 can generally be relatively thin such that optical loss due to absorption in the window can be minimized (*e.g.*, to under about 10%). Typical window implementations can be in a range of about 1-3 mm thick, whereas particular embodiments can allow for such a window thickness of from about 200 μm to about 300 μm. Further, a transparent window in certain embodiments can be formed of any suitable material that is transparent to the spectrum of light (*e.g.*, SiO_2, PDMS, cyclic olefin copolymer (COC) polymer, or any ultraviolet (UV) transparent plastics, *etc.*).

[0095] FIG. 3B shows an example assembled discovery tool device. Bonding the three separated units shown in FIG. 3A into the assembly of FIG. 3B can include using covalent bonding between silicon dioxide on silicon surface (*e.g.*, polycrystalline silicon layers 104-0, 104-1) and active siloxane groups on PDMS surfaces (*e.g.*, 306-0 and 306-1). The assembly can also include formation of microfluidic optical chamber 318 for analysis of a sample fluid received via inlet 302 and output via outlet 304.

[0096] Generally, certain embodiments can include an instrumentation portion discussed in more detail below, as well as an integrated circuit (IC) portion 210. Transparent window 310 may serve to isolate IC portion 210 from the instrumentation portion. The IC portion can include semiconductor material 102, with via-holes 116 therein to accommodate inlet 302 and outlet 304 ports as shown. Semiconductor material 102 can include any suitable semiconductor material, such as silicon (Si), germanium, silicon dioxide, gallium arsenide (GaAs), *etc.* Suitable semiconductor materials for the wafer include, but are not limited to, elements of Groups II-VI (ZnS, ZnSe, ZnTe, CdS, CdSe, CdTe, HgS, HgSe, HgTe, MgS, MgSe, MgTe, CaS, CaSe, CaTe, SrS, SrSe, SrTe, BaS, BaSe, BaTe, *etc.*) and III-V (GaN, GaP, GaAs, GaSb, InN, InP, InAs, InSb, *etc.*) and IV (Ge, Si, *etc.*) groups on the periodic table, and alloys or mixtures thereof.

[0097] In certain embodiments, mixing of a sample solution can be controlled for optical chamber 318 in order to observe real-time reactions of different chemicals and/or multiple components being pumped into the inlet at the same time. Further, inlet 302 and/or outlet

304 can be coupled to any suitable type of tubing (*e.g.*, plastic tubing), and the diameter of the via-holes can range from about 100 μm to about 1 mm. Further, sizes of the inlet and outlet channels or ports can be varied, thus providing a filtering function by allowing for different sample volumes, molecule sizes, *etc.*, depending upon the particular application.

[0098] In one embodiment, through-holes can provide ducts for a liquid sample flowing through microfluidic optical chamber 318, such that that liquid handling units can be installed on a side of the silicon chip other than the side where the microscale optical chambers are positioned. Without having the liquid handling units (*e.g.*, reservoirs, connectors, tubings, or pumps) obstructing the microscale optical chamber, optical systems can have substantial exposure to chamber 318. Also, chamber 318 in certain embodiments may extend in length in a range of from about 10 μm to about 10 cm long, such as from about 500 μm to about 2 cm, and more specifically about 1 cm, to accommodate a variety of enzymatic substrate extensions 206. A depth of chamber 318 can range from about 10 μm to about 200 μm for providing a μL or sub-μL sample volume. For example, chamber 318 may hold a sample volume in a range of from about 0.10 μL to about 2 μL of fluid.

[0099] Inlet 302 and/or outlet 304 may be coupled to multiple channels, where these pathways can be routed, and may be arranged in an array format to allow easy loading via robots (*e.g.*, to accommodate standard distances for such loading). A polymer bonding layer may also be used in the assembly, and may include any suitable layer of soft or hard plastic (*e.g.*, PDMS, epoxy, adhesive rubber, a metal, *etc.*). The surface of the silicon device may also be oxidized by plasma enhanced chemical vapor deposition (PECVD), or electron beam evaporation. In addition, a liquid handling package can surround left and right edges of the structure, as well as covering the top portion along with a sealing material (*e.g.*, epoxy, PDMS, rubber, glass, quartz, *etc.*).

[00100] Referring now to FIG. 4A, an example top view of microfabrication masks for making two-channel devices in accordance with embodiments of the present invention is shown. In this example, a silicon wafer 402 can be defined with device masking, inlet/outlet reservoir 404 masking, microfluidic optical chamber 406 masking, and via-hole masking layers. As shown in the example close-up top view of the mask structures in FIG. 4B, via-hole masking layer 408 can be aligned with an edge of microfluidic optical chamber 406, and within the inlet/outlet reservoir 404 masking layer.

[00101] Referring now to FIGS. 5A and 5B, shown are principles of protease and nuclease biomarker detections in an exemplary microfluidic SERS chip in accordance with

embodiments of the present invention. Different line types on the SERS substrate surface 114 represent exemplary peptide/nucleotide enzymatic substrate extensions, such as 206-3 and 206-4. The triangle pairs (*e.g.*, 502 and 504) represent exemplary protease and/or nuclease biomarkers in biofluidic samples.

[00102] FIG. 5B shows decomposed procedures of biomarker enzymatic reactions, following a sequence of 510 (introduction of biomarker enzymes 502 and 504), 512 (specific binding of biomarker enzymes 502 and 504 with enzymatic substrate extensions 206-3 and 206-4), 514 (restrictive cleavage of enzymatic substrate extensions), and 516 (washing of reaction residues to leave modified enzymatic substrate extensions 206-3' and 206-4').

[00103] Referring now to FIGS. 6A and 6B, shown are principles of kinase biomarker detection in another exemplary microfluidic SERS chip in accordance with embodiments of the present invention. Different line types on the SERS substrate surface 114 represent exemplary enzymatic substrate extensions, such as 206-1 and 206-2. The triangle pairs (*e.g.*, 602 and 604) represent kinase biomarkers in biofluidic samples. It is noted that the substrate extensions are not limited to enzymes, but may include various other molecules mentioned herein, such as, for example, antibodies, aptamers, DNA or RNA oligonucleotides and longer extensions, including non-enzymatic peptides, polysaccharides, polymers, small molecules, *etc.*, all of which may be acted upon and/or modified by molecules in the incoming biofluidic sample. All such substrate extensions are capable of being chemically linked to the surfaces of the microfluidic chamber in the chip. Likewise, 602 and 604 do not necessarily represent enzymatic biomarkers in all embodiments of the invention. Rather, incoming biomarkers to be analyzed may include nucleic acids (DNA and RNA), other non-enzymatic proteins, peptides, sugars/carbohydrates, metabolites and small chemical compounds.

[00104] FIG. 6B shows decomposed procedures of exemplary biomarker enzymatic reactions, following a sequence of 610 (introduction of biomarker enzymes 602 and 604), 612 (specific binding biomarker enzymes 602 and 604 with enzymatic substrate extensions 206-1 and 206-2), 614 (phosphorylation 606 of enzymatic substrate extensions), and 616 (washing of reaction residues).

[00105] Referring now to FIG. 7A, an example top view of an integrated well plate and silicon microfluidic device structure in accordance with embodiments of the present invention is shown. FIG. 7B shows a cross-section view of the example structure of FIG.

7A. Silicon device 704 can be topped by microfluidic network layer (*e.g.*, PDMS) 706, and well plate 702. Thus, such a multichannel version can have access holes through to the top of the structure for a microfluidic channel or routing layer. In this fashion, a microfluidics optical chip can be integrated with 96, 384, 1536, *etc.*, micro well plates that may comply with standard micro well plate dimensions. The assembly of the microfluidics optical chip with the micro well plates may then be compatible with standard robotic liquid handling systems.

[00106] Referring now to FIG. 8, shown is an example configuration of a fluorescence detection system for a microfluidic protease/nuclease biomarker diagnostic device in accordance with embodiments of the present invention. The fluorescence enzymatic substrate extensions at a free end of each peptide/nucleotide may be removed with the proteolytic/nucleolytic reactions, and serve as optical beacons for biomarker diagnosis.

[00107] In this fashion, enzymatic substrate extensions can provide targets for enzymes in the sample solution, whereby proteases may attach in dynamic recognition followed by catalysis. Thus, in particular embodiments, a chemical reaction occurs on enzymatic substrate extensions (*e.g.*, 206-3, 206-4, *etc.*). In contrast, conventional approaches typically include a DNA probe on the surface, which measures other DNA in the solution, but does not actually change the substrate, but instead provides a binding or recognition result. In certain embodiments, initial binding occurs, however, this may be followed by an observed catalysis. This is due to the fact that an enzyme in the solution for analysis effectively changes the substrate (*e.g.*, by removing a phosphate group from the substrate, for example).

[00108] In FIG. 8, light source 802 can provide light beams that are filtered using fluorescence excitation filter 814. Filtered light beams can then be reflected by dichroic mirror 822, and passed via objective lens 820 for focusing and input to microfluidic optical chamber 318 through optically transparent window 310. Light source 802 can provide an illumination/excitation light beam that may be any suitable form of light, such as white light, laser light (*e.g.*, visible laser, ultraviolet (UV) laser, near infrared (IR) laser, *etc.*), light emitting diode (LED), super luminescent diode, polarized light, halogen lamp-generated light, continuous or pulsed Xenon Lamp, Mercury light source, Argon light source, Deuterium light source, Tungsten light source and Deuterium-Tungsten-Halogen mixed light source, *etc.* Generally, microfluidic optical chamber 318 can be populated by

molecules of a liquid or sample to be characterized, where the liquid is received via inlet port 302, and can also be discharged via outlet port 304.

[00109] Once the light is reflected in microfluidic optical chamber 318 off a selected enzymatic substrate extension, absorbance can occur via objective lens 820, pass off mirror 822, and be sent to fluorescence emission filter 824, for receipt in detector 830. Detector 830 may also include a charge coupled device (CCD) for analysis of the various wavelengths contained in the received light beam. In this fashion, one or more characteristics of the sample found in chamber 318 can be determined based on analysis of received fluorescence and/or absorbance light in detector 830. Further, and as will be discussed in more detail below, the microscale dimensions of the optical chamber presented herein can allow for integration of multiple individual optical chambers in one chip, such that the multiplexed optical spectroscopy of 2, 96, and even 384 samples, can be accomplished.

[00110] Referring now to FIG. 9, shown is an example configuration of a Raman detection system for an exemplary microfluidic protease/nuclease and/or kinase/phosphorylase biomarker diagnostic device in accordance with embodiments of the present invention. The Raman enzymatic substrate extensions at a free end of each peptide/nucleotide can be removed as a result of proteolytic/nucleolytic reactions. They may also be modified by phosphorylation/dephosphorylation reactions. As such, they may serve as optical beacons for biomarker diagnosis.

[00111] In this particular example, a point detection method allows for the detection of one enzymatic substrate extension at a time. Therefore, the microfluidic optical device and/or the associated instrumentation may be translated for detection of each enzymatic substrate extension. Further, other microfluidic optical devices (*e.g.*, arranged as shown in FIG. 4A) can also be accessed by translating or stepping an instrumentation portion. Here, the instrumentation portion includes laser 902, which can provide a laser beam for reflection off mirror 906. Beam splitter 908 can receive reflected laser beam from mirror 906, and may provide a split beam via lens 904 for microfluidic optical chamber 318. Reflected light is returned via lens 904, passed via beam splitter 908, mirrors 912 and 910, and then provided for analysis to spectrometer 914.

[00112] In this example, spectrometer 914 shows a spectrum or range of wavelengths that show no reaction, while a different spectrum may show that there was a reaction on a particular enzymatic substrate extension. Determining whether a reaction has taken place,

or determining another characteristic of the liquid sample, can include an appearance of a new peak, disappearance of an existing peak, shifting of an existing peak, merging of multiple peaks, splitting of peaks, or any alteration as can be measured by spectrometry. In this fashion, chemical alterations can be detected using optical and/or electromagnetic properties of enzymatic substrate extensions and surrounding regions. Thus, fluorescence labeling of the enzyme substrates may not be required in certain embodiments. In such embodiments, detection of chemical, electromagnetic, acoustic, or any suitable properties possessing complex information for observation is utilized.

[00113] Observable changes may be relatively subtle such that a combination of suitable nanostructures (*e.g.*, nanopyramids on a surface of layer 114) may be added to enhance localized electromagnetic fields near the enzymatic substrate extensions (*e.g.*, 206-3, 206-4, *etc.*) and thereby increase detection. In addition, the analysis in particular embodiments, while not necessarily utilizing a labeling step, may be performed in real-time. This is because the substrate may not need purification, and because time may not be needed to allow for any florescent reaction to take place.

[00114] In one example, a tumor may be metastasized in the blood, affecting kinase activity profiles as compared to normal cells. Measuring kinase activity can convey the particular group or stage of the cancer, so that it may be treated with appropriate chemo- and/or immunotherapy, for example. In cancer, certain proteases may be upregulated. They may also exhibit altered enzymatic profiles, which can be identified using particular embodiments of the claimed invention. A biopsy may be placed in solution, and mild detergents used to lyse the cells, providing μL-range volumes for analysis in a lysate. A lysate may contain numerous enzymes (*e.g.*, proteases, nucleases, kinases, phosphatases, *etc.*). In order to observe different enzymes, correspondingly different enzymatic substrate extensions are placed on the microarray (see, *e.g.*, arrangement of FIG. 4A). Distinct enzymatic substrate extensions may be situated on the microarray in order to measure multiple enzymatic reactions simultaneously. Further, particular embodiments of the claimed invention can also measure binding reactions in addition to enzymatic reactions. In such embodiments, protein:protein binding and/or interactions may be detected using surface plasmon resonance (SPR), for example.

[00115] Particular embodiments of the invention may also utilize an antibody array such that different antibodies can have different spectral signatures (*e.g.*, peaks for different events, such as cleaving, different chemical reactions, binding and/or recognition events).

Particular embodiments can analyze any plasma or fluid (*e.g.*, saliva, urine, spinal fluid, *etc.*) that can be used without substantial processing or sample preparation. However, the measurement of processes in prepared samples may be improved relative to corresponding unprepared samples due to possibly interfering fluid constituents. Spectrometer 914 supports a relatively large range which allows for the isolation of measurable signals from disturbing background noise.

[00116] Referring now to FIG. 10, shown is an example configuration of a high throughput Raman detection system for a microfluidic protease/nuclease biomarker diagnostic device in accordance with embodiments of the present invention. A fast scanning mirror 1006 may be used in an optical path to convert a point-like laser excitation into a line-like laser excitation, such that multiple enzymatic substrate extensions on the SERS substrate surface can be excited and detected simultaneously by using a two-dimensional spectrograph 1014 to record the SERS spectra of the substrate extensions at a time.

[00117] As discussed above, particular embodiments may also include a scanning platform in order to scan different enzymatic substrate extensions one by one. A scanning mirror 1006, as well as a moving stage for one or more components of the instrumentation portion, are included; each of which may be motor-step driven for high precision. Further, certain embodiments can also include autofocusing and/or other pattern recognition for proper light beam positioning relative to enzymatic substrate extensions for analysis.

[00118] In certain embodiments, a digital light processing ("DLP") device can be used for fine adjustments of the light incident angle with computerized feedback control. For example, such a DLP can replace scanning mirror 1006 in the example configuration shown in FIG. 10.

[00119] In addition to SERS, other spectroscopy modules and/or types of scattering may be employed, such as, for example, mechanical, electromagnetic and/or optical, *etc.*). For example, vibration of a molecule may change with different chemical reactions, where different frequencies of electromagnetic and acoustic ways, and IR may be used to measure rotation or tumbling as to an internal frequency for a molecule to be measured (*e.g.*, from very low to very high, such as microwave frequencies).

[00120] Referring now to FIG. 11, shown is an example Raman signal enhancement of peptide probes in kinase biomarker detection, in accordance with embodiments of the present invention. Because the SERS substrate in certain embodiments includes polysilicon and metal, the substrate with schematic substrate extensions is electrically

conductive. For phosphorylation detection, a positive DC voltage may be applied on the SERS substrate (*e.g.*, metal portion 114), and a DC negative voltage can be applied in an associated reaction buffer. In 1102, positively charged peptide extensions may be repelled and straightened, while the negatively charged kinase enzymes are brought closer to the peptides. In 1104, kinase enzymes can bind to the peptide due to their proximity. In 1106, after the phosphorylation reaction, the peptides carry a negatively charged phosphate group and can thus be attracted to the SERS substrate surface, while the kinase enzymes lose negative charges and may be repelled away. The relatively large conformational change of the peptide after the phosphorylation reaction will likely induce more dramatic changes in the SERS spectra for analysis.

[00121] In the detection or instrumentation module, absorbance and/or fluorescence of the supplied light can be analyzed. Typically, the fluorescence light is at higher wavelengths than the excitation light. Particular embodiments can also support photonic or multi-photonic excitation, where the excitation wavelengths are higher than the emission wavelengths, as well as epi-fluorescence applications that may utilize a separate filter.

[00122] Certain embodiments can also accommodate measurement of scattering light (*e.g.*, X-ray small angle scattering spectroscopy). Measurements may also be taken using polarized light in circular dichrotomomy (CD) applications, which involves measurement of the response degree of angle movement of sample molecules. The fluorescence lifetimes can also be measured for Fourier transformed infrared (FTIR) applications, as well as Raman scattering, and luminescence.

[00123] SPR and nuclear magnetic resonance (NMR) spectroscopy can also be accommodated in particular embodiments. For such applications, the illumination window can receive optically pumped hyper-polarized light, and such optical pumping, as well as the optical realization, can generally occur in close proximity. NMR may typically utilize a homogeneous field for measurement because this approach usually makes use of a metal coil, where the magnetic field can be reversed, and the optical pumping can be through chamber 318, where the magnetic field is around chamber 318. In this fashion, the microfluidic optical chamber can be optically activated.

[00124] Other electromagnetic sources can also be incorporated for manipulating the material sample in the microfluidic optical chamber. For example, particular embodiments can allow for manipulation of sample physical properties using thermal, electromagnetic, optical, dielectric, inhomogeneality, *etc.*

[00125] Another aspect of a particular embodiment of the invention involves the relatively strong thermal conducting nature of silicon material 102, thus allowing the temperature of chamber 318 to be controlled by coupling to a thermal device (heating and/or cooling). For example, a metal block or junction can be used to measure sample material not only at room temperature, but as low as from about 0°C up to about 300°C, or as otherwise determined by the limits of the sample material itself. Thus, if a protein is active and in order to prevent denaturing at higher temperature, a sample measurement can be performed at about 37°C. In another embodiment, thermostable enzymes (*e.g.*, Taq polymerase, and other thermal stable enzymes isolated or engineered from thermophilic microbes) can allow higher temperature (*e.g.*, up to about 99°C) measurements. This type of measurement may not be possible with standard cuvettes without relatively bulky heating/cooling elements being coupled thereto.

[00126] In particular embodiments, such temperature control and an associated sensing unit can be integrated with the microfluidics optical device. For example, such an integrated temperature control and sensing unit can be a Peltier junction heater or metal line resistance heater. This approach can allow for thermocycling analysis of samples at varying temperatures, such as relatively low temperatures to prevent heat-denaturation of proteins, and higher temperatures for real-time genetic amplification using polymerase chain reactions (PCR).

[00127] In this fashion, measurement of chemical, biological, and/or physical reactions to temperature can be accommodated in chamber 318. Any temperature dependent characteristic can be isolated, such as measurement of the melting point of chemicals for assessing chemical purity. Further, some applications may also include a camera. PCR can include a cycling temperature (*e.g.*, between about 55°C and about 95°C), with observance of fluorescence in the reaction (*e.g.*, about 10 ms per frame to about one second per frame) in order to observe a real-time PCR signal. In addition, the concentration and activities of any number of different enzymes such as, but not limited to, nucleases, proteases, kinases, polymerases, glycosylases, topoisomerases, ligases, and phosphatasess can be measured using the microfluidic optical chambers of particular embodiments of the invention.

[00128] Referring now to FIG. 12, shown is a flow diagram of an example method of fabricating a structure for a microfluidic optical device in accordance with embodiments of the present invention. The flow begins (1202), and polycrystalline silicon layers may be

deposited on each side of a single crystal silicon wafer (1204). Via-holes can then be formed, such as by chemical etching or laser drilling (1206). Areas for subsequent etching on the front side of the wafer can then be pattern using photolithography (1208). Silicon nanostructures can then be etched (*e.g.*, using plasma) in the patterned areas (1210). For example, such nanostructures can provide a surface roughness of any suitable shape, such as nanopyramidal arrays. Metal (*e.g.*, gold, silver, *etc.*) can then be deposited on the etched areas (1212). Remaining photoresist can be removed, and the thin metal nanoparticles can be annealed (1214), completing the flow (1216).

[00129] Referring now to FIG. 13, shown is a flow diagram of an example method of making a device for discovery of characteristics of a fluid sample in accordance with embodiments of the present invention. The flow begins (1302), and at least one enzymatic substrate extension may be placed on a metallized nanostructure surface (1304). A structure including the enzymatic substrate extensions can be inverted such that the extensions can reside in a microfluidic optical chamber (1306). A top layer having inlet and outlet ports can then be bonded to the structure (1308). A bottom layer having a transparent window to the structure to form a discovery device with an optical chamber for microfluidic analysis can then be bonded thereto (1310), completing the flow (1312).

[00130] Referring now to FIG. 14, shown is a flow diagram of an example method of using a discovery device for fluid sample analysis in accordance with embodiments of the present invention. The flow begins (1402), and a fluid sample can be received in a microfluidic optical chamber for analysis (1404). Excitation light (*e.g.*, from a laser) can then be provided on an enzymatic substrate extension through a transparent window of the microfluidic optical chamber (1406). Return light from the enzymatic substrate extension can then be received (1408). For example, lenses, mirrors, and splitters can be employed to collect such return light. The return light can then be analyzed (*e.g.*, using a spectrometer or spectrograph) to determine whether a reaction has occurred to modify the enzymatic substrate extension (1410), completing the flow (1412).

[00131] Referring now to FIG. 15, shown is a flow diagram of an example method using a high speed system in accordance with embodiments of the invention. A motorized, rotating, glavo mirror (1506) allows for a quick scan of multiple coordinates on a SERS surface. Each coordinate may be bound by a different biomolecule (1518), which may be targeted by an enzyme or other molecule of interest, for example. Excitation light, *e.g.*, from a laser (1502) contacts a mirror (1504) and is redirected to a rotating, glavo mirror

(1506). Light passes from here to a dichroic mirror (1508) and through to an objective lens (1510). A Raman filter (long pass) (1512) precedes a spectrograph (1514). Each biomolecule (1518) is tethered to a chip surface (1516).

[00132] As depicted in FIG. 15, particular embodiments involve biomolecules that are tethered to the surface. For example, such biomolecules can include nucleic acids (DNA and RNA), proteins, peptides, sugar/carbohydrates, metabolites and small chemical compounds. Further, the surface-tethered biomolecules and chemical molecules may be patterned to form a microscale array of a biochemical assay. Various biochemical libraries may also be deposited on the surface of the microfluidics optical chamber for combinatorial detection. Functional groups can include reactive groups. Functional groups can also include bifunctional crosslinkers having two reactive groups capable of forming a bond with two or more different functional targets (*e.g.*, peptides, proteins, macromolecules, surface coating/surface, *etc.*). In some embodiments, the bifunctional crosslinkers are heterobifunctional crosslinkers with two different reactive groups. To allow covalent conjugation of biomolecule to the surface, suitable reactive groups include, *e.g.*, thiol (-SH), carboxylate (COOH), carboxyl (-COOH), carbonyl, amine (NH_2), hydroxyl (-OH), aldehyde (-CHO), alcohol (ROH), ketone (R_2CO), active hydrogen, ester, sulfhydryl (SH), phosphate ($-PO_3$), or photoreactive moieties. Amine reactive groups can include, *e.g.*, isothiocyanates, isocyanates, acyl azides, NHS esters, sulfonyl chlorides, aldehydes and glyoxals, epoxides and oxiranes, carbonates, arylating agents, imidoesters, carbodiimides, and anhydrides. Thiol-reactive groups include, *e.g.*, haloacetyl and alkyl halide derivates, maleimides, aziridines, acryloyl derivatives, arylating agents, and thiol-disulfides exchange reagents. Carboxylate reactive groups include, *e.g.*, diazoalkanes and diazoacetyl compounds, such as carbonyldiimidazoles and carbodiimides. Hydroxyl reactive groups include, *e.g.*, epoxides and oxiranes, carbonyldiimidazole, oxidation with periodate, N,N'-disuccinimidyl carbonate or N-hydroxylsuccimidyl chloroformate, enzymatic oxidation, alkyl halogens, and isocyanates. Aldehyde and ketone reactive groups include, *e.g.*, hydrazine derivatives for schiff base formation or reduction amination. Active hydrogen reactive groups include, *e.g.*, diazonium derivatives for mannich condensation and iodination reactions. Photoreactive groups include, *e.g.*, aryl azides and halogenated aryl azides, benzophenones, diazo compounds, and diazirine derivatives.

[00133] In one embodiment, a heterobifunctional crosslinker includes two different reactive groups that form a heterocyclic ring that can interact with a substrate peptide. For example, a heterobifunctional crosslinker, such as cysteine, may include an amine reactive group and a thiol-reactive group that interacts with an aldehyde on a derivatized peptide. Additional combinations of reactive groups for heterobifunctional crosslinkers include, *e.g.*, amine and sulfhydryl reactive groups, carbonyl and sulfhydryl reactive groups, amine and photoreactive groups, sulfhydryl and photoreactive groups, carbonyl and photoreactive groups, carboxylate and photoreactive groups, and arginine and photoreactive groups.

[00134] Also in particular embodiments, the microfluidic optical chip can be automatically transported and aligned with an associated spectroscopic imaging system. For example, such transportation and/or alignment may be controlled by a computer using optimization algorithms. Also, special markers can be included on the microfluidic chips, and may be used in automated pattern recognition.

[00135] Certain embodiments can also provide electrodes integrated into the channels such that a voltage potential can be applied across the microfluidics optical chamber to form a capillary electrophoresis system. For example, DNA and protein separation using electrophoresis and isoelectrical focusing can then be realized, and the optical spectra of the biomolecules can be monitored in real-time.

[00136] Also in certain embodiments, the content within the microfluidic optical chamber can be gas phase material, rather than liquid. The optical properties of gas can be measured or monitored continuously in real-time. For example, concentration of particulates in the air can be monitored.

[00137] In certain embodiments, antibodies are tethered to the chip surface. The presence and/or concentration of the corresponding antigen in a sample may be measured. Antibodies specific for a certain cancer biomarker are tethered to the surface in embodiments directed to cancer diagnosis. Among receptor tyrosine kinases, the EGF receptor gene family including *EGFR* and *erb B2*, which are most frequently implicated in human cancers. For example, amplification of *EGFR* and *erb B2* genes for human gastric cancers has been determined at around 3-5% and 10-20% respectively (Albino et al., (1995) Eur. J. Surg. Oncol., 21:56-60; Sato et al., (1997) Pathol. Int., 47, 179-182; Hung and Lao, (1999) Semin. Oncol., 26:51-59). Coamplification of *gastrin* and *erb B2* has been reported for intestinal-type gastric cancers (Vidgren et al., (1999) Genes Chromosomes Cancer, 24, 24-29). Thus, an increase in levels of EGFR and erb B2 proteins accompanied

by elevated levels of gastrin is indicative of intestinal cancer. The sensitivity of the instant invention facilitates detection of marginal increases in levels of these proteins. This improved sensitivity is significant as most gastric cancer is not diagnosed until the cancer has advanced to more serious stages. Moreover, measurement of the protein levels in the method of the invention requires minute sample volumes, making it suitable for testing biopsy samples. A multitude of antibodies suitable for use in the present invention are commercially available from vendors such as AbCam, BioMol, Sigma, *etc.*

[00138] In particular embodiments, enzymatic activity and concentration may also be detected. The substrate for an enzyme is tethered to the nanostructure of the surface and a test sample comprising the enzyme passed over/incubated with the substrate in the conditions conducive to the occurrence of the catalytic reaction. The substrates can be those for proteases, kinases, phosphatases, nucleases, methyltransferases, acetyltransferases, acyltransferases, transaminases, glycosyltransferases, and the like.

[00139] The substrates typically range in length from at least about four residues to up to about 10, 30, 50, 200 or 500 residues. Thus, the substrate for a protease is about four amino acids, and may be up to about 50, 200 or 500 amino acids. Such a substrate may have one or more recognition sequences recognized by the enzyme. Such a substrate may additionally be comprised of non-naturally occurring amino acid, nucleotide, and/or sugar residues. In addition, such a substrate may be modified by enzyme or chemical processes to add or remove functional groups.

Detection of protease activity

[00140] In particular embodiments, the present invention is used to detect protease activity. Proteases are required not only for maintenance of normal cellular functions but are often central to pathogenesis of a variety of human diseases. Parasitic, fungal, viral infections, cancer, inflammatory, respiratory, cardiovascular, and neurodegenerative diseases require proteolytic activity for progression. Detection of protease concentration and/or activity is valuable as a diagnostic /prognostic marker for the presence or likelihood of the disease. Further, detection of inhibition of protease activity is useful in screening for protease inhibitors for treatment of a number of pathologies.

[00141] A "protease" that can be detected and/or quantitated according to the invention is an enzyme that typically hydrolyzes a peptide bond between a pair of amino acids in a protein/peptide, producing a shorter protein/peptide. This activity also referred to as

proteolysis. Proteolysis of the protein/peptide substrate is detectable by changes in spectrum obtained by SERS, electromagnetic resonance measurement or acoustic measurement. Proteases are typically defined by reference to the nucleophile in the catalytic center of the enzyme. The most common nucleophiles arise from the side chains of serine, aspartic acid and cysteine. Accordingly, proteases are classified into protease families such as serine proteases (Paetzel et al. (1997) Trends Biochem. Sci. 22:28-31), aspartyl proteases (Spinelli et al. (1991) Biochemie 73: 1391-1396), and cysteine proteases (Altschuh et al. (1994) Prot. Eng. 7:769-75, 1994). Metalloproteases usually contain a zinc catalytic metal ion at the catalytic center (Klimpel et al. (1994) Mol. Microbiol. 13: 1093-1100).

A "protease recognition site" is a sequence of amino acids in a peptide or protein that contain a pair of amino acids that are hydrolyzed by a particular protease. The specific sequence of amino acids in the protease recognition site typically depends on the catalytic mechanism of the protease, which is defined by the nature of the functional group at the protease's active site. Thus, a protease such as trypsin hydrolyzes peptide bonds whose carbonyl function is donated by either a lysine or arginine residue, regardless of the length or amino acid sequence of the peptide/protein. Other proteases have a higher specificity, *e.g.*, Factor Xa recognizes the sequence Ile-Glu-Gly-Arg and hydrolyses peptide bonds on the C-terminal side of the Arg.

Various preferred protease recognition site include, but are not limited to protease recognition sites for proteases from the serine protease family, or from metallopproteases, or from cysteine proteases, and/or the aspartic acid protease family, and/or the glutamic acid protease family.

Protease recognition sites are well known to those of skill in the art. Recognition sites have been identified for virtually all known proteases. Thus, for example, recognition sites (peptide substrates) for caspases are described by Earnshaw et al. (1999) Annu. Rev. Biochem. 68: 383-424, which is incorporated herein by reference.

[00142] In certain embodiments, substrates for kinases or phosphatases are attached to the nanostructure surface of the device. The attachment is achieved via contact pins, injectors or covalent bonds. Different kinase or phosphatase substrates can be localized at specific locations on the surface, thereby providing an array for the detection of one or more kinases and/or phosphatases and/or the quantitation of the activity of one or more kinases and/or phosphatases. It will be recognized that while the apparatus, methods and

compositions are described with respect to detecting phosphorylation of a substrate, these apparatus, methods and compositions are also useful in detecting dephosphorylation of a substrate.

Kinase/phosphatase activity detection

[00143] Phosphorylation is a common posttranslational modification of proteins and plays a key role on protein structure and function and in all aspects of cell physiology. Protein kinases contain well conserved motifs and constitute the largest family of proteins in the human genome. Mutations of protein kinases are involved in carcinogenesis and several other pathological conditions. Phosphorylations of other biomolecules also play a critical role in the physiology and pathology of cells. Lipid kinases such as the phosphoinositide-3 kinase family members are key modulators of the cellular response to growth factors, hormones, and neurotransmitters and are involved in cancer. Nucleotide and nucleoside kinases regulate the intracellular levels of phosphate donors and nucleic acid precursors and are involved in the cellular response to injury and ischemia. Sugar kinases regulate the rates of sugar metabolism, energy generation, and transcription activation and are involved in the process of cellular transformation and apoptosis. Thus detecting and/or measuring kinase activity is useful in detecting changes in cell/tissue homeostasis, physiology, diagnosing disease conditions and the like.

[00144] Any molecule that can be phosphorylated by a kinase and/or dephosphorylated by a phosphatase can be used as a kinase/phosphatase substrate in the apparatus, methods and compositions described herein. These molecules include proteins, peptides, sugars (*e.g.*, hexose, glucose, fructose *etc.*), nucleic acids, acetate, butyrate, lipids, ceramide and the like. Table 1 provides an exemplary list of known kinases and their Enzyme Commission numbers (EC numbers), which can be detected by employing the methods of the invention. The name of the kinase usually identifies the substrate the enzyme acts upon. It is well known that most substrates that are modified by phosphorylation can be dephosphoryated by a phosphatase. Thus, a surface on which kinase substrates are attached can be used in a phosphatase assay by first modifying the substrates by phosphorylating them.

[00145] **Table 1.** Illustrative kinases and corresponding Enzyme Commission (EC) Numbers

E.C. No.	Kinase	E.C.No.	Kinase
2.7.1.32	Choline kinase	2.7.1.90	Diphosphate fructose-6-phosphate 1-phosphotransferase
2.7.1.37	Phosphorylase kinase	2.7.1.91	Sphinganine kinase
2.7.1.39	Homoserine kinase	2.7.1.107	Diacylglycerol kinase
2.7.1.67	1-phosphatidylinositol 4-kinase	2.7.1.138	Ceramide kinase
2.7.1.72	Streptomycin 6-kinase	2.7.1.2	Glucokinase
2.7.1.82	Ethanolamine kinase	2.7.1.3	Ketohexokinase
2.7.1.87	Streptomycin 3 "-kinase	2.7.1.4	Fructokinase
2.7.1.95	Kanamycin kinase	2.7.1.11	6-phosphofructokinase
2.7.1.100	5-methylthioribose kinase	2.7.1.15	Ribokinase
2.7.1.103	Viomycin kinase	2.7.1.20	Adenosine kinase
2.7.1.109	[Hydroxymethylglutaryl-CoA reductase (NADPH2)] kinase	2.7.1.35	Pyridoxal kinase
2.7.1.112	Protein-tyrosine kinase	2.7.1.45	2-dehydfo-3-deoxygluconokinase
2.7.1.116	[Isocitrate dehydrogenase (NADP+)] kinase	2.7.1.49	Hydroxymethylpyrimidine kinase
2.7.1.117	[Myosin light-chain] kinase	2.7.1.50	Hydroxyethylthiazole kinase
2.7.1.119	Hygromycin-B kinase	2.7.1.56	1 -phosphofructokinase
2.7.1.123	Calcium/calmodulin dependent protein kinase	2.7.1.73	Inosine kinase
2.7.1.125	Rhodopsin kinase	2.7.1.92	5-dehydro-2-deoxygluconokinase
2.7.1.126	[Beta-ad renergic-receptor] kinase	2.7.1.144	Tagatose-6-phosphate kinase
2.7.1.129	[Myosin heavy-chain] kinase	2.7.1.146	ADP-dependent phosphofructokinase
2.7.1.135	[Tau protein] kinase	2.7.1.147	ADP-dependent glucokinase
2.7.1.136	Macrolide 2' -kinase	2.7.4.7	Phosphomethylpyrimidine kinase
2.7.1.137	1-phosphatidylinositol 3-kinase	2.7.6.2	Thiamin pyrophosphokinase
2.7.1.141	[RNA-polymerase] -	2.7.1.31	Glycerate kinase

	subunit kinase		
2.7.1.153	Phosphatidylinositol-4,5-bisphosphate 3-kinase	2.7.4.6	Nucleoside-diphosphate kinase
2.7.1.154	Phosphatidylinositol-4-phosphate 3- kinase	2.7.6.3	2-amino-4-hydroxy-6-hydroxymethyldihydropteridine pyrophosphokinase
2.7.1.68	1 -phosphatidylinositol-4-phosphate 5-kinase	2.7.3.1	Guanidoacetate kinase
2.7.1.127	ID-myo-inositol-trisphosphate 3-kinase	2.7.3.2	Creatine kinase
2.7.1.140	Inositol-tetrakisphosphate 5-kinase	2.7.3.3	Arginine kinase
2.7.1.149	1-phosphatidylinositol 5-phosphate 4-kinase	2.7.3.5	Lombricine kinase
2.7.1.150	1-phosphatidylinositol 3-phosphate 5-kinase	2.7.1.37	Protein kinase (Histidine kinase)
2.7.1.151	Inositol-polyphosphate multikinase	2.7.1.99	[Pyruvate dehydrogenase(Kpoamide)] kinase
2.7.4.21	Inositol-hexakisphosphate kinase	2.7.1.115	[3-methyl-2-oxobutanoate dehydrogenase (lipoamide)] kinase
2.7.1.134	Inositol-tetrakisphosphate 1-kinase	2.7.1.1	Hexokinase
2.7.9.1	Pyravate, phosphate dikinase	2.7.1.2	Glucokinase
2.7.9.2	Pyravate, water dikinase	2.7.1.4	Fructokinase
2.7.1.12	Gluconokinase	2.7.1.5	Rhamnulokinase
2.7.1.19	Phosphoribulokinase	2.7.1.7	Mannokinase
2.7.1.21	Thymidine kinase	2.7.1.12	Gluconokinase
2.7.1.22	Ribosylnicotinamide kinase	2.7.1.16	L-ribulokinase
2.7.1.24	Dephospho-CoA kinase	2.7.1.17	Xylulokinase
2.7.1.25	Adenylylsulfate kinase	2.7.1.27	Erythritol kinase
2.7.1.33	Pantothenate kinase	2.7.1.30	Glycerol kinase
2.7.1.37	Protein kinase (bacterial)	2.7. 1.33	Pantothenate kinase
2.7.1.48	Uridine kinase	2.7.1.47	D-ribulokinase

2.7.1.71	Shikimate kinase	2.7.1.51	L-fuculokinase
2.7.1.74	Deoxycytidine kinase	2.7.1.53	L-xylulokinase
2.7.1.76	Deoxyadenosine kinase	2.7.1.55	Allose kinase
2.7.1.78	Polynucleotide 5'-hydroxylkinase	2.7.1.58	2-dehydro-3-deoxygalactonokinase
2.7.1.105	6-phosphofructo-2-kinase 2.7.1.113 Deoxyguanosine kinase	2.7.1.59	N-acetylglucosamine kinase
2.7.1.130	Tetraacyldisaccharide 4'-kinase	2.7. 1.60	N-acylmannosamine kinase
2.7.1.145	Deoxynucleoside kinase 2.7.1.156 Adenosylcobinamide kinase	2.7.1.63	Polyphosphate-glucose ph osphotransf erase
2.7.4.1	Polyphosphate kinase 2.7.4.2 Phosphomevalonate kinase	2.7.1.85	Beta-glucoside kinase
2.7.4.3	Adenylate kinase	2.7.2.1	Acetate kinase
2.7.4.4	Nucleoside-phosphate kinase	2.7.2.7	Butyrate kinase
2.7.4.8	Guanylate kinase	2.7.2.14	Branched-ehain-fatty-acid kinase
2.7.4.9	Thymidylate kinase	2.7.2.	Propionate kinase
2.7.4.10	Nucleoside-triphosphate -adenylate kinase	2.7.1.40	Pyravate kinase
2.7.4.13	(Deoxy)nucleoside-phosphate kinase	2.7.1.36	Mevalonate kinase
2.7.4.14	Cytidylate kinase	2.7.1.39	Homoserine kinase
2.7.4.	Uridylate kinase	2.7.1.46	L-arabinokinase
2.7.1.37	Protein kinase (HPr kinase/ phosphatase)	2.7.1.52	Fucokinase
4.1.1.32	Phosphoenolpyruvate carboxykinase (GTP)	2.7.1.71	Shikimate kinase
4.1.1.49	Phosphoenolpyruvate carboxykinase (ATP)	2.7.1.148	4-(cytidine 5'-diphospho)-2-Cmethyl-D- erythritol kinase
2.7.2.3	Phosphoglycerate kinase	2.7.4.2	Phosphoraevalonate kinase

[00146] The substrate and/or the substrate consensus sequence for a majority of kinases and phosphatases are known. Short synthetic peptides based on consensus motifs are typically excellent substrates for kinases and phosphatases. Table 2 summarizes some of the known data about specific motifs for various well-studied protein kinases, along with examples of known phosphorylation sites in specific proteins, which can be detected by employing the methods of the invention. A more extensive list is present in Pearson and Kemp (1991) Meth. Enzymol., 200:68-82, which is incorporated herein by reference.

[00147] **Table 2.** Recognition motifs and substrate sequences for some known kinases are listed. The amino acid phosphorylated by the corresponding kinase is underlined. Slash (/) indicates amino acids that can functionally substitute each other. Amino acids not contributing to the substrate recognition sequence are indicated by "X".

Kinase	Recognition Motif(s)	Phosphorylation Sites	Protein substrate
cAMP-dependent Protein Kinase (PKA, cAPK)	R-X-S/T (SEQ ID NO:1)	Y_7LRRASLAQLT (SEQ ID NO:3)	pyruvate kinase
	R-R/K-X-S/T (SEQ ID NO:2)	F_1RRLSIST (SEQ ID NO:4)	phosphorylase kinase α-chain
		A_{29}GARRKASGPP (SEQ ID NO:5)	histone HI, bovine
Casein Kinase I (CKI, CK-1)	S(P)-X-X-S/T (SEQ ID NO:6)	R_4TLS(P)VSSLPGL (SEQ ID NO:7)	glycogen synthase,
		D_{43}IGS(P)ES(P)TEDQ (SEQ ID NO:8)	rabbit muscle (αsi-casein
Casein Kinase n (CKII, CK-2)	S/T-X-X-E (SEQ ID NO:9)	A_{72}DSESEDEED (SEQ ID NO: 10)	PKA regulatory subunit, R_{II}
		L_{37}ESEEEGVPST (SEQ ID NO: 11)	$p34^{cdc2}$, human

			acetyl-CoA carboxylase
Glycogen Synthase Kinase 3 (GSK-3)	S-X-X-X-S(P) (SEQIDNO:13)	S_{641}VPPSPSLS(P) (SEQ ID NO: 14) S_{641}VPPS (P)PSLS(P) (SEQ ID NO: 15)	glycogen synthase, human (site 3b) glycogen synthase, human (site 3a)
Cdc2 Protein Kinase; CDK2-cyclin A	S/T-P-X-R/K (SEQIDNO:16)	P_{13}AKUPVK (SEQ ID NO: 17) H_{122}STPPKKKRK (SEQ ED NO:18)	histone HI, calf thymus large T antigen
Calmodulin-dependent Protein Kinase II (CaMKH)	R-X-X-S/T R-X-X-S/T-V	N_2YLRRRLSDSN (SEQIDNO:19) K_{191}MARVFSVLR (SEQIDNO:20)	synapsin (site 1) calcineurin
Mitogen-activated Protein Kinase (Extracellular Signal-regulated Kinase) (MAPK, Erk)	P-X-S/T-P (SEQ ID NO:21) X-X-S/T-P (SEQ ID NO:22)	P_{24}4LSP (SEQIDNO:23) P_{92}SSP (SEQ ED NO:24) V_{420}LSP (SEQIDNO:25)	c-Jun cyclin B Elk-1
Abl Tyrosine Kinase	I/V/L-Y-X-X-P/F (SEQ ED NO:26)		

[00148] Many kinase substrates are commercially available from various vendors such as Sigma, BioMol International, Bio-Rad, *etc.* Preferred kinase substrates include but are not limited to substrates for histidine, serine, threonine, and tyrosine kinases and/or the corresponding phosphatases. Multiple susbtrates for these kinases are well known in the art. In addition, methods are known for identification of substrates. For example, the program PREDIKIN is used to predict substrates for serine/threonine protein kinases based on the primary sequence of the kinase catalytic domain. Methods for using PREDIKIN to design substrates are described by Ross et al. (2003) PNAS, USA, 100 (1):74-79, which is

incorporated herein by reference. Other programs serving the same function are well known in the art.

[00149] A number of substrates specific to a type of protein kinase are known. Table 3 lists well known tyrosine kinase substrates.

[00150] **Table 3.** Partial list of known tyrosine kinase substrates and the position of the phosphorylated tyrosine residue is indicated. Shown are other post-translational protein modifications that can be detected by the methods of the invention.

Substrate	Phosphorylation Site	Substrate	Phosphorylation Site
KDR	Tyr996	PLCg	Tyr771/775
STAT3	Tyr705	T-cell activation antigen	Tyr217
cdc2	Tyrl5	T-cell Receptor Zeta chain	Tyrl52
JAK1	Tyrl022/1023	ERK5	Tyr215/220
KDR	Tyrl054/1059	GSK3	Tyr284
Paxillin	TyrSl	JNK1	Tyrl90
Pyk2	Tyr402	TrkC	Tyr705
She	Tyr317	Zinc Finger Protein 145	Tyr70
STAT1	Tyr701	TIF	Tyr495
TrkA	Tyr490	c-Kit (Y900)	64
TrkA	Tyr785	PTP1B	Tyr66
Tyk2	Tyrl054/1055	SHP-2 (Try542)	63
Zap70	Tyr493	PI3K	Tyr688
STAT6	Tyr641	Src	Tyr416
HER2	Tyrl248	c-FGR	Tyr412

STAT5	Tyr694	EGFR	Tyrll73
CTD	Tyr	ERa	Tyr537
FAK	Tyr577	IRS1	Tyr891
STAT4	Tyr693	ER.S2	Tyr766
PDGFR	Tyr775	JAK2	TyrlOOS
STAT2	Tyr690	PTEN	Tyr315
JAK1	Tyrl023	c-Cbl	Tyr700
Liver Glycogen Synthase	Tyr637	Dynaminl/n	Tyr231
NLK-1	TyrlSl	P62Dok	Tyr398
PDGFR	Tyr771	R-Ras	Tyr66
Signal Transduction Protein	Tyrl60	PTEN	Tyr336
TLE2	Tyr226	VEGFR1	Tyr 12 13
beta-adrenergic receptor	Tyr350	VEGFR2	Tyrl212
CSBP1	Tyr 182	Zap70	Tyr319
doublecortin	Tyr345	c-Cbl	Tyr774
HER2	Tyrl248	Met	Tyr 1349
Insulin Receptor Precursor	Tyr992	Met	Tyrl356

[00151] The foregoing kinase/phosphatase substrates are intended to be illustrative and not limiting. Using teachings provided herein and those well known in the art, other kinase substrates will be readily available to one of skill in the art for use in the apparatus, methods and compositions described herein.

Attachment of kinase/phosphatase substrates to the SERS substrate device

[00152] The kinase and/or phosphatase substrates may be attached to nanoparticle(s) or to features present on a surface (*e.g.*, a Raman active surface) by any of a number of methods well known to those of skill in the art. Such methods include but are not limited to using microscale contact pins or injectors or covalent bonds.

[00153] For example, in certain embodiments that include a gold nanostructure, the kinase and/or phosphatase substrates are tethered onto a gold nanostructure by a covalent bond formed by a gold-thiol reaction between a cysteine group at the terminus of the substrate (*e.g.*, peptide) and the gold surface. In various embodiments, the array surface and/or the kinase and/or phosphatase substrate can be derivatized with, for example, amine, carboxyl groups, alkyl groups, alkyene groups, hydroxyl groups, or other functional groups so that the peptide (or other substrate) can be linked directly to the surface or coupled through a linker. In other embodiments, the surface can be functionalized, *e.g.*, with amine, carboxyl, or other functional groups for attachment to the kinase and/or phosphatase substrate(s).

[00154] Suitable linkers include, but are not limited to hetero- or homo-bifunctional molecules that contain two or more reactive sites that may each form a covalent bond with the respective binding partner (kinase/phosphatase substrate, surface, or functional group thereon, *etc.*). Linkers suitable for joining such moieties are well known to those of skill in the art. For example, a protein molecule can readily be linked by any of a variety of linkers including, but not limited to a peptide linker, a straight or branched chain carbon chain linker, or by a heterocyclic carbon linker. Heterobifunctional cross-linking reagents such as active esters of N-ethylmaleimide have been widely used to link proteins to other moieties (see, *e.g.*, Lerner et al. (1981) Proc. Nat Acad. Sci. (USA), 78: 3403-3407; Kitagawa et al. (1976) J. Biochem., 79: 233-236; Birch and Lennox (1995) Chapter 4 in Monoclonal Antibodies: Principles and Applications, Wiley-Liss, N.Y., and the like).

[00155] In certain embodiment, the kinase and/or phosphatase substrate can be attached to the surface utilizing a biotin/avidin interaction. In certain embodiments, biotin or avidin, *e.g.*, with a photolabile protecting group can be affixed to the surface and/or to the kinase/phosphatase substrate(s). Irradiation of the surface in the presence of the desired kinase and/or phosphatase substrate bearing the corresponding avidin or streptavidin, or biotin, results in coupling of the substrate to the surface.

[00156] In various embodiments, multiple kinase and/or phosphatase substrates, usually at least about five, preferably at least ten, or at least 20, 50, 100, 500, 1000, 10,000 or 100, 1000 are attached to the surface. The kinase/phosphatase substrate can be a single substrate

attached in multiple copies on to the surface or attached in varying densities across the surface. Varying the density of the substrate will facilitate quantitation of the kinase/phosphatase activity. Thus, if a new peak appears upon the occurrence of a phopsphorylation reaction, the amplitude of the peak corresponding to different locations of the nanostrcuture surface will increase in accordance with the increase in density of the attached substrate. Alternatively, pluralities of substrates are attached at different locations on the surface. Thus, several positions are tethered with positive control substrates, at various densities and at other positions, negative control substrates, also at various densities.

[00157] In certain embodiments, the surface provides a high density array of kinase and/or phosphatase substrates. In various embodiments, such an array can comprise at least 100 or at least 200 different substrates/cm^2, preferably at least 300,400, 500, or 1000 different substrates/cm^2, and more preferably at least 1,500, 2,000,4,000,10,000, or 50,000, or 100,000 different substrates/cm^2.

[00158] Methods for patterning molecules on surfaces at high density are well known to those of skill in the art. Such methods include, for example, the use of high density microarray printers (See, *e.g.*, Heller (2002) Ann. Rev. Biomed. Eng. 4: 129-153). Other microarray printers utilize "on-demand" piezoelectric droplet generators (*e.g.*, inkjet printers) (see, *e.g.*, U.S. Patent Nos. 6,395,562; 6,365,378; 6,228,659; and WO 95/251116 and WO/2003/028868) which are incorporated herein by reference. Other approaches involve *de novo* synthesis (see, *e.g.*, Fodor et al. (1991) Science, 251:767-773 and U.S. Patent Nos. 6,269,846, 6,271,957 and 6,480,324 which are incorporated herein by reference). A number of printers are commercially available (*see e.g.*, VERSA Mini Spot-printing workstation from Aurora Biomed, BIOODYSSEY CALLIGRAPHER MiniArrayer from Bio-Rad, OmniGrid Accent from Genomic Solutions and the like).

Substrate phosphorylation/dephosphorylation assay

[00159] Where it is desirable to detect and/or measure the activity of a single type of kinase and/or phosphatase in a sample, a single type of substrate is tethered to the SERS surface of the microfluidic device. In embodiments pertaining to detection of a plurality of kinases and/or phosphatases in a sample, a plurality of substrates is tethered to the SERS surface of the microfluidic device.

[00160] The kinase and/or phosphatase activity detection/measurement described herein can be performed on any of a number of different samples. For example, in screening systems for the identification of kinase antagonists or agonists, cells/cell lines and/or lysates thereof, or appropriate buffer systems comprising the kinase(s) of interest can be contacted / administered as one or more test compounds. The samples derived therefrom can then be screened for kinase activity by identifying which test compounds show activty, *e.g.*, as kinase inhibitors and/or phosphatase agonists, and which kinase/phosphatase enzymes they inhibit and/or agonize.

[00161] In various diagnostic embodiments, the existence of the kinase and/or phosphatase enzyme(s), and/or concentration, and/or activity thereof, is determined in a biological sample. The biological sample can include essentially any biomaterial that is to be assayed. Such biomaterials include, but are not limited to biofluids such as blood or blood fractions, plasma, lymphatic fluid, tears, spinal and pulmonary fluid, cerebrospinal fluid, seminal fluid, urine, saliva and the like, tissue samples, cell samples, tissue or organ biopsies or aspirates, histological specimens, and the like.

[00162] In certain embodiments the raw cell lysate can be directly introduced into the microfluidic device and the measurement can be done during the incubation. Samples are introduced into the reaction chamber through microfluidic channels. The total sample volume may be reduced to sub-microliter volume.

[00163] Phosphorylation of a kinase substrate or dephosphorylation of a phosphatase substrate is detectable by changes in the spectrum obtained by SERS, electromagnetic resonance measurement, or acoustic measurement. Changes in the spectrum of the SERS surface compared to a control (no sample or control sample) may be indicative of kinase/phosphatase activity. The change in the spectrum could be appearance of a new peak accompanied by the disappearance of an existing peak, a shifting of peaks, as well as the merging and/or splitting of peaks.

[00164] Such a surface provides an effective tool for real-time screening for the concentration and/or activity of one or a plurality of kinases and/or phosphatases and/or for quantification of the kinetics of one or more kinases and/or phosphatases. Such a surface can also be readily used to screen for kinase and/or phosphatase inhibitor activity of one or a plurality of test agents (*e.g.* a chemical library).

[00165] In certain embodiments the kinase/phosphatase activity detection and/or measurements can be used in personalized molecular diagnostics for cancers by physicians

and hospital personnel. In one embodiment, the instant invention is used to detect the presence of molecular markers specific to a particular type of cancer.

EXAMPLE 1

Detection of altered protease activity

[00166] Real-time *in situ* detection of proteases is crucial for early-stage cancer screening as well as for assessing the efficacy of a treatment method. In one illustrative example, the instant invention is used to detect activity of a protease, prostate-specific antigen (PSA), in a biological sample. PSA levels are increased in prostate cancer. Thus, PSA serves as a biomarker for prostate cancer. Measurement of plasma PSA concentration does not differentiate prostate cancer patients from those with benign prostatic hyperplasia, leading to a high false-positive rate. Efforts to enhance the clinical value of PSA as an early detection marker for prostate cancer have included the characterization of various molecular isoforms of PSA. Among the various isoforms, the proteolytically active subpopulation of PSA is accepted as a more useful tumor marker and malignancy predictor than the serum PSA concentration (Wu et al. (2004) Prostate 58: 345-353; Wu et al. (2004) Clin. Chem., 50: 125-129).

[00167] The peptide substrate used for detection of PSA protease activity incorporates the amino acid sequence of the active site of PSA-specific peptides with serine residues and flanking sequences that can be recognized by PSA. Thus, the peptide includes the sequence HSSKLQ-LAAAC which is known to have a very high specificity for proteolytically active PSA (Denmeade et al., (1997) Cancer Res 57:4924-4930). It has also been shown that HSSKLQ-L is cleaved by PSA but not by any other proteases *in vivo* in a mouse model (Denmeade et al., (2003) J. Natl. Cancer Inst. 95: 990-1000). Thus, a screen may be performed wherein multiple peptides are attached to the nanostructure of a SERS substrate surface, each having a random or known sequence portion, and the PSA specific sequence HSSKLQ-LAAAC or HSSKLQ-L. The PSA hydrolysis site is between Q and L. Proteolysis results in shortening of the peptide, which is detectable by changes in the spectrum associated with the peptides. This may then be observed in the resulting spectrograph.

[00168] In this particular example, a SERS substrate surface has a gold nanostructure. The peptides are attached to the surface via a gold-thiol covalent bond formed between cysteine at the carboxyl terminus of the peptide and the gold nanostructure. The sample to be tested

is introduced into the microfluidic chamber where the temperature is maintained at 37°C. The sample is maintained in contact with the peptide substrates on the SERS surface in the device for about 2 hours. The spectrum obtained from the plasma sample from a patient with suspected prostate cancer is compared to that of an age matched non-afflicted person. Purified PSA is used as a positive control for the detection assay.

[00169] Further, proteolysis dynamics may be monitored in real-time by time-resolved spectra acquisitions. Thus, the disappearance, appearance, shifting, merging, or splitting in peaks can be followed real-time.

[00170] The use of a nanostructure facilitates the detection of changes in spectra associated with a particular molecule attached to the SERS surface. Thus, the fusion of an enzyme substrate to fluorescent or radioactive tags is not necessary.

EXAMPLE 2

Detection of altered kinase activity

[00171] Protein kinases represent approximately 1.7% of all human genes and not surprisingly are important cellular regulatory proteins (Manning et al. (2002) Science 298: 1912-1934). Most of the 30 known tumor suppressor genes and more than 100 dominant oncogenes are protein kinases (Futreal et al. (2001) Nature 409: 850-852). Tyrosine-kinase receptors are key molecules in signaling pathways leading to growth and differentiation of normal cells. Mutations leading to inactivation of certain tyrosine kinases and increased activity of others is a hallmark of tumor cells. The instant invention may be used to provide a tyrosine kinase activity profile associated with a certain tissue of interest. In this example, the tissue is a biopsy sample of the colon obtained from a person free of colon cancer (for obtaining a normal kinase activity profile) and from a patient afflicted with colon cancer (for obtaining a kinase activity profile from a positive control). Once the tyrosine kinase activity profile for normal tissue and control tissue is obtained, the same procedure is performed with a colon biopsy sample from a patient suspected of having colon cancer. A significant departure from the normal kinase activity profile spectrum and/or similarity to the positive control kinase activity profile spectrum is indicative of colon cancer.

[00172] Biopsy samples are transferred to ceramic beads-containing special centritubes (Roche, Penzberg, Germany) with 0.1 mL of pre-chilled TLysis buffer. The tissue may be subjected to oscillation made by the MagNA Lyser machine at 6500 r/min for 120

seconds. The lysate is then centrifuged at 100,000 g for 1 h at 4°C, and the supernatant is saved and assayed for protein concentration (Lowry method).

[00173] Tyrosine kinase substrates of Table 3 are tethered to the nanostructure surface of the instant invention. The tissue lysate may be introduced into the microfluidic chamber, which is maintained at 37°C. The lysate is incubated with tyrosine kinase substrates for 1 hour. The spectrum associated with the enzyme substrates attached to the nanostructure surface is measured before the introduction of the lysate, during the incubation and after washing away of the lysate. Thus, phosphorylation dynamics are monitored in real-time by time-resolved spectra acquisitions. This time-dependent tyrosine kinase activity profile increases the accuracy of data interpretation.

EXAMPLE 3

Transcription factor activity profiling

[00174] Gene expression profiling is increasingly used to characterize cell samples such as tumor biopsies. By measuring the levels of selected messenger RNAs in a sample, inferences may be drawn concerning the subtype or molecular profile of the sample, providing information that may support medical decisions, including treatment alternatives. A potentially more informative alternative to measuring RNA levels is to directly measure the activity of proteins in a tumor biopsy or other cell sample. DNA binding transcription factors are a class of proteins that are particularly informative for molecular profiling, providing information about the detailed transcriptional state of cells in a sample.

[00175] In this example, the activity of DNA binding transcription factors in a cell sample are dynamically measured using a microfluidic SERS detection apparatus. The apparatus is prepared such that one or potentially many individually addressed oligonucleotide probes are attached to the nanostructure of the SERS substrate surface, with each oligonucleotide having a sequence comprising a binding site for a particular transcription factor of interest. For example, a 25-mer double stranded DNA oligonucleotide including the E-box hexamer sequence CACGTG may be used to interrogate the activity of a subclass of basic helix-loop-helix transcription factors. Mismatch oligonucleotides may also be used as controls for nonspecific binding, and identical sequences may be redundantly arrayed to increase measurement accuracy. Evaluation of SERS spectra provides dynamic information about the binding of transcription factors to the oligonucleotide probes as well as the formation of

DNA-transcription factor super-complexes that may include additional transcription cofactors and TAF proteins.

[00176] A needle biopsy containing $1x10^4$ cells is taken and the nuclear extract isolated at 4° C using Sigma NXTRACT CELLYTIC NUCLEAR extraction kit. The nuclear extract is then resuspended in 19 µl cold 10mM Tris-HCL buffer containing 1mM DTT. 1 µl Sigma protease inhibitor cocktail P8340 is added, and the solution is transferred to the microfluidic SERS detection apparatus. At 25° C, the sample enters the microscale chamber and DNA binding events are measured in real-time using incident laser light and detection of transmitted SERS spectra. Transcription factor binding activity profiles are developed or calculated from one or more of the following measurements, for each oligonucelotide sequence: (1) the occupancy of bound oligonucleotides as a fraction of total available sites; (2) the average stability of DNA-protein complexes in seconds; and (3) the total number of binding events per unit time. Comparison of transcription factor binding activity profiles across tissue types and across diseased versus normal tissues characterize the molecular pathology of a tissue sample and are potentially diagnostic for treatment alternatives.

[00177] **Table 4.** Additional proteases are presented, the concentration and activity of which may be detected and quantitated using embodiments of the methods of the invention.

Protease Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
PGA3	A01.001	643834	3.4.23.1	11q12.2	pepsinogen 3, group I (pepsinogen A)
PGA@	A01.001	5219	-	11q13	pepsinogen A gene cluster
PGC	A01.003	5225	3.4.23.3	6p21.3-p21.1	progastricsin (pepsinogen C)
BACE1	A01.004	23621	-	11q23.2-q23.3	beta-site APP-cleaving enzyme 1
CYMP	A01.006	1542	-	1p13.3	chymosin pseudogene
REN	A01.007	5972	3.4.23.15	1q32	renin
CTSD	A01.009	1509	3.4.23.5	11p15.5	cathepsin D (lysosomal aspartyl protease)
CTSE	A01.010	1510	3.4.23.5	1q31	cathepsin E
BACE2	A01.041	25825	-	21q22.3	beta-site APP-cleaving enzyme 2
NAPSA	A01.046	9476	-	19q13.33	napsin A aspartic peptidase
PGA5	A01.071	5222	3.4.23.1	11q13	pepsinogen 5, group I (pepsinogen A)
NAPSB	A01.P01	256236	-	19q13.33	napsin B aspartic peptidase pseudogene
SASP	A02.059	151516	-	2p13.3	hypothetical protein FLJ25084

Protease Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
DDI1	A02.xxx	AK093336	-	-	-
DDI2	A02.xxx	BN000122	-	-	-
NRIP2	A02.xxx	83714	-	12p13.33	nuclear receptor interacting protein 2
NRIP3	A02.xxx	56675	-	11p15.3	nuclear receptor interacting protein 3
PSEN1	A22.001	5663	-	14q24.3	presenilin 1 (Alzheimer disease 3)
PSEN2	A22.002	5664	-	1q31-q42	presenilin 2 (Alzheimer disease 4)
HM13	A22.003	81502	-	20q11.21	histocompatibility (minor) 13
PSH4	A22.004	56928	-	19p13.3	signal peptide peptidase-like 2B
PSH1	A22.005	121665	-	12q24.31	signal peptide peptidase 3
IMP5	A22.006	162540	-	17q21.31	intramembrane protease 5
PSH5	A22.007	84888	-	15q21.2	putative intramembrane cleaving protease
PIP	Ax1.xxx	5304	-	7q34	prolactin-induced protein
CTSL2	C01.009	1515	-	9q22.2	cathepsin L2
CTSZ	C01.013	1522	-	20q13	cathepsin Z
CTSLL2	C01.014	1517	-	10q	cathepsin L-like 2
CTSLL3	C01.015	1518	-	10q22.3-q23.1	cathepsin L-like 3
CTSF	C01.018	8722	-	11q13	cathepsin F
CTSL	C01.032	1514	3.4.22.15	9q21-q22	cathepsin L
CTSS	C01.034	1520	3.4.22.27	1q21	cathepsin S
CTSO	C01.035	1519	-	4q31-q32	cathepsin O
CTSK	C01.036	1513	-	1q21	cathepsin K (pycnodysostosis)
CTSW	C01.037	1521	-	11q13.1	cathepsin W (lymphopain)
CTSH	C01.040	1512	3.4.22.16	15q24-q25	cathepsin H
CTSB	C01.060	1508	3.4.22.1	8p22	cathepsin B
CTSC	C01.070	1075	-	11q14.1-q14.3	cathepsin C
BLMH	C01.084	642	-	17q11.2	bleomycin hydrolase
TINAG	C01.973	27283	-	6p11.2-p12	tubulointerstitial nephritis antigen
LCN7	C01.975	64129	-	1p35.2	lipocalin 7
CTSLL1	C01.P02	1516	-	10q	cathepsin L-like 1
CAPN1	C02.001	823	3.4.22.17	11q13	calpain 1, (mu/I) large subunit
CAPN2	C02.002	824	3.4.22.17	1q41-q42	calpain 2, (m/II) large subunit
CAPN3	C02.004	825	3.4.22.17	15q15.1-q21.1	calpain 3, (p94)
CAPN9	C02.006	10753	-	1q42.11-q42.3	calpain 9
CAPN8	C02.007	AA043093	-	-	-
CAPN7	C02.008	23473	-	3p24	calpain 7
SOLH	C02.010	6650	-	16p13.3	small optic lobes homolog

Protease Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
					(Drosophila)
CAPN5	C02.011	726	-	11q14	calpain 5
CAPN11	C02.013	11131	-	6p12	calpain 11
CAPN12	C02.017	147968	-	19q13.2	calpain 12
CAPN10	C02.018	11132	-	2q37.3	calpain 10
CAPN13	C02.020	92291	-	2p22-p21	calpain 13
CAPN14	C02.021	440854	-	2p23.1-p21	calpain 14
CAPN6	C02.971	827	-	xq23	calpain 6
C6orf103	C02.972	79747	-	6q24.3	chromosome 6 open reading frame 103
UCHL1	C12.001	7345	3.4.19.12	4p14	ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)
UCHL3	C12.003	7347	3.2.1.15	13q22.2	ubiquitin carboxyl-terminal esterase L3 (ubiquitin thiolesterase)
BAP1	C12.004	8314	-	3p21.31-p21.2	BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase)
UCHL5	C12.005	51377	-	1q32	ubiquitin carboxyl-terminal hydrolase L5
LGMN	C13.004	5641	-	14q32.1	legumain
PIGK	C13.005	10026	-	1p31.1	phosphatidylinositol glycan, class K
LGMN2P	C13.P01	122199	-	13q21.31	legumain 2 pseudogene
CASP1	C14.001	834	-	11q23	caspase 1, apoptosis-related cysteine protease (interleukin 1, beta, convertase)
CASP3	C14.003	836	-	4q34	caspase 3, apoptosis-related cysteine protease
CASP7	C14.004	840	-	10q25	caspase 7, apoptosis-related cysteine protease
CASP6	C14.005	839	-	4q25	caspase 6, apoptosis-related cysteine protease
CASP2	C14.006	835	-	7q34-q35	caspase 2, apoptosis-related cysteine protease (neural precursor cell expressed, developmentally down-regulated 2)
CASP4	C14.007	837	-	11q22.2-q22.3	caspase 4, apoptosis-related cysteine protease
CASP5	C14.008	838	-	11q22.2-q22.3	caspase 5, apoptosis-related cysteine protease
CASP8	C14.009	841	-	2q33-q34	caspase 8, apoptosis-related cysteine protease
CASP9	C14.010	842	-	1p36.3-p36.1	caspase 9, apoptosis-related cysteine protease
CASP10	C14.011	843	-	2q33-q34	caspase 10, apoptosis-related cysteine protease
CASP14	C14.018	23581	-	19p13.1	caspase 14, apoptosis-related cysteine protease
MALT1	C14.026	10892	-	18q21	mucosa associated lymphoid tissue lymphoma translocation gene 1

Protease Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
CFLAR	C14.971	8837	-	2q33-q34	CASP8 and FADD-like apoptosis regulator
CASP14L	C14.975np	197350	-	16p13.3	hypothetical protein LOC197350
CASP12P1	C14.P01	120329	-	11q22.3	caspase 12 pseudogene 1
PGPEP1	C15.010	54858	3.4.19.3	19p13.11	pyroglutamyl-peptidase I
PGPEP2	C15.011	145814	-	15q26.3	hypothetical protein LOC145814
USP5	C19.001	8078	-	12p13	ubiquitin specific protease 5 (isopeptidase T)
USP6	C19.009	9098	-	17q11	ubiquitin specific protease 6 (Tre-2 oncogene)
USP4	C19.010	7375	-	3p21.3	ubiquitin specific protease 4 (proto-oncogene)
USP8	C19.011	9101	-	15q21.2	ubiquitin specific protease 8
USP13	C19.012	8975	-	3q26.2-q26.3	ubiquitin specific protease 13 (isopeptidase T-3)
USP2	C19.013	9099	-	11q23.3	ubiquitin specific protease 2
USP11	C19.014	8237	-	xp11.23	ubiquitin specific protease 11
USP14	C19.015	9097	-	18p11.32	ubiquitin specific protease 14 (tRNA-guanine transglycosylase)
USP7	C19.016	7874	-	16p13.3	ubiquitin specific protease 7 (herpes virus-associated)
USP9X	C19.017	8239	-	xp11.4	ubiquitin specific protease 9, X-linked (fat facets-like, Drosophila)
USP10	C19.018	9100	-	16q24.1	ubiquitin specific protease 10
USP1	C19.019	7398	-	1p32.1-p31.3	ubiquitin specific protease 1
USP12	C19.020	9959	-	5q33-q34	ubiquitin specific protease 12 pseudogene 1
USP16	C19.021	10600	-	21q22.11	ubiquitin specific protease 16
USP15	C19.022	9958	-	12q14	ubiquitin specific protease 15
USP17	C19.023	391627	-	4p15	ubiquitin specific peptidase 17
USP19	C19.024	10869	-	3p21.31	ubiquitin specific protease 19
USP20	C19.025	10868	-	9q34.11	ubiquitin specific protease 20
USP3	C19.026	9960	-	15q22.3	ubiquitin specific protease 3
USP9Y	C19.028	8287	-	yq11.2	ubiquitin specific protease 9, Y-linked (fat facets-like, Drosophila)
USP18	C19.030	11274	-	22q11.21	ubiquitin specific protease 18
USP21	C19.034	27005	-	1q22	ubiquitin specific protease 21
USP22	C19.035	23326	-	17p11.2	ubiquitin specific protease 22
USP33	C19.037	23032	-	1p31.1	ubiquitin specific protease 33
USP29	C19.040	57663	-	19q13.43	ubiquitin specific protease 29
USP25	C19.041	29761	-	21q11.2	ubiquitin specific protease 25
USP36	C19.042	57602	-	17q25.3	ubiquitin specific protease 36
USP32	C19.044	84669	-	17q23.2	ubiquitin specific protease 32
USP26	C19.046	83844	3.1.2.15	xq26.2	ubiquitin specific protease 26

Protease Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
USP24	C19.047	23358	-	1p32.3	ubiquitin specific protease 24
USP42	C19.048	84132	-	7p22.1	ubiquitin specific protease 42
USP46	C19.052	64854	-	4q12	ubiquitin specific protease 46
USP37	C19.053	57695	-	2q35	ubiquitin specific protease 37
USP28	C19.054	57646	-	11q23	ubiquitin specific protease 28
USP47	C19.055	55031	-	11p15.3	ubiquitin specific protease 47
USP38	C19.056	84640	-	4q31.1	ubiquitin specific protease 38
USP44	C19.057	84101	-	12q22	ubiquitin specific protease 44
USP50	C19.058	373509	-	15q21.1	ubiquitin specific protease 50
USP50	C19.058np	AI990110	-	-	-
USP35	C19.059	57558	-	11q14.1	ubiquitin specific protease 35
USP30	C19.060	84749	-	12q24.11	ubiquitin specific protease 30
USP45	C19.064	85015	-	6q16.3	ubiquitin specific protease 45
USP51	C19.065	158880	-	xp11.22	ubiquitin specific protease 51
USP51	C19.065	BF741256	-	-	-
USP34	C19.067	9736	-	2p15	ubiquitin specific protease 34
USP48	C19.068	84196	-	1p36.12	ubiquitin specific protease 48
USP40	C19.069	55230	-	2q37.1	ubiquitin specific protease 40
USP41	C19.070	150200	-	22q11.21	ubiquitin specific peptidase 41
USP31	C19.071	57478	-	16p12.1	ubiquitin specific protease 31
USP49	C19.073	25862	-	6p21	ubiquitin specific protease 49
USP27X	C19.075	373504	-	xp11	ubiquitin specific protease 27, X-linked
USP27	C19.075	AW851065	-	-	-
USP54	C19.080	159195	-	10q22.2	ubiquitin specific protease 54
USP53	C19.081	54532	-	4q26	ubiquitin specific protease 53
USP39	C19.972	10713	-	2p11.2	ubiquitin specific protease 39
USP43	C19.976	124739	-	17p13.1	ubiquitin specific protease 43
USP52	C19.978	9924	-	12q13.2-q13.3	ubiquitin specific protease 52
USP8P	C19.980	394216	-	6p21	ubiquitin specific protease 8 pseudogene
UBADC1	C19.M01	10422	-	9q34.3	ubiquitin associated domain containing 1
NEK2P	C19.P01	326302	-	14q11.2	NEK2 pseudogene
USP17L	C19.xxx	BN000116	-	-	-
GGH	C26.001	8836	3.4.19.9	8q12.3	gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)
GMPS	C26.950	8833	6.3.5.2	3q24	guanine monphosphate synthetase
PPAT	C44.001	5471	2.4.2.14	4q12	phosphoribosyl pyrophosphate amidotransferase
GFPT1	C44.970	2673	2.6.1.16	2p13	glutamine-fructose-6-phosphate

Protease Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
					transaminase 1
GFPT2	C44.972	9945	-	5q34-q35	glutamine-fructose-6-phosphate transaminase 2
ASNS	C44.974	440	6.3.5.4	7q21.3	asparagine synthetase
SHH	C46.002	6469	-	7q36	sonic hedgehog homolog (Drosophila)
IHH	C46.003	3549	-	2q33-q35	Indian hedgehog homolog (Drosophila)
DHH	C46.004	50846	-	12q12-q13.1	desert hedgehog homolog (Drosophila)
SENP1	C48.002	29843	-	12q13.1	SUMO1/sentrin specific protease 1
SENP3	C48.003	26168	-	17p13	SUMO1/sentrin/SMT3 specific protease 3
SENP6	C48.004	26054	-	6q13-q14.3	SUMO1/sentrin specific protease 6
SENP2	C48.007	59343	-	3q27.2	SUMO1/sentrin/SMT3 specific protease 2
SENP5	C48.008	205564	-	3q29	SUMO1/sentrin specific protease 5
SENP7	C48.009	57337	-	3q12	SUMO1/sentrin specific protease 7
SENP8	C48.011	123228	-	15q23	SUMO/sentrin specific protease family member 8
ESPL1	C50.001	9700	3.4.22.49	12q	extra spindle poles like 1 (S. cerevisiae)
ATG4A	C54.002	115201	-	xq22.1-q22.3	APG4 autophagy 4 homolog A (S. cerevisiae)
ATG4B	C54.003	23192	-	2q37.3	APG4 autophagy 4 homolog B (S. cerevisiae)
ATG4C	C54.004	84938	-	1p31.3	APG4 autophagy 4 homolog C (S. cerevisiae)
ATG4D	C54.005	84971	-	19p13.2	APG4 autophagy 4 homolog D (S. cerevisiae)
PARK7	C56.002	11315	-	1p36.33-p36.12	Parkinson disease (autosomal recessive, early onset) 7
PFAS	C56.972	5198	6.3.5.3	17p13.1	phosphoribosylformylglycinamidine synthase (FGAR amidotransferase)
ZA20D1	C64.001	56957	-	1q21.2	zinc finger, A20 domain containing 1
C15orf16	C64.002	161725	-	15q13.3	chromosome 15 open reading frame 16
TNFAIP3	C64.003	7128	-	6q23	tumor necrosis factor, alpha-induced protein 3
ZRANB1	C64.004	54764	-	10q26.13	zinc finger, RAN-binding domain containing 1
OTUB1	C65.001	55611	-	11q13.1	OTU domain, ubiquitin aldehyde binding 1
OTUB2	C65.002	78990	-	14q32.13	OTU domain, ubiquitin aldehyde binding 2
CYLD	C67.001	1540	-	16q12.1	cylindromatosis (turban tumor syndrome)
SCRN1	C69.003	9805	-	7p14.3-p14.1	secernin 1
SCRN2	C69.004	90507	-	17q21.32	secernin 2
SCRN3	C69.005	79634	-	2q31.1	secernin 3

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OTUD4	Cx1.xxx	54726	-	4q31.21	HIV-1 induced protein HIN-1
HSHIN1L	Cx1.xxx	BN000160	-	-	-
CXorf45	Cx1.xxx	79868	-	xq23	chromosome X open reading frame 45
HSHIN3	Cx1.xxx	23252	-	1p36.13	KIAA0459 protein
OTUD1	Cx1.xxx	220213	-	10p12.31	OTU domain containing 1
OTUD5	Cx1.xxx	55593	-	xp11.23	hypothetical protein DKFZp761A052
OTUD6A	Cx1.xxx	139562	-	xq13.1	HIN-6 protease
HSHIN7	Cx1.xxx	BI829009	-	-	-
OTUD6B	Cx1.xxx	51633	-	8q21.3	CGI-77 protein
TTC28	Cx2.xxxnp	23331	-	22q12.1	KIAA1043 protein
ANPEP	M01.001	290	3.4.11.2	15q25-q26	alanyl (membrane) aminopeptidase (aminopeptidase N, aminopeptidase M, microsomal aminopeptidase, CD13, p150)
ENPEP	M01.003	2028	3.4.11.7	4q25	glutamyl aminopeptidase (aminopeptidase A)
LTA4H	M01.004	4048	3.3.2.6	12q22	leukotriene A4 hydrolase
TRHDE	M01.008	29953	3.4.19.6	12q15-q21	thyrotropin-releasing hormone degrading ectoenzyme
NPEPPS	M01.010	9520	-	17q21	aminopeptidase puromycin sensitive
LNPEP	M01.011	4012	3.4.11.3	5q15	leucyl/cystinyl aminopeptidase
RNPEP	M01.014	6051	3.4.11.6	1q32	arginyl aminopeptidase (aminopeptidase B)
ERAP1	M01.018	51752	-	5q15	type 1 tumor necrosis factor receptor shedding aminopeptidase regulator
RNPEPL1	M01.022	57140	-	2q37.3	arginyl aminopeptidase (aminopeptidase B)-like 1
ERAP2	M01.023	64167	-	16	leukocyte-derived arginine aminopeptidase
AQPEP	M01.027	BG623101	-	-	-
C9orf3	M01.028	84909	-	9q22.32	chromosome 9 open reading frame 3
TAF2	M01.972	6873	-	8q24.12	TAF2 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 150kDa
ACE2	M02.006	59272	3.4.15.1	xp22	angiotensin I converting enzyme (peptidyl-dipeptidase A) 2
THOP1	M03.001	7064	3.4.24.15	19q13.3	thimet oligopeptidase 1
NLN	M03.002	57486	3.4.24.16	5q12.3	neurolysin (metallopeptidase M3 family)
MIPEP	M03.006	4285	3.4.24.59	13q12	mitochondrial intermediate peptidase
LMLN	M08.003	89782	3.4.24.36	3q29	leishmanolysin-like (metallopeptidase M8 family)
MMP1	M10.001	4312	3.4.24.7	11q22.3	matrix metalloproteinase 1 (interstitial collagenase)
MMP8	M10.002	4317	3.4.24.34	11q22.3	matrix metalloproteinase 8 (neutrophil collagenase)

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MMP2	M10.003	4313	3.4.24.24	16q13-q21	matrix metalloproteinase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)
MMP9	M10.004	4318	3.4.24.35	20q11.2-q13.1	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)
MMP3	M10.005	4314	3.4.24.17	11q22.3	matrix metalloproteinase 3 (stromelysin 1, progelatinase)
MMP10	M10.006	4319	3.4.24.22	11q22.3	matrix metalloproteinase 10 (stromelysin 2)
MMP11	M10.007	4320	-	22q11.23	matrix metalloproteinase 11 (stromelysin 3)
MMP7	M10.008	4316	3.4.24.23	11q21-q22	matrix metalloproteinase 7 (matrilysin, uterine)
MMP12	M10.009	4321	-	11q22.3	matrix metalloproteinase 12 (macrophage elastase)
MMP13	M10.013	4322	-	11q22.3	matrix metalloproteinase 13 (collagenase 3)
MMP14	M10.014	4323	-	14q11-q12	matrix metalloproteinase 14 (membrane-inserted)
MMP15	M10.015	4324	-	16q13-q21	matrix metalloproteinase 15 (membrane-inserted)
MMP16	M10.016	4325	-	8q21	matrix metalloproteinase 16 (membrane-inserted)
MMP17	M10.017	4326	-	12q24.3	matrix metalloproteinase 17 (membrane-inserted)
MMP20	M10.019	9313	-	11q22.3	matrix metalloproteinase 20 (enamelysin)
MMP19	M10.021	4327	-	12q14	matrix metalloproteinase 19
MMP23B	M10.022	8510	-	1p36.3	matrix metalloproteinase 23B
MMP24	M10.023	10893	-	20q11.2	matrix metalloproteinase 24 (membrane-inserted)
MMP25	M10.024	64386	-	16p13.3	matrix metalloproteinase 25
MMP21	M10.026	118856	-	10q26.2	matrix metalloproteinase 21
MMP27	M10.027	64066	-	11q24	matrix metalloproteinase 27
MMP26	M10.029	56547	-	11p15	matrix metalloproteinase 26
MMP28	M10.030	79148	-	17q11-q21.1	matrix metalloproteinase 28
MMP23A	M10.037	8511	-	1p36.3	matrix metalloproteinase 23A
MMPL1	M10.973	4328	-	16p13.3	matrix metalloproteinase-like 1
MEP1A	M12.002	4224	3.4.24.18	6p12-p11	meprin A, alpha (PABA peptide hydrolase)
MEP1B	M12.004	4225	3.4.24.18	18q12.2-q12.3	meprin A, beta
BMP1	M12.005	649	3.4.24.19	8p21	bone morphogenetic protein 1
TLL1	M12.016	7092	-	4q32-q33	tolloid-like 1
TLL2	M12.018	7093	-	10q23-q24	tolloid-like 2
ADAMTS9	M12.021	56999	-	3p14.3-p14.2	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 9

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ADAMTS14	M12.024	140766	-	10q2	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 14
ADAMTS15	M12.025	170689	-	11q25	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 15
ADAMTS16	M12.026	170690	-	5p15	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 16
ADAMTS17	M12.027	170691	-	15q24	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 17
ADAMTS18	M12.028	170692	-	16q23	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 18
ADAMTS19	M12.029	171019	-	5q31	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 19
ADAM1	M12.201	8759	-	12q24.12-q24.13	a disintegrin and metalloproteinase domain 1 (fertilin alpha) pseudogene
ADAM8	M12.208	101	-	10q26.3	a disintegrin and metalloproteinase domain 8
ADAM9	M12.209	8754	-	8p11.23	a disintegrin and metalloproteinase domain 9 (meltrin gamma)
ADAM10	M12.210	102	-	15q22	a disintegrin and metalloproteinase domain 10
ADAM12	M12.212	8038	-	10q26.3	a disintegrin and metalloproteinase domain 12 (meltrin alpha)
ADAM19	M12.214	8728	-	5q32-q33	a disintegrin and metalloproteinase domain 19 (meltrin beta)
ADAM15	M12.215	8751	-	1q21.3	a disintegrin and metalloproteinase domain 15 (metargidin)
ADAM17	M12.217	6868	-	2p25	a disintegrin and metalloproteinase domain 17 (tumor necrosis factor, alpha, converting enzyme)
ADAM20	M12.218	8748	-	14q24.1	a disintegrin and metalloproteinase domain 20
ADAMDEC1	M12.219	27299	-	8p21.2	ADAM-like, decysin 1
ADAMTS3	M12.220	9508	-	4q13.3	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 3
ADAMTS4	M12.221	9507	-	1q21-q23	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 4
ADAMTS1	M12.222	9510	-	21q21.2	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 1
ADAM28	M12.224	10863	-	8p21.2	a disintegrin and metalloproteinase domain 28
ADAMTS5	M12.225	11096	-	21q21.3	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 5 (aggrecanase-2)

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ADAMTS8	M12.226	11095	-	11q25	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 8
ADAMTS6	M12.230	11174	-	5q12	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 6
ADAMTS7	M12.231	11173	-	15q24.2	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 7
ADAM30	M12.232	11085	-	1p13-p11	a disintegrin and metalloproteinase domain 30
ADAM21	M12.234	8747	-	14q24.1	a disintegrin and metalloproteinase domain 21
ADAMTS10	M12.235	81794	-	19p13.3-p13.2	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 10
ADAMTS12	M12.237	81792	-	5q35	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 12
ADAMTS13	M12.241	11093	-	9q34	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 13
ADAM33	M12.244	80332	-	20p13	a disintegrin and metalloproteinase domain 33
ASTL	M12.245	431705	3.4.24.21	2q11.1	astacin-like metalloendopeptidase (M12 family)
HAMET	M12.245	AJ537600	-	-	-
ADAMTS20	M12.246	80070	-	12q12	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 20
ADAMTS2	M12.301	9509	-	5qter	a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 2
ADAM2	M12.950	2515	-	8p11.2	a disintegrin and metalloproteinase domain 2 (fertilin beta)
ADAM7	M12.956	8756	-	8p21.2	a disintegrin and metalloproteinase domain 7
ADAM18	M12.957	8749	-	8p11.22	a disintegrin and metalloproteinase domain 18
ADAM32	M12.960	203102	-	8p11.23	a disintegrin and metalloproteinase domain 32
ADAM3A	M12.974	1587	-	8p21-p12	a disintegrin and metalloproteinase domain 3a (cyritestin 1)
ADAM3B	M12.975	1596	-	16q12.1	a disintegrin and metalloproteinase domain 3b (cyritestin 2)
ADAM11	M12.976	4185	-	17q21.3	a disintegrin and metalloproteinase domain 11
ADAM22	M12.978	53616	-	7q21	a disintegrin and metalloproteinase domain 22
ADAM23	M12.979	8745	-	2q33	a disintegrin and metalloproteinase domain 23
ADAM29	M12.981	11086	-	4q34	a disintegrin and metalloproteinase domain 29

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MME	M13.001	4311	3.4.24.11	3q25.1-q25.2	membrane metallo-endopeptidase (neutral endopeptidase, enkephalinase, CALLA, CD10)
ECE1	M13.002	1889	-	1p36.1	endothelin converting enzyme 1
ECE2	M13.003	9718	-	3q28-q29	endothelin converting enzyme 2
ECEL1	M13.007	9427	-	2q36-q37	endothelin converting enzyme-like 1
MELL1	M13.008	79258	-	1p36	mel transforming oncogene-like 1
KEL	M13.090	3792	-	7q33	Kell blood group
PHEX	M13.091	5251	-	xp22.2-p22.1	phosphate regulating endopeptidase homolog, X-linked (hypophosphatemia, vitamin D resistant rickets)
CPA1	M14.001	1357	3.4.17.1	7q32	carboxypeptidase A1 (pancreatic)
CPA2	M14.002	1358	3.4.17.15	7q32	carboxypeptidase A2 (pancreatic)
CPB1	M14.003	1360	3.4.17.2	3q24	carboxypeptidase B1 (tissue)
CPN1	M14.004	1369	-	10q24.2	carboxypeptidase N, polypeptide 1, 50kD
CPE	M14.005	1363	3.4.17.10	4q32.3	carboxypeptidase E
CPM	M14.006	1368	3.4.17.12	12q14.3	carboxypeptidase M
CPB2	M14.009	1361	-	13q14.11	carboxypeptidase B2 (plasma, carboxypeptidase U)
CPA3	M14.010	1359	3.4.2.1	3q21-q25	carboxypeptidase A3 (mast cell)
CPZ	M14.012	8532	-	4p16.1	carboxypeptidase Z
CPA4	M14.017	51200	-	7q32	carboxypeptidase A4
CPA6	M14.018	57094	-	8q13.2	carboxypeptidase A6
CPA5	M14.020	93979	-	7q32	carboxypeptidase A5
CPO	M14.021	130749	-	2q33.3	carboxypeptidase O
AGBL3	M14.026	340351	-	7q33	hypothetical protein LOC340351
AGBL4	M14.027	84871	-	1p33	hypothetical protein FLJ14442
AGTPBP1	M14.028	23287	-	9q21.33	ATP/GTP binding protein 1
AGBL2	M14.029	79841	-	11p11.2	hypothetical protein FLJ23598
AEBP1	M14.951	165	-	7p13	AE binding protein 1
CPXM	M14.952	56265	-	20p13-p12.3	carboxypeptidase X (M14 family)
CPXM2	M14.954	119587	-	10q26.13	carboxypeptidase X (M14 family), member 2
IDE	M16.002	3416	-	10q23-q25	insulin-degrading enzyme
PMPCB	M16.003	9512	-	7q22-q32	peptidase (mitochondrial processing) beta
NRD1	M16.005	4898	-	1p32.2-p32.1	nardilysin (N-arginine dibasic convertase)
PITRM1	M16.009	10531	-	10p15.2	pitrilysin metalloproteinase 1
PMPCA	M16.971	23203	-	9q34.3	peptidase (mitochondrial processing) alpha

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UQCRC1	M16.973	7384	1.10.2.2	3p21.3	ubiquinol-cytochrome c reductase core protein I
UQCRC2	M16.974	7385	1.10.2.2	16p12	ubiquinol-cytochrome c reductase core protein II
AMPP	M16.976np	133083	-	4q22.2-q22.3	similar to PMPCA protein
LAP3	M17.001	51056	3.4.11.1	4p15.32	leucine aminopeptidase 3
NPEPL1	M17.006	79716	-	20q13.32	aminopeptidase-like 1
DNPEP	M18.002	23549	-	2q35	aspartyl aminopeptidase
DPEP1	M19.001	1800	3.4.13.11	16q24.3	dipeptidase 1 (renal)
DPEP2	M19.002	64174	-	16q22.1	dipeptidase 2
DPEP3	M19.004	64180	-	16q22.1	dipeptidase 3
CNDP2	M20.005	55748	3.4.13.18	18q22.3	CNDP dipeptidase 2 (metallopeptidase M20 family)
CNDP1	M20.006	84735	-	18q22.3	carnosine dipeptidase 1 (metallopeptidase M20 family)
ACY1L2	M20.971	135293	-	6q15	aminoacylase 1-like 2
ACY1	M20.973	95	3.5.1.14	3p21.1	aminoacylase 1
OSGEP	M22.003	55644	3.4.24.57	14q11.2	O-sialoglycoprotein endopeptidase
OSGEPL1	M22.004	64172	-	2q32.2	O-sialoglycoprotein endopeptidase-like 1
METAP1	M24.001	23173	-	4q23	methionyl aminopeptidase 1
METAP2	M24.002	10988	-	12q22	methionyl aminopeptidase 2
XPNPEP2	M24.005	7512	3.4.11.9	xq25	X-prolyl aminopeptidase (aminopeptidase P) 2, membrane-bound
PEPD	M24.007	5184	3.4.13.9	19q12-q13.2	peptidase D
XPNPEP1	M24.009	7511	3.4.11.9	10q25.3	X-prolyl aminopeptidase (aminopeptidase P) 1, soluble
XPNPEP3	M24.026	63929	-	22q13.31-q13.33	hypothetical protein LOC63929
MAP1D	M24.028	254042	-	2q31.1	methionine aminopeptidase 1D
PA2G4	M24.973	5036	-	12q13	proliferation-associated 2G4, 38kDa
SUPT16H	M24.974	11198	-	14q11.2	suppressor of Ty 16 homolog (S. cerevisiae)
FOLH1	M28.010	2346	-	11p11.2	folate hydrolase (prostate-specific membrane antigen) 1
NAALADL1	M28.011	10004	-	11q12	N-acetylated alpha-linked acidic dipeptidase-like 1
NAALAD2	M28.012	10003	-	11q14.3-q21	N-acetylated alpha-linked acidic dipeptidase 2
PGCP	M28.014	10404	-	8q22.2	plasma glutamate carboxypeptidase
QPCTL	M28.016	54814	-	19q13.32	glutaminyl-peptide cyclotransferase-like
KIAA1815	M28.018	79956	-	9p24	KIAA1815
TFRC	M28.972	7037	-	3q29	transferrin receptor (p90, CD71)
TFR2	M28.973	7036	-	7q22	transferrin receptor 2

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QPCT	M28.974	25797	2.3.2.5	2p22.2	glutaminyl-peptide cyclotransferase (glutaminyl cyclase)
NAALADL 2	M28.975	254827	-	3q26.31	N-acetylated alpha-linked acidic dipeptidase 2
NCLN	M28.978	56926	-	19p13.3	nicalin homolog (zebrafish)
CAD	M38.972	790	2.1.3.2, 3.5.2.-	2p22-p21	carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase
DPYS	M38.973	1807	-	8q22	dihydropyrimidinase
CRMP1	M38.974	1400	-	4p16.1-p15	collapsin response mediator protein 1
DPYSL2	M38.975	1808	-	8p22-p21	dihydropyrimidinase-like 2
DPYSL3	M38.976	1809	-	5q32	dihydropyrimidinase-like 3
DPYSL4	M38.977	10570	-	10q26	dihydropyrimidinase-like 4
DPYSL5	M38.978	56896	-	2p23.3	dihydropyrimidinase-like 5
GDA	M38.981	9615	-	9q21.11-21.33	guanine deaminase
YME1L1	M41.004	10730	-	10p14	YME1-like 1 (S. cerevisiae)
SPG7	M41.006	6687	-	16q24.3	spastic paraplegia 7, paraplegin (pure and complicated autosomal recessive)
AFG3L2	M41.007	10939	-	18p11	AFG3 ATPase family gene 3-like 2 (yeast)
AFG3L1	M41.010	172	-	16q24.3	AFG3 ATPase family gene 3-like 1 (yeast)
PAPPA	M43.004	5069	-	9q33.2	pregnancy-associated plasma protein A, pappalysin 1
PAPPA2	M43.005	60676	-	1q23-q25	pappalysin 2
CHMP1A	M47.001	5119	-	16q24.3	procollagen (type III) N-endopeptidase
ZMPSTE24	M48.003	10269	-	1p34	zinc metallopeptidase (STE24 homolog, yeast)
OMA1	M48.017	115209	-	1p32.2-p32.1	OMA1 homolog, zinc metallopeptidase (S. cerevisiae)
DPP3	M49.001	10072	3.4.14.4	11q12-q13.1	dipeptidylpeptidase 3
MBTPS2	M50.001	51360	-	xp22.1-p22.2	membrane-bound transcription factor protease, site 2
PSMD14	M67.001	10213	-	2q24.2	proteasome (prosome, macropain) 26S subunit, non-ATPase, 14
COPS5	M67.002	10987	-	8q13.2	COP9 constitutive photomorphogenic homolog subunit 5 (Arabidopsis)
STAMBPL1	M67.003	57559	-	10q23.31	associated molecule with the SH3 domain of STAM (AMSH) like protein
CXorf53	M67.004	79184	-	xq28	chromosome X open reading frame 53
MYSM1	M67.005	114803	-	1p32.1	KIAA1915 protein
STAMBP	M67.006	10617	-	2p13.1	STAM binding protein
EIF3S3	M67.971	8667	-	8q24.11	eukaryotic translation initiation factor 3, subunit 3 gamma, 40kDa
COPS6	M67.972	10980	-	7q22.1	COP9 constitutive photomorphogenic homolog subunit 6 (Arabidopsis)

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PSMD7	M67.973	5713	-	16q23-q24	proteasome (prosome, macropain) 26S subunit, non-ATPase, 7 (Mov34 homolog)
EIF3F	M67.974	8665	-	11p15.4	eukaryotic translation initiation factor 3, subunit 5 epsilon, 47kDa
EIF3FP	M67.975	83880	-	13p13	IFP38
MPND	M67.xxx	84954	-	19p13.3	hypothetical protein FLJ14981
PRPF8	M67.xxxnp	10594	-	17p13.3	PRP8 pre-mRNA processing factor 8 homolog (yeast)
ASPA	Mx2.xxxnp	443	3.5.1.15	17pter-p13	aspartoacylase (aminoacylase 2, Canavan disease)
ACY3	Mx2.xxxnp	91703	-	11q13.2	aspartoacylase (aminocyclase) 3
ACE	XM02-001	1636	3.4.15.1	17q23	angiotensin I converting enzyme (peptidyl-dipeptidase A) 1
CPD	XM14-001	1362	-	17p11.1-q11.2	carboxypeptidase D
GZMB	S01.010	3002	-	14q11.2	granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1)
PRSS21	S01.011	10942	-	16p13.3	protease, serine, 21 (testisin)
TPSAB1	S01.015	7177	-	16p13.3	tryptase alpha/beta 1
TPSB2	S01.015	64499	-	16p13.3	tryptase beta 2
KLK5	S01.017	25818	-	19q13.3-q13.4	kallikrein 5
CORIN	S01.019	10699	-	4p13-p12	corin, serine protease
KLK12	S01.020	43849	-	19q13.3-q13.4	kallikrein 12
TMPRSS11 E	S01.021	28983	-	4q13.2	DESC1 protein
TPSG1	S01.028	25823	-	16p13.3	tryptase gamma 1
KLK14	S01.029	43847	-	19q13.3-q13.4	kallikrein 14
HABP2	S01.033	3026	-	10q25.3	hyaluronan binding protein 2
TMPRSS4	S01.034	56649	-	11q23.3	transmembrane protease, serine 4
TMPRSS11 D	S01.047	9407	-	4q13.2	airway trypsin-like protease
TPSD1	S01.054	23430	-	16p13.3	tryptase delta 1
TMPRSS7	S01.072	344805	-	3q13.2	transmembrane serine protease 7
PRSS27	S01.074	83886	-	16p13.3	pancreasin
PRSS33	S01.075	260429	-	16p13.3	protease, serine, 33
TESSP1	S01.076	BN000124	-	-	-
TMPRSS3	S01.079	64699	-	21q22.3	transmembrane protease, serine 3
KLK15	S01.081	55554	-	19q13.41	kallikrein 15
TMPRSS13	S01.087	84000	-	11q23	mosaic serine protease
PRSS1	S01.127	5644	3.4.21.4	7q34	protease, serine, 1 (trypsin 1)
ELA2	S01.131	1991	3.4.21.37	19p13.3	elastase 2, neutrophil
MASP1	S01.132	5648	-	3q27-q28	mannan-binding lectin serine protease 1 (C4/C2 activating component of Ra-

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					reactive factor)
CTSG	S01.133	1511	-	14q11.2	cathepsin G
PRTN3	S01.134	5657	-	19p13.3	proteinase 3 (serine proteinase, neutrophil, Wegener granulomatosis autoantigen)
GZMA	S01.135	3001	-	5q11-q12	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)
GZMM	S01.139	3004	-	19p13.3	granzyme M (lymphocyte met-ase 1)
CMA1	S01.140	1215	3.4.21.39	14q11.2	chymase 1, mast cell
GZMK	S01.146	3003	-	5q11-q12	granzyme K (serine protease, granzyme 3; tryptase II)
GZMH	S01.147	2999	-	14q11.2	granzyme H (cathepsin G-like 2, protein h-CCPX)
CTRB1	S01.152	1504	3.4.21.1	16q23-q24.1	chymotrypsinogen B1
ELA1	S01.153	1990	3.4.21.36	12q13	elastase 1, pancreatic
ELA3A	S01.154	10136	-	1p36.12	elastase 3A, pancreatic (protease E)
ELA2A	S01.155	63036	-	1p36.21	elastase 2A
PRSS7	S01.156	5651	-	21q21.1	protease, serine, 7 (enterokinase)
CTRC	S01.157	11330	-	1p36.21	chymotrypsin C (caldecrin)
PRSS8	S01.159	5652	-	16p11.2	protease, serine, 8 (prostasin)
KLK1	S01.160	3816	3.4.21.35	19q13.3	kallikrein 1, renal/pancreas/salivary
KLK2	S01.161	3817	3.4.21.35	19q13.41	kallikrein 2, prostatic
KLK3	S01.162	354	-	19q13.41	kallikrein 3, (prostate specific antigen)
PRSS3	S01.174	5646	3.4.21.4	9p11.2	protease, serine, 3 (mesotrypsin)
C1RL	S01.189	51279	-	12p13.31	complement component 1, r subcomponent-like
DF	S01.191	1675	-	19p13.3	D component of complement (adipsin)
C1R	S01.192	715	3.4.21.41	12p13	complement component 1, r subcomponent
C1S	S01.193	716	3.4.21.42	12p13	complement component 1, s subcomponent
C2	S01.194	717	-	6p21.3	complement component 2
BF	S01.196	629	3.4.21.47	6p21.3	B-factor, properdin
IF	S01.199	3426	3.4.21.45	4q25	I factor (complement)
ELA3B	S01.205	23436	-	1p36.12	elastase 3B, pancreatic
ELA2B	S01.206	51032	-	1p36.21	elastase 2B
F12	S01.211	2161	3.4.21.38	5q33-qter	coagulation factor XII (Hageman factor)
KLKB1	S01.212	3818	-	4q34-q35	kallikrein B, plasma (Fletcher factor) 1

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F11	S01.213	2160	3.4.21.27	4q35	coagulation factor XI (plasma thromboplastin antecedent)
F9	S01.214	2158	3.4.21.22	xq27.1-q27.2	coagulation factor IX (plasma thromboplastic component, Christmas disease, hemophilia B)
F7	S01.215	2155	-	13q34	coagulation factor VII (serum prothrombin conversion accelerator)
F10	S01.216	2159	3.4.21.6	13q34	coagulation factor X
F2	S01.217	2147	3.4.21.5	11p11-q12	coagulation factor II (thrombin)
PROC	S01.218	5624	-	2q13-q14	protein C (inactivator of coagulation factors Va and VIIIa)
ACR	S01.223	49	3.4.21.10	22q13.33	acrosin
HPN	S01.224	3249	-	19q11-q13.2	hepsin (transmembrane protease, serine 1)
HGFAC	S01.228	3083	3.4.21.-	4p16	HGF activator
MASP2	S01.229	10747	-	1p36.3-p36.2	mannan-binding lectin serine protease 2
PLAU	S01.231	5328	3.4.21.31	10q24	plasminogen activator, urokinase
PLAT	S01.232	5327	-	8p12	plasminogen activator, tissue
PLG	S01.233	5340	-	6q26	plasminogen
KLK6	S01.236	5653	-	19q13.3	kallikrein 6 (neurosin, zyme)
PRSS12	S01.237	8492	-	4q28.1	protease, serine, 12 (neurotrypsin, motopsin)
KLK8	S01.244	11202	-	19q13.3-q13.4	kallikrein 8 (neuropsin/ovasin)
KLK10	S01.246	5655	-	19q13.3-q13.4	kallikrein 10
TMPRSS2	S01.247	7113	-	21q22.3	transmembrane protease, serine 2
KLK4	S01.251	9622	-	19q13.41	kallikrein 4 (prostase, enamel matrix, prostate)
PRSS22	S01.252	64063	-	16p13.3	protease, serine, 22
CTRL	S01.256	1506	-	16q22.1	chymotrypsin-like
KLK11	S01.257	11012	-	19q13.3-q13.4	kallikrein 11
PRSS2	S01.258	5645	-	7q34	protease, serine, 2 (trypsin 2)
PRSS11	S01.277	5654	-	10q26.3	protease, serine, 11 (IGF binding)
PRSS25	S01.278	27429	-	2p12	protease, serine, 25
HTRA3	S01.284	94031	-	4p16.1	HtrA serine peptidase 3
HTRA4	S01.285	203100	-	8p11.23	HtrA serine peptidase 4
TYSND1	S01.286	219743	-	10q22.1	trypsin domain containing 1
TMPRSS12	S01.291	283471	-	12q13.12	hypothetical protein MGC57341
TMPRSS11A	S01.292	339967	-	4q13.2	epidermal type II transmembrane serine protease
HATL1	S01.292	BN000133	-	-	-
TMPRSS8	S01.298	AJ488946	-	-	-
KLK7	S01.300	5650	-	19q13.41	kallikrein 7 (chymotryptic, stratum corneum)

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ST14	S01.302	6768	-	11q24-q25	suppression of tumorigenicity 14 (colon carcinoma, matriptase, epithin)
KLK13	S01.306	26085	-	19q13.3-q13.4	kallikrein 13
KLK9	S01.307	23579	-	-	-
TMPRSS6	S01.308	164656	-	22q12.3-q13.1	transmembrane protease, serine 6
PRSS23	S01.309	11098	-	11q14.1	protease, serine, 23
TMPRSS5	S01.313	80975	-	11q	transmembrane protease, serine 5 (spinesin)
TESSP2	S01.317	AJ544583	-	-	-
MPN2	S01.318	BN000131	-	-	-
PRSSL1	S01.319	400668	-	19p13.3	protease, serine-like 1
OVCH2	S01.320	341277	-	11p15.4	oviductin protease
OVTN	S01.320	BN000130	-	-	-
TMPRSS11 F	S01.321	389208	-	4q13.2	FLJ16046 protein
OVCH1	S01.322	341350	-	12p11.22	ovochymase 1
OVCH	S01.322	BN000128	-	-	-
TMPRSS9	S01.357	360200	-	19p13.3	transmembrane serine protease 9
TMPRSS11 B	S01.365	132724	-	4q13.2	hypothetical protein DKFZp686L1818
PRSS36	S01.414	146547	-	16p11.2	polyserase-2
KLKBL2	S01.415	203074	-	8p23.1	tryptophan/serine protease
TESSP5	S01.968np	BN000137	-	-	-
AZU1	S01.971	566	-	19p13.3	azurocidin 1 (cationic antimicrobial protein 37)
HP	S01.972	3240	-	16q22.1	haptoglobin
HPR	S01.974	3250	-	16q22.1	haptoglobin-related protein
MST1	S01.975	4485	-	3p21	macrophage stimulating 1 (hepatocyte growth factor-like)
HGF	S01.976	3082	-	7q21.1	hepatocyte growth factor (hepapoietin A; scatter factor)
PROZ	S01.979	8858	-	13q34	protein Z, vitamin K-dependent plasma glycoprotein
TRYX2	S01.989np	136242	-	7q34	similar to RIKEN cDNA 1700016G05
KLKBL4	S01.992np	221191	-	16q21	hypothetical protein FLJ25339
TSP50	S01.993np	29122	-	3p14-p12	testes-specific protease 50
PRSS35	S01.994	167681	-	6q14.2	protease, serine, 35
PROCL	S01.998np	25891	-	11p13	regeneration associated muscle protease
LPA	S01.999	4018	-	6q26-q27	lipoprotein, Lp(a)
KLKP1	S01.P08	606293	-	19q13.41	kallikrein pseudogene 1
VKORC1	S01.xxx	79001	-	16p11.2	vitamin K epoxide reductase complex, subunit 1
ESSPL	S01.xxx	BN000134	-	-	-

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PRSS7L	S01.xxx	BQ638967	-	-	-
TMPRSS7	S01.xxx	BN000125	-	-	-
PCSK9	S08.039	255738	-	1p32.3	proprotein convertase subtilisin/kexin type 9
MBTPS1	S08.063	8720	-	16q24	membrane-bound transcription factor protease, site 1
FURIN	S08.071	5045	-	15q26.1	furin (paired basic amino acid cleaving enzyme)
PCSK1	S08.072	5122	-	5q15-q21	proprotein convertase subtilisin/kexin type 1
PCSK2	S08.073	5126	-	20p11.2	proprotein convertase subtilisin/kexin type 2
PCSK4	S08.074	54760	-	19p13.3	proprotein convertase subtilisin/kexin type 4
PCSK6	S08.075	5046	-	15q26	proprotein convertase subtilisin/kexin type 6
PCSK5	S08.076	5125	-	9q21.3	proprotein convertase subtilisin/kexin type 5
PCSK7	S08.077	9159	-	11q23-q24	proprotein convertase subtilisin/kexin type 7
TPP2	S08.090	7174	3.4.14.10	13q32-q33	tripeptidyl peptidase II
PREP	S09.001	5550	3.4.21.26	6q22	prolyl endopeptidase
DPP4	S09.003	1803	3.4.14.5	2q24.3	dipeptidylpeptidase 4 (CD26, adenosine deaminase complexing protein 2)
APEH	S09.004	327	3.4.19.1	3p21.31	N-acylaminoacyl-peptide hydrolase
FAP	S09.007	2191	-	2q23	fibroblast activation protein, alpha
PREPL	S09.015	9581	-	2p22.1	putative prolyl oligopeptidase
DPP8	S09.018	54878	-	15q22	dipeptidylpeptidase 8
DPP9	S09.019	91039	-	19p13.3	dipeptidylpeptidase 9
C13orf6	S09.051	84945	-	13q33.3	chromosome 13 open reading frame 6
C19orf27	S09.052	81926	-	19p13.3	chromosome 19 open reading frame 27
FAM108C1	S09.053	58489	-	15q25.1	hypothetical protein from EUROIMAGE 588495
C20orf22	S09.054	26090	-	20p11.21	chromosome 20 open reading frame 22
C9orf77	S09.055	51104	-	9q21.13	chromosome 9 open reading frame 77
C14orf29	S09.061	145447	-	14q22.1	chromosome 14 open reading frame 29
ABHD10	S09.062	55347	-	3q13.2	abhydrolase domain containing 10
BAT5	S09.065	7920	-	6p21.3	HLA-B associated transcript 5
DPP6	S09.973	1804	-	7q36.2	dipeptidylpeptidase 6
DPP10	S09.974	57628	-	2q14.1	dipeptidylpeptidase 10
C20orf135	S09.976	140701	-	20q13.33	chromosome 20 open reading frame 135
AFMID	S09.977	125061	3.5.1.9	17q25.3	arylformamidase

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TG	S09.978	7038	-	8q24.2-q24.3	thyroglobulin
ACHE	S09.979	43	3.1.1.7	7q22	acetylcholinesterase (YT blood group)
BCHE	S09.980	590	3.1.1.8	3q26.1-q26.2	butyrylcholinesterase
CES1	S09.982	1066	3.1.1.1	16q13-q22.1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)
CES3	S09.983	23491	-	16	carboxylesterase 3 (brain)
CES2	S09.984	8824	-	16q22.1	carboxylesterase 2 (intestine, liver)
CEL	S09.985	1056	3.1.1.3, 3.1.1.13	9q34.3	carboxyl ester lipase (bile salt-stimulated lipase)
CES4	S09.986	51716	-	16q12.2	carboxylesterase 4-like
NLGN3	S09.987	54413	-	xq13.1	neuroligin 3
NLGN4X	S09.988	57502	-	xp22.32-p22.31	neuroligin 4, X-linked
NLGN4Y	S09.989	22829	-	yq11.221	neuroligin 4, Y-linked
ESD	S09.990	2098	3.1.1.1	13q14.1-q14.2	esterase D/formylglutathione hydrolase
AADAC	S09.991	13	-	3q21.3-q25.2	arylacetamide deacetylase (esterase)
AADACL1	S09.992	57552	-	3q26.31	KIAA1363 protein
LIPE	S09.993	3991	3.1.1.-	19q13.2	lipase, hormone-sensitive
NLGN1	S09.994	22871	-	3q26.31	neuroligin 1
NLGN2	S09.995	57555	-	17p13.1	neuroligin 2
PPGB	S10.002	5476	-	20q13.1	protective protein for beta-galactosidase (galactosialidosis)
CPVL	S10.003	54504	-	7p15-p14	carboxypeptidase, vitellogenic-like
SCPEP1	S10.013	59342	-	17q23.2	serine carboxypeptidase 1
LACTB	S12.004	114294	-	15q22.1	lactamase, beta
CLPP	S14.003	8192	-	19p13.3	ClpP caseinolytic protease, ATP-dependent, proteolytic subunit homolog (E. coli)
PRSS15	S16.002	9361	-	19p13.2	protease, serine, 15
LONP2	S16.006	83752	-	16q12.1	peroxisomal lon protease
SEC11L1	S26.009	23478	-	15q25.3	SEC11-like 1 (S. cerevisiae)
SEC11L3	S26.010	90701	-	18q21.32	SEC11-like 3 (S. cerevisiae)
IMMP2L	S26.012	83943	-	7q31	IMP2 inner mitochondrial membrane protease-like (S. cerevisiae)
IMMP1L	S26.013	196294	-	11p13	hypothetical protein FLJ25059
FREM1	S26.xxx	158326	-	9p22.3	FRAS1 related extracellular matrix 1
PRCP	S28.001	5547	-	11q14	prolylcarboxypeptidase (angiotensinase C)
DPP7	S28.002	29952	-	9q34.3	dipeptidylpeptidase 7
PRSS16	S28.003	10279	-	6p21	protease, serine, 16 (thymus)
ABHD8	S33.011	79575	-	19p13.11	abhydrolase domain containing 8
SERHL	S33.012	253190	-	22q13	kraken-like

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ABHD4	S33.013	63874	-	14q11.2	abhydrolase domain containing 4
EPHX1	S33.971	2052	3.3.2.3	1q42.1	epoxide hydrolase 1, microsomal (xenobiotic)
MEST	S33.972	4232	-	7q32	mesoderm specific transcript homolog (mouse)
EPHX2	S33.973	2053	-	8p21-p12	epoxide hydrolase 2, cytoplasmic
ABHD7	S33.974	253152	-	1p22.1	abhydrolase domain containing 7
ABHD5	S33.975	51099	-	3p21	abhydrolase domain containing 5
ABHD11	S33.976	83451	-	7q11.23	abhydrolase domain containing 11
ABHD6	S33.977	57406	-	3p14.3	abhydrolase domain containing 6
ABHD9	S33.978	79852	-	19p13.12	abhydrolase domain containing 9
MGLL	S33.980	11343	-	3q21.3	monoglyceride lipase
ABHD14A	S33.981	25864	-	3p21.1	DKFZP564O243 protein
BPHL	S33.982	670	-	6p25	biphenyl hydrolase-like (serine hydrolase; breast epithelial mucin-associated antigen)
NDRG4	S33.986	65009	-	16q21-q22.1	NDRG family member 4
NDRG3	S33.987	57446	-	20q11.21-q11.23	NDRG family member 3
NDRG1	S33.988	10397	-	8q24.3	N-myc downstream regulated gene 1
RBP3	S41.950	5949	-	10q11.2	retinol binding protein 3, interstitial
TPP1	S53.003	1200	-	11p15	tripeptidyl peptidase I
RHBDL2	S54.002	54933	-	1p34.3	rhomboid, veinlet-like 2 (Drosophila)
RHBDL1	S54.005	9028	-	16p13.3	rhomboid, veinlet-like 1 (Drosophila)
RHBDL4	S54.006	162494	-	17q11.2	rhomboid, veinlet-like 4 (Drosophila)
PSARL	S54.009	55486	-	3q27.1	presenilin associated, rhomboid-like
RHBDF1	S54.952	64285	-	16p13.3	rhomboid family 1 (Drosophila)
RHBDL6	S54.953	79651	-	17q25.1	rhomboid, veinlet-like 6 (Drosophila)
RHBDD2	S54.955	57414	-	7q11.23	rhomboid, veinlet-like 7 (Drosophila)
RHBDD1	S54.xxx	84236	-	2q36.3	hypothetical protein DKFZp547E052
RHBDL7	S54.xxxnp	AC005067	-	-	-
NUP98	S59.001	4928	-	11p15.5	nucleoporin 98kDa
LTF	S60.001	4057	-	3q21-q23	lactotransferrin
TF	S60.972	7018	-	3q22.1	transferrin
MFI2	S60.973	4241	-	3q28-q29	antigen p97 (melanoma associated) identified by monoclonal antibodies 133.2 and 96.5
EMR2	S63.001	30817	-	19p13.1	egf-like module containing, mucin-like, hormone receptor-like 2
CD97	S63.002	976	-	19p13	CD97 antigen
EMR3	S63.003	84658	-	19p13.1	egf-like module containing, mucin-like, hormone receptor-like 3
EMR1	S63.004	2015	-	19p13.3	egf-like module containing, mucin-like, hormone receptor-like 1

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EMR4	S63.008	326342	-	19p13.3	egf-like module containing, mucin-like, hormone receptor-like 4
CELSR2	S63.009	1952	-	1p21	cadherin, EGF LAG seven-pass G-type receptor 2 (flamingo homolog, Drosophila)
RELN	Sx1.xxx	5649	-	7q22	reelin
HSP90B1	Sx2.xxx	7184	-	12q24.2-q24.3	tumor rejection antigen (gp96) 1
HSP90AA1	Sx2.xxxnp	3320	-	14q32.33	heat shock 90kDa protein 1, alpha
HSP90AB1	Sx2.xxxnp	3326	-	6p12	heat shock 90kDa protein 1, beta
TRAP1	Sx2.xxxnp	10131	-	16p13.3	TNF receptor-associated protein 1
PSMB6	T01.010	5694	-	17p13	proteasome (prosome, macropain) subunit, beta type, 6
PSMB7	T01.011	5695	-	9q34.11-q34.12	proteasome (prosome, macropain) subunit, beta type, 7
PSMB5	T01.012	5693	-	14q11.2	proteasome (prosome, macropain) subunit, beta type, 5
PSMB9	T01.013	5698	-	6p21.3	proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional protease 2)
PSMB10	T01.014	5699	-	16q22.1	proteasome (prosome, macropain) subunit, beta type, 10
PSMB8	T01.015	5696	-	6p21.3	proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional protease 7)
LMP7L	T01.016	122706	-	14q11.2	similar to RIKEN cDNA 5830406J20
PSMA6	T01.971	5687	-	14q13	proteasome (prosome, macropain) subunit, alpha type, 6
PSMA2	T01.972	5683	-	7p14.1	proteasome (prosome, macropain) subunit, alpha type, 2
PSMA4	T01.973	5685	-	15q25.1	proteasome (prosome, macropain) subunit, alpha type, 4
PSMA7	T01.974	5688	-	20q13.33	proteasome (prosome, macropain) subunit, alpha type, 7
PSMA5	T01.975	5686	-	1p13	proteasome (prosome, macropain) subunit, alpha type, 5
PSMA1	T01.976	5682	-	11p15.1	proteasome (prosome, macropain) subunit, alpha type, 1
PSMA3	T01.977	5684	-	14q23	proteasome (prosome, macropain) subunit, alpha type, 3
PSMA8	T01.978	143471	-	18q11.2	proteasome (prosome, macropain) subunit, alpha type, 8
PSMB3	T01.983	5691	-	17q12	proteasome (prosome, macropain) subunit, beta type, 3
PSMB2	T01.984	5690	-	1p34.2	proteasome (prosome, macropain) subunit, beta type, 2
PSMB1	T01.986	5689	-	6q27	proteasome (prosome, macropain) subunit, beta type, 1
PSMB4	T01.987	5692	-	1q21	proteasome (prosome, macropain) subunit, beta type, 4
PSMB3P	T01.P02	121131	-	12q13.2	proteasome (prosome, macropain) subunit, beta type, 3 pseudogene

Protease Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
AGA	T02.001	175	3.5.1.26	4q32-q33	aspartylglucosaminidase
ASRGL1	T02.002	80150	-	11q12.3	asparaginase like 1
TASP1	T02.004	55617	3.4.25.-	20p12.1	chromosome 20 open reading frame 13
GGTLA1	T03.002	2687	-	22q11.23	gamma-glutamyltransferase-like activity 1
GGT1	T03.006	2678	2.3.2.2	22q11.23	gamma-glutamyltransferase 1
GGT2	T03.015	2679	-	22q11.23	gamma-glutamyltransferase 2
GGTL4	T03.016	91227	-	22q11.22	gamma-glutamyltransferase-like 4
GGTL3	T03.017	2686	-	20q11.22	gamma-glutamyltransferase-like 3
RCE1	U48.002	9986	-	11q13	RCE1 homolog, prenyl protein protease (S. cerevisiae)
BDNF	Uxx.xxx	627	-	11p13	brain-derived neurotrophic factor
CST3	Uxx.xxx	1471	-	20p11.21	cystatin C (amyloid angiopathy and cerebral hemorrhage)
KNG1	Uxx.xxx	3827	-	3q27	kininogen 1
NEDD8	Uxx.xxx	4738	-	14q11.2	neural precursor cell expressed, developmentally down-regulated 8
PDGFA	Uxx.xxx	5154	-	7p22	platelet-derived growth factor alpha polypeptide
SERPINF2	Uxx.xxx	5345	-	17p13	serine (or cysteine) proteinase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member 2
SFRS2IP	Uxx.xxx	9169	-	12q13.11	splicing factor, arginine/serine-rich 2, interacting protein
BIRC8	Uxx.xxx	112401	-	19q13.3-q13.4	baculoviral IAP repeat-containing 8

[00178] **Table 5.** Additional kinases are presented, the concentration and activity of which may be detected and quantitated using embodiments of the methods of the invention.

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
AKT1	AGC,AKT,SK018, AKT1	207	2.7.1.37	14q32.32	v-akt murine thymoma viral oncogene homolog 1
AKT2	AGC,AKT,SK019, AKT2	208	2.7.1.37	19q13.1-q13.2	v-akt murine thymoma viral oncogene homolog 2
AKT3	AGC,AKT,SK020, AKT3	10000	2.7.1.37	1q43-q44	v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)
CRIK	AGC,DMPK,SK695,CRIK	11113	-	12q24	citron (rho-interacting, serine/threonine kinase 21)
DMPK1	AGC,DMPK,GEK,SK111,DMPK1	1760	-	19q13.3	dystrophia myotonica-protein kinase
MRCKa	AGC,DMPK,GEK,SK299,MRCKa	8476	-	1q42.11	CDC42 binding protein kinase alpha (DMPK-like)
MRCKb	AGC,DMPK,GEK,SK241,MRCKb	9578	-	14q32.3	CDC42 binding protein kinase beta (DMPK-like)

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
DMPK2	AGC,DMPK,GEK ,SK112,DMPK2	55561	-	11q13.1	CDC42 binding protein kinase gamma (DMPK-like)
ROCK1	AGC,DMPK,ROC K,SK331,ROCK1	6093	2.7.1.37	18q11.1	Rho-associated, coiled-coil containing protein kinase 1
ROCK2	AGC,DMPK,ROC K,SK263,ROCK2	9475	2.7.1.37	2p24	Rho-associated, coiled-coil containing protein kinase 2
BARK1	AGC,GRK,BARK, SK045,BARK1	156	-	11q13	adrenergic, beta, receptor kinase 1
BARK2	AGC,GRK,BARK, SK478,BARK2	157	-	22q12.1	adrenergic, beta, receptor kinase 2
GPRK4	AGC,GRK,GRK,S K156,GPRK4	2868	-	4p16.3	G protein-coupled receptor kinase 4
GPRK5	AGC,GRK,GRK,S K157,GPRK5	2869	-	10q24-qter	G protein-coupled receptor kinase 5
GPRK6	AGC,GRK,GRK,S K158,GPRK6	2870	-	5q35	G protein-coupled receptor kinase 6
RHOK	AGC,GRK,GRK,S K327,RHOK	6011	2.7.1.125	13q34	G protein-coupled receptor kinase 1
GPRK7	AGC,GRK,GRK,S K578,GPRK7	131890	-	3q21-q23	G protein-coupled receptor kinase 7
MAST1	AGC,MAST,SK34 5,MAST1	22983	-	19p13.2	microtubule associated serine/threonine kinase 1
MAST3	AGC,MAST,SK19 6,MAST3	23031	-	19p13.11	microtubule associated serine/threonine kinase 3
MAST2	AGC,MAST,SK21 6,MAST2	23139	-	1p34.1	microtubule associated serine/threonine kinase 2
MAST4	AGC,MAST,SK70 1,MAST4	375449	-	5q12.3	similar to microtubule associated testis specific serine/threonine protein kinase
MASTL	AGC,MAST,SK45 5,MASTL	84930	-	10p12.1	microtubule associated serine/threonine kinase-like
LATS1	AGC,NDR,SK441, LATS1	9113	-	6q24-q25.1	LATS, large tumor suppressor, homolog 1 (Drosophila)
NDR1	AGC,NDR,SK249, NDR1	11329	-	6p21	serine/threonine kinase 38
NDR2	AGC,NDR,SK500, NDR2	23012	-	12p11.23	serine/threonine kinase 38 like
LATS2	AGC,NDR,SK442, LATS2	26524	-	13q11-q12	LATS, large tumor suppressor, homolog 2 (Drosophila)
PDK1	AGC,PDK1,SK27 6,PDK1	5170	-	16p13.3	3-phosphoinositide dependent protein kinase-1
PKACa	AGC,PKA,SK300, PKACa	5566	2.7.1.37	19p13.1	protein kinase, cAMP-dependent, catalytic, alpha
PKACb	AGC,PKA,SK301, PKACb	5567	2.7.1.37	1p36.1	protein kinase, cAMP-dependent, catalytic, beta
PKACg	AGC,PKA,SK302, PKACg	5568	2.7.1.37	9q13	protein kinase, cAMP-dependent, catalytic, gamma
PRKX	AGC,PKA,SK313, PRKX	5613	-	xp22.3	protein kinase, X-linked
PRKY	AGC,PKA,SK320, PRKY	5616	-	yp11.2	protein kinase, Y-linked
PKCa	AGC,PKC,Alpha, SK303,PKCa	5578	2.7.1.37	17q22-q23.2	protein kinase C, alpha
PKCb	AGC,PKC,Alpha,	5579	2.7.1.37	16p11.2	protein kinase C, beta 1

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
	SK304,PKCb				
PKCg	AGC,PKC,Alpha, SK307,PKCg	5582	2.7.1.37	19q13.4	protein kinase C, gamma
PKCd	AGC,PKC,Delta,S K305,PKCd	5580	2.7.1.37	3p21.31	protein kinase C, delta
PKCt	AGC,PKC,Delta,S K310,PKCt	5588	2.7.1.37	10p15	protein kinase C, theta
PKCe	AGC,PKC,Eta,SK 306,PKCe	5581	2.7.1.37	2p21	protein kinase C, epsilon
PKCh	AGC,PKC,Eta,SK 270,PKCh	5583	2.7.1.37	14q22-q23	protein kinase C, eta
PKCi	AGC,PKC,Iota,SK 308,PKCi	5584	2.7.11.13	3q26.3	protein kinase C, iota
PKCz	AGC,PKC,Iota,SK 311,PKCz	5590	2.7.1.37	1p36.33-p36.2	protein kinase C, zeta
PKG1	AGC,PKG,SK073, PKG1	5592	2.7.1.37	10q11.2	protein kinase, cGMP-dependent, type I
PKG2	AGC,PKG,SK075, PKG2	5593	2.7.1.37	4q13.1-q21.1	protein kinase, cGMP-dependent, type II
PKN1	AGC,PKN,SK317, PKN1	5585	-	19p13.1-p12	protein kinase N1
PKN2	AGC,PKN,SK318, PKN2	5586	-	1p22.2	protein kinase N2
PKN3	AGC,PKN,SK511, PKN3	29941	-	9q34.11	protein kinase N3
MSK2	AGC,RSK,MSK,S K243,MSK2	8986	-	11q11-q13	ribosomal protein S6 kinase, 90kDa, polypeptide 4
MSK1	AGC,RSK,MSK,S K242,MSK1	9252	-	14q31-q32.1	ribosomal protein S6 kinase, 90kDa, polypeptide 5
p70S6K	AGC,RSK,p70,SK 265,p70S6K	6198	-	17q23.2	ribosomal protein S6 kinase, 70kDa, polypeptide 1
p70S6Kb	AGC,RSK,p70,SK 266,p70S6Kb	6199	-	11q13.2	ribosomal protein S6 kinase, 70kDa, polypeptide 2
RSK3	AGC,RSK,RSK,S K338,RSK3	6195	-	1p	ribosomal protein S6 kinase, 90kDa, polypeptide 1
RSK1	AGC,RSK,RSK,S K336,RSK1	6196	-	6q27	ribosomal protein S6 kinase, 90kDa, polypeptide 2
RSK2	AGC,RSK,RSK,S K337,RSK2	6197	-	xp22.2-p22.1	ribosomal protein S6 kinase, 90kDa, polypeptide 3
RSK4	AGC,RSK,RSK,S K518,RSK4	27330	-	xq21	ribosomal protein S6 kinase, 90kDa, polypeptide 6
RSKL1	AGC,RSKL,SK51 7,RSKL1	26750	-	1q41	ribosomal protein S6 kinase, 52kDa, polypeptide 1
RSKL2	AGC,RSKL,SK47 3,RSKL2	83694	-	14q24.3	ribosomal protein S6 kinase-like 1
SgK494	AGC,RSKR,SK49 1,SgK494	124923	-	17q11.2	hypothetical protein FLJ25006
SGK1	AGC,SGK,SK346, SGK	6446	-	6q23	serum/glucocorticoid regulated kinase
SGK2	AGC,SGK,SK523, SGK2	10110	-	20q13.2	serum/glucocorticoid regulated kinase 2
SGK3	AGC,SGK,SK525, SGK3	23678	-	8q12.3-8q13.1	serum/glucocorticoid regulated kinase-like
YANK2	AGC,YANK,SK48	55351	-	4p16.2	serine/threonine kinase 32B

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
	1,YANK2				
YANK1	AGC,YANK,SK624,YANK1	202374	-	5q32	serine/threonine kinase 32A
YANK3	AGC,YANK,SK469,YANK3	282974	-	10q26.3	serine/threonine kinase 32C
ADCK3	Atypical,ABC1,ABC1-A,SK609,ADCK3	56997	-	1q42.13	chaperone, ABC1 activity of bc1 complex like (S. pombe)
ADCK4	Atypical,ABC1,ABC1-A,SK013,ADCK4	79934	-	19q13.2	aarF domain containing kinase 4
ADCK1	Atypical,ABC1,ABC1-B,SK401,ADCK1	57143	-	14q24.3	aarF domain containing kinase 1
ADCK5	Atypical,ABC1,ABC1-B,SK780,ADCK5	203054	-	8q24.3	aarF domain containing kinase 5
ADCK2	Atypical,ABC1,ABC1-C,SK712,ADCK2	90956	-	7q32-q34	aarF domain containing kinase 2
AlphaK1	Atypical,Alpha,SK765,AlphaK1	57538	-	15q25.2	alpha-kinase 3
AlphaK3	Atypical,Alpha,SK755,AlphaK3	80216	-	4q25	alpha-kinase 1
AlphaK2	Atypical,Alpha,SK754,AlphaK2	115701	-	18q21.31	alpha-kinase 2
ChaK1	Atypical,Alpha,ChaK,SK423,ChaK1	54822	-	15q21	transient receptor potential cation channel, subfamily M, member 7
ChaK2	Atypical,Alpha,ChaK,SK746,ChaK2	140803	-	9q21.13	transient receptor potential cation channel, subfamily M, member 6
eEF2K	Atypical,Alpha,eEF2K,SK117,eEF2K	29904	-	16p12.1	eukaryotic elongation factor-2 kinase
BCR	Atypical,BCR,SK047,BCR	613	-	22q11.23	breakpoint cluster region
BRDT	Atypical,BRD,SK764,BRDT	676	-	1p22.1	bromodomain, testis-specific
BRD2	Atypical,BRD,SK761,BRD2	6046	-	6p21.3	bromodomain containing 2
BRD3	Atypical,BRD,SK762,BRD3	8019	-	9q34	bromodomain containing 3
BRD4	Atypical,BRD,SK763,BRD4	23476	-	19p13.1	bromodomain containing 4
FASTK	Atypical,FAST,SK139,FASTK	10922	-	7q35	FAST kinase
G11	Atypical,G11,SK756,G11	8859	-	6p21.3	serine/threonine kinase 19
H11	Atypical,H11,SK782,H11	26353	-	12q24.23	heat shock 22kDa protein 8
BCKDK	Atypical,PDHK,SK046,BCKDK	10295	-	16p11.2	branched chain ketoacid dehydrogenase kinase
PDHK1	Atypical,PDHK,SK277,PDHK1	5163	-	2q31.1	pyruvate dehydrogenase kinase, isoenzyme 1
PDHK2	Atypical,PDHK,S	5164	-	17q21.33	pyruvate dehydrogenase kinase,

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
	K278,PDHK2				isoenzyme 2
PDHK3	Atypical,PDHK,SK279,PDHK3	5165	-	xp22.11	pyruvate dehydrogenase kinase, isoenzyme 3
PDHK4	Atypical,PDHK,SK280,PDHK4	5166	-	7q21.3-q22.1	pyruvate dehydrogenase kinase, isoenzyme 4
ATM	Atypical,PIKK,ATM,SK038,ATM	472	-	11q22-q23	ataxia telangiectasia mutated (includes complementation groups A, C and D)
ATR	Atypical,PIKK,ATR,SK039,ATR	545	-	3q22-q24	ataxia telangiectasia and Rad3 related
DNAPK	Atypical,PIKK,DNAPK,SK113,DNAPK	5591	-	8q11	protein kinase, DNA-activated, catalytic polypeptide
FRAP	Atypical,PIKK,FRAP,SK152,FRAP	2475	-	1p36.2	FK506 binding protein 12-rapamycin associated protein 1
SMG1	Atypical,PIKK,SMG1,SK665,SMG1	23049	-	16p12.3	PI-3-kinase-related kinase SMG-1
TRRAP	Atypical,PIKK,TRRAP,SK380,TRRAP	8295	-	7q21.2-q22.1	transformation/transcription domain-associated protein
RIOK1	Atypical,RIO,RIO1,SK615,RIOK1	83732	-	6p24.3	RIO kinase 1 (yeast)
RIOK2	Atypical,RIO,RIO2,SK753,RIOK2	55781	-	5q15	RIO kinase 2 (yeast)
RIOK3	Atypical,RIO,RIO3,SK606,RIOK3	8780	-	18q11.2	RIO kinase 3 (yeast)
TAF1	Atypical,TAF1,SK772,TAF1	6872	-	xq13.1	TAF1 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 250kDa
TAF1L	Atypical,TAF1,SK781,TAF1L	138474	-	9p21.1	TAF1-like RNA polymerase II, TATA box binding protein (TBP)-associated factor, 210kDa
TIF1a	Atypical,TIF1,SK783,TIF1a	8805	-	7q32-q34	transcriptional intermediary factor 1
TIF1b	Atypical,TIF1,SK784,TIF1b	10155	-	19q13.4	tripartite motif-containing 28
TIF1g	Atypical,TIF1,SK785,TIF1g	51592	-	1p13.1	tripartite motif-containing 33
CaMK4	CAMK,CAMK1,SK061,CaMK4	814	2.7.11.17	5q21.3	calcium/calmodulin-dependent protein kinase IV
CaMK1a	CAMK,CAMK1,SK056,CaMK1a	8536	-	3p25.3	calcium/calmodulin-dependent protein kinase I
CaMK1d	CAMK,CAMK1,SK572,CaMK1d	57118	-	10p13	calcium/calmodulin-dependent protein kinase ID
CaMK1g	CAMK,CAMK1,SK021,CaMK1g	57172	-	1q32-q41	calcium/calmodulin-dependent protein kinase IG
CaMK1b	CAMK,CAMK1,SK662,CaMK1b	139728	-	xq28	pregnancy upregulated non-ubiquitously expressed CaM kinase
CaMK2a	CAMK,CAMK2,SK057,CaMK2a	815	2.7.11.17	5q32	calcium/calmodulin-dependent protein kinase (CaM kinase) II alpha
CaMK2b	CAMK,CAMK2,SK058,CaMK2b	816	-	7p14.3-p14.1	calcium/calmodulin-dependent protein kinase (CaM kinase) II beta
CaMK2d	CAMK,CAMK2,S	817	-	4q26	calcium/calmodulin-dependent

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
	K703,CaMK2d				protein kinase (CaM kinase) II delta
CaMK2g	CAMK,CAMK2,SK060,CaMK2g	818	-	10q22	calcium/calmodulin-dependent protein kinase (CaM kinase) II gamma
AMPKa1	CAMK,CAMKL,AMPK,SK032,AMPKa1	5562	-	5p12	protein kinase, AMP-activated, alpha 1 catalytic subunit
AMPKa2	CAMK,CAMKL,AMPK,SK033,AMPKa2	5563	-	1p31	protein kinase, AMP-activated, alpha 2 catalytic subunit
BRSK2	CAMK,CAMKL,BRSK,SK015,BRSK2	9024	-	11p15.5	BR serine/threonine kinase 2
BRSK1	CAMK,CAMKL,BRSK,SK598,BRSK1	84446	-	19q13.4	BR serine/threonine kinase 1
CHK1	CAMK,CAMKL,CHK1,SK078,CHK1	1111	-	11q24-q24	CHK1 checkpoint homolog (S. pombe)
HUNK	CAMK,CAMKL,HUNK,SK502,HUNK	30811	-	21q22.1	hormonally upregulated Neu-associated kinase
LKB1	CAMK,CAMKL,LKB,SK208,LKB1	6794	-	19p13.3	serine/threonine kinase 11 (Peutz-Jeghers syndrome)
MARK2	CAMK,CAMKL,MARK,SK120,MARK2	2011	-	11q12-q13	MAP/microtubule affinity-regulating kinase 2
MARK1	CAMK,CAMKL,MARK,SK215,MARK1	4139	-	1q41	MAP/microtubule affinity-regulating kinase 1
MARK3	CAMK,CAMKL,MARK,SK096,MARK3	4140	-	14q32.3	MAP/microtubule affinity-regulating kinase 3
MARK4	CAMK,CAMKL,MARK,SK515,MARK4	57787	-	19q13.3	MAP/microtubule affinity-regulating kinase 4
MELK	CAMK,CAMKL,MELK,SK298,MELK	9833	-	9p13.2	maternal embryonic leucine zipper kinase
NIM1	CAMK,CAMKL,NIM1,SK449,NIM1	167359	-	5p12	hypothetical protein MGC42105
NuaK1	CAMK,CAMKL,NuaK,SK195,NuaK1	9891	-	12q23.3	AMP-activated protein kinase family member 5
NuaK2	CAMK,CAMKL,NuaK,SK472,NuaK2	81788	-	1q32.1	likely ortholog of rat SNF1/AMP-activated protein kinase
PASK	CAMK,CAMKL,PASK,SK499,PASK	23178	-	2q37.3	PAS domain containing serine/threonine kinase
QIK	CAMK,CAMKL,QIK,SK513,QIK	23235	-	11q23.1	SNF1-like kinase 2

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
QSK	CAMK,CAMKL, QIK,SK501,QSK	23387	-	11q23.3	KIAA0999 protein
SIK	CAMK,CAMKL, QIK,SK604,SIK	150094	-	21q22.3	SNF1-like kinase
SNRK	CAMK,CAMKL,S NRK,SK625,SNR K	54861	-	3p22.1	SNF-1 related kinase
STK33	CAMK,CAMK-Unique,SK463,ST K33	65975	-	11p15.3	serine/threonine kinase 33
VACAMKL	CAMK,CAMK-Unique,SK062,VA CAMKL	79012	-	3p21.31	hypothetical protein MGC8407
CASK	CAMK,CASK,SK 064,CASK	8573	-	xp11.4	calcium/calmodulin-dependent serine protein kinase (MAGUK family)
DAPK1	CAMK,DAPK,SK 103,DAPK1	1612	-	9q34.1	death-associated protein kinase 1
DAPK3	CAMK,DAPK,SK 716,DAPK3	1613	-	19p13.3	death-associated protein kinase 3
DAPK2	CAMK,DAPK,SK 104,DAPK2	23604	-	15q22.31	death-associated protein kinase 2
DRAK2	CAMK,DAPK,SK 487,DRAK2	9262	-	2q32.3	serine/threonine kinase 17b (apoptosis-inducing)
DRAK1	CAMK,DAPK,SK 486,DRAK1	9263	-	7p12-p14	serine/threonine kinase 17a (apoptosis-inducing)
DCLK1	CAMK,DCAMKL ,SK063,DCAMKL 1	9201	-	13q13	doublecortin and CaM kinase-like 1
DCLK3	CAMK,DCAMKL ,SK459,DCAMKL 3	85443	-	3p22.3	doublecortin and CaM kinase-like 3
DCLK2	CAMK,DCAMKL ,SK527,DCAMKL 2	166614	-	4q31.23	doublecortin and CaM kinase-like 2
MAPKAPK 3	CAMK,MAPKAP K,MAPKAPK,SK 213,MAPKAPK3	7867	-	3p21.3	mitogen-activated protein kinase-activated protein kinase 3
MAPKAPK 5	CAMK,MAPKAP K,MAPKAPK,SK 214,MAPKAPK5	8550	-	12q24.12	mitogen-activated protein kinase-activated protein kinase 5
MAPKAPK 2	CAMK,MAPKAP K,MAPKAPK,SK 212,MAPKAPK2	9261	-	1q32	mitogen-activated protein kinase-activated protein kinase 2
MNK2	CAMK,MAPKAP K,MNK,SK236,M NK2	2872	-	19p13.3	MAP kinase interacting serine/threonine kinase 2
MNK1	CAMK,MAPKAP K,MNK,SK235,M NK1	8569	-	1p33	MAP kinase interacting serine/threonine kinase 1
smMLCK	CAMK,MLCK,SK 231,smMLCK	4638	2.7.11.18	3q21	myosin, light polypeptide kinase
TTN	CAMK,MLCK,SK 372,TTN	7273	-	2q31	titin

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
skMLCK	CAMK,MLCK,SK675,skMLCK	85366	2.7.11.18	20q13.31	myosin light chain kinase 2, skeletal muscle
caMLCK	CAMK,MLCK,SK536,caMLCK	91807	-	16q11.2	myosin light chain kinase (MLCK)
SgK085	CAMK,MLCK,SK709,SgK085	340156	-	6p25.2	hypothetical protein LOC340156
PHKg1	CAMK,PHK,SK283,PHKg1	5260	2.7.1.38	7p12-q21	phosphorylase kinase, gamma 1 (muscle)
PHKg2	CAMK,PHK,SK284,PHKg2	5261	-	16p12.1-p11.2	phosphorylase kinase, gamma 2 (testis)
PIM1	CAMK,PIM,SK291,PIM1	5292	-	6p21.2	pim-1 oncogene
PIM2	CAMK,PIM,SK292,PIM2	11040	-	xp11.23	pim-2 oncogene
PIM3	CAMK,PIM,SK200,PIM3	415116	-	22q13	pim-3 oncogene
PRKD1	CAMK,PKD,SK309,PKD1	5587	2.7.1.37	14q11	protein kinase D1
PKD3	CAMK,PKD,SK489,PKD3	23683	-	2p21	protein kinase D3
PRKD2	CAMK,PKD,SK480,PKD2	25865	-	19q13.3	protein kinase D2
PSKH1	CAMK,PSK,SK322,PSKH1	5681	-	16q22.1	protein serine kinase H1
PSKH2	CAMK,PSK,SK602,PSKH2	85481	-	8q21.3	protein serine kinase H2
CHK2	CAMK,RAD53,SK079,CHK2	11200	-	22q12.1	CHK2 checkpoint homolog (S. pombe)
SgK495	CAMK,CAMK-Unique,SK492,SgK495	83931	-	1p34.3	Ser/Thr-like kinase
Trb1	CAMK,Trbl,SK014,Trb1	10221	-	8q24.13	tribbles homolog 1 (Drosophila)
Trb2	CAMK,Trbl,SK160,Trb2	28951	-	2p24.3	tribbles homolog 2 (Drosophila)
Trb3	CAMK,Trbl,SK694,Trb3	57761	-	20p13-p12.2	tribbles homolog 3 (Drosophila)
Obscn	CAMK,Trio,SK601,Obscn	84033	-	1q42.13	obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF
SPEG	CAMK,Trio,SK537,SPEG	729871	-	2q35	SPEG complex locus
Trio	CAMK,Trio,SK376,Trio	7204	-	5p15.1-p14	triple functional domain (PTPRF interacting)
Trad	CAMK,Trio,SK533,Trad	8997	-	3q21.1-q21.2	huntingtin-associated protein interacting protein (duo)
TSSK2	CAMK,TSSK,SK474,TSSK2	23617	-	22q11.21	serine/threonine kinase 22B (spermiogenesis associated)
TSSK3	CAMK,TSSK,SK471,TSSK3	81629	-	1p35-p34	serine/threonine kinase 22C (spermiogenesis associated)
TSSK1	CAMK,TSSK,SK705,TSSK1	83942	-	5q22.2	serine/threonine kinase 22D (spermiogenesis associated)
SSTK	CAMK,TSSK,SK524,SSTK	83983	-	19p13.11	serine/threonine protein kinase SSTK
TSSK4	CAMK,TSSK,SK5	283629	-	14q11.2	chromosome 14 open reading

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	34,TSSK4				frame 20
CK1a	CK1,CK1,CK1-A,SK082,CK1a	1452	-	5q32	casein kinase 1, alpha 1
CK1a2	CK1,CK1,CK1-A,SK541,CK1a2	122011	-	13q13.3	casein kinase 1, alpha 1-like
CK1d	CK1,CK1,CK1-D,SK083,CK1d	1453	-	17q25	casein kinase 1, delta
CK1e	CK1,CK1,CK1-E,SK084,CK1e	1454	-	22q13.1	casein kinase 1, epsilon
CK1g2	CK1,CK1,CK1-G,SK086,CK1g2	1455	-	19p13.3	casein kinase 1, gamma 2
CK1g3	CK1,CK1,CK1-G,SK087,CK1g3	1456	-	5q23	casein kinase 1, gamma 3
CK1g1	CK1,CK1,CK1-G,SK647,CK1g1	53944	-	15q22.1-q22.31	casein kinase 1, gamma 1
TTBK1	CK1,TTBK,SK526,TTBK1	84630	-	6p21.1	tau tubulin kinase 1
TTBK2	CK1,TTBK,SK453,TTBK2	146057	-	15q15.2	tau tubulin kinase 2
VRK1	CK1,VRK,SK389,VRK1	7443	-	14q32	vaccinia related kinase 1
VRK2	CK1,VRK,SK390,VRK2	7444	-	2p16-p15	vaccinia related kinase 2
VRK3	CK1,VRK,SK535,VRK3	51231	-	19q13	vaccinia related kinase 3
CCRK	CMGC,CDK,SK483,CCRK	23552	-	9q22.1	cell cycle related kinase
CDC2	CMGC,CDK,CDC2,SK065,CDC2	983	-	10q21.1	cell division cycle 2, G1 to S and G2 to M
CDK2	CMGC,CDK,CDC2,SK067,CDK2	1017	-	12q13	cyclin-dependent kinase 2
CDK3	CMGC,CDK,CDC2,SK068,CDK3	1018	-	17q22-qter	cyclin-dependent kinase 3
CDK10	CMGC,CDK,CDK10,SK294,CDK10	8558	-	16q24	cyclin-dependent kinase (CDC2-like) 10
CDK4	CMGC,CDK,CDK4,SK069,CDK4	1019	-	12q14	cyclin-dependent kinase 4
CDK6	CMGC,CDK,CDK4,SK071,CDK6	1021	-	7q21-q22	cyclin-dependent kinase 6
CDK5	CMGC,CDK,CDK5,SK070,CDK5	1020	-	7q36	cyclin-dependent kinase 5
CDK7	CMGC,CDK,CDK7,SK055,CDK7	1022	-	5q12.1	cyclin-dependent kinase 7 (MO15 homolog, Xenopus laevis, cdk-activating kinase)
CDK8	CMGC,CDK,CDK8,SK072,CDK8	1024	-	13q12	cyclin-dependent kinase 8
CDK11	CMGC,CDK,CDK8,SK443,CDK11	23097	-	6q21	cell division cycle 2-like 6 (CDK8-like)
CDK9	CMGC,CDK,CDK9,SK295,CDK9	1025	-	9q34.1	cyclin-dependent kinase 9 (CDC2-related kinase)
CHED	CMGC,CDK,CRK7,SK076,CHED	8621	-	7p13	cell division cycle 2-like 5 (cholinesterase-related cell division controller)
CRK7	CMGC,CDK,CRK	51755	-	17q12	CDC2-related protein kinase 7

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	7,SK485,CRK7				
PCTAIRE1	CMGC,CDK,TAIRE,SK271,PCTAIRE1	5127	-	xp11.3-p11.23	PCTAIRE protein kinase 1
PCTAIRE2	CMGC,CDK,TAIRE,SK272,PCTAIRE2	5128	-	12q23.1	PCTAIRE protein kinase 2
PCTAIRE3	CMGC,CDK,TAIRE,SK273,PCTAIRE3	5129	-	1q31-q32	PCTAIRE protein kinase 3
PFTAIRE1	CMGC,CDK,TAIRE,SK282,PFTAIRE1	5218	-	7q21-q22	PFTAIRE protein kinase 1
PFTAIRE2	CMGC,CDK,TAIRE,SK462,PFTAIRE2	65061	-	2q33.2	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 7
PITSLRE	CMGC,CDK,PITSLRE,SK297,PITSLRE	985	-	1p36.3	cell division cycle 2-like 2 (PITSLRE proteins)
CDKL5	CMGC,CDKL,SK361,CDKL5	6792	-	xp22	cyclin-dependent kinase-like 5
CDKL1	CMGC,CDKL,SK203,CDKL1	8814	-	14q21.3	cyclin-dependent kinase-like 1 (CDC2-related kinase)
CDKL2	CMGC,CDKL,SK202,CDKL2	8999	-	4q21.1	cyclin-dependent kinase-like 2 (CDC2-related kinase)
CDKL3	CMGC,CDKL,SK509,CDKL3	51265	2.7.11.22	5q31	cyclin-dependent kinase-like 3
CDKL4	CMGC,CDKL,SK466,CDKL4	344387	-	2p22.1	cyclin-dependent kinase-like 4
CK2a1	Other,CK2,SK088,CK2a1	1457	-	20p13	casein kinase 2, alpha 1 polypeptide
CK2a2	Other,CK2,SK089,CK2a2	1459	-	16p13.3-p13.2	casein kinase 2, alpha prime polypeptide
CLK1	CMGC,CLK,SK090,CLK1	1195	-	2q33	CDC-like kinase 1
CLK2	CMGC,CLK,SK091,CLK2	1196	-	1q21	CDC-like kinase 2
CLK3	CMGC,CLK,SK092,CLK3	1198	-	15q24	CDC-like kinase 3
CLK4	CMGC,CLK,SK484,CLK4	57396	-	5q35	CDC-like kinase 4
DYRK1A	CMGC,DYRK,DYRK1,SK234,DYRK1A	1859	-	21q22.13	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A
DYRK1B	CMGC,DYRK,DYRK1,SK114,DYRK1B	9149	-	19q12-13.1	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1B
DYRK3	CMGC,DYRK,DYRK2,SK488,DYRK3	8444	-	1q32.1	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 3
DYRK2	CMGC,DYRK,DYRK2,SK115,DYRK2	8445	-	12q15	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2
DYRK4	CMGC,DYRK,DY	8798	-	12p13.32	dual-specificity tyrosine-(Y)-

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	RK2,SK116,DYRK4				phosphorylation regulated kinase 4
HIPK3	CMGC,DYRK,HIPK,SK314,HIPK3	10114	-	11p13	homeodomain interacting protein kinase 3
HIPK2	CMGC,DYRK,HIPK,SK495,HIPK2	28996	-	7q32-q34	homeodomain interacting protein kinase 2
HIPK4	CMGC,DYRK,HIPK,SK582,HIPK4	147746	-	19q13.2	homeodomain interacting protein kinase 4
HIPK1	CMGC,DYRK,HIPK,SK169,HIPK1	204851	-	1p13.2	homeodomain interacting protein kinase 1
PRP4	CMGC,DYRK,PRP4,SK321,PRP4	8899	-	6p25.2	PRP4 pre-mRNA processing factor 4 homolog B (yeast)
GSK3A	CMGC,GSK,SK162,GSK3A	2931	-	19q13.2	glycogen synthase kinase 3 alpha
GSK3B	CMGC,GSK,SK163,GSK3B	2932	-	3q13.3	glycogen synthase kinase 3 beta
Erk2	CMGC,MAPK,ERK,SK135,Erk2	5594	2.7.1.37	22q11.21	mitogen-activated protein kinase 1
Erk1	CMGC,MAPK,ERK,SK134,Erk1	5595	2.7.1.37	16p12-p11.2	mitogen-activated protein kinase 3
Erk4	CMGC,MAPK,ERK,SK137,Erk4	5596	-	18q12-q21	mitogen-activated protein kinase 4
Erk3	CMGC,MAPK,ERK,SK136,Erk3	5597	-	15q21	mitogen-activated protein kinase 6
Erk5	CMGC,MAPK,ERK,SK408,Erk5	5598	-	17p11.2	mitogen-activated protein kinase 7
Erk7	CMGC,MAPK,Erk7,SK465,Erk7	225689	-	8q24.3	extracellular signal-regulated kinase 8
MAPK8	CMGC,MAPK,JNK,SK188,JNK1	5599	2.7.1.37	10q11.22	mitogen-activated protein kinase 8
MAPK9	CMGC,MAPK,JNK,SK189,JNK2	5601	2.7.1.37	5q35	mitogen-activated protein kinase 9
MAPK10	CMGC,MAPK,JNK,SK190,JNK3	5602	2.7.1.37	4q22.1-q23	mitogen-activated protein kinase 10
NLK	CMGC,MAPK,nmo,SK255,NLK	51701	-	17q11.2	nemo like kinase
p38a	CMGC,MAPK,p38,SK264,p38a	1432	-	6p21.3-p21.2	mitogen-activated protein kinase 14
p38b	CMGC,MAPK,p38,SK342,p38b	5600	2.7.1.37	22q13.33	mitogen-activated protein kinase 11
p38d	CMGC,MAPK,p38,SK344,p38d	5603	2.7.1.37	6p21.31	mitogen-activated protein kinase 13
p38g	CMGC,MAPK,p38,SK343,p38g	6300	2.7.1.37	22q13.33	mitogen-activated protein kinase 12
MAK	CMGC,RCK,SK211,MAK	4117	-	6q22	male germ cell-associated kinase
MOK	CMGC,RCK,SK505,MOK	5891	-	14q32	renal tumor antigen
ICK	CMGC,RCK,SK497,ICK	22858	-	6p12.3-p11.2	intestinal cell (MAK-like) kinase
SRPK1	CMGC,SRPK,SK358,SRPK1	6732	-	6p21.3-p21.2	SFRS protein kinase 1
SRPK2	CMGC,SRPK,SK359,SRPK2	6733	-	7q22-q31.1	SFRS protein kinase 2

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MSSK1	CMGC,SRPK,SK507,MSSK1	26576	-	xq28	serine/threonine kinase 23
AurA	Other,AUR,SK407,AurA	6790	-	20q13.2-q13.3	serine/threonine kinase 6
AurC	Other,AUR,SK043,AurC	6795	-	19q13.43	aurora kinase C
AurB	Other,AUR,SK406,AurB	9212	-	17p13.1	aurora kinase B
BUB1	Other,BUB,SK409,BUB1	699	-	2q14	BUB1 budding uninhibited by benzimidazoles 1 homolog (yeast)
BUBR1	Other,BUB,SK053,BUBR1	701	-	15q15	BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)
PRPK	Other,Bud32,SK464,PRPK	112858	-	20q13.2	TP53 regulating kinase
CaMKK2	Other,CAMKK,Meta,SK482,CaMKK2	10645	-	12q24.2	calcium/calmodulin-dependent protein kinase kinase 2, beta
CaMKK1	Other,CAMKK,Meta,SK697,CaMKK1	84254	-	17p13.2	calcium/calmodulin-dependent protein kinase kinase 1, alpha
CDC7	Other,CDC7,SK066,CDC7	8317	-	1p22	CDC7 cell division cycle 7 (S. cerevisiae)
Haspin	Other,Haspin,SK692,Haspin	83903	-	17p13	germ cell associated 2 (haspin)
IKKa	Other,IKK,SK175,IKKa	1147	-	10q24-q25	conserved helix-loop-helix ubiquitous kinase
IKKb	Other,IKK,SK176,IKKb	3551	-	8p11.2	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta
IKKe	Other,IKK,SK193,IKKe	9641	-	1q32.1	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase epsilon
TBK1	Other,IKK,SK531,TBK1	29110	-	12q14.1	TANK-binding kinase 1
IRE1	Other,IRE,SK182,IRE1	2081	-	17q24.2	endoplasmic reticulum to nucleus signalling 1
IRE2	Other,IRE,SK498,IRE2	10595	-	16p12.2	endoplasmic reticulum to nucleus signalling 2
KIS	Other,Other-Unique,SK661,KIS	127933	-	1q23.3	U2AF homology motif (UHM) kinase 1
MOS	Other,MOS,SK237,MOS	4342	-	8q11	v-mos Moloney murine sarcoma viral oncogene homolog
AAK1	Other,NAK,SK422,AAK1	22848	-	2p24.3-p14	AP2 associated kinase 1
BIKE	Other,NAK,SK704,BIKE	55589	-	4q21.21	BMP2 inducible kinase
GAK	Other,NAK,SK155,GAK	2580	-	4p16	cyclin G associated kinase
MPSK1	Other,NAK,SK506,MPSK1	8576	-	2q34-q37	serine/threonine kinase 16
NEK1	Other,NEK,SK250,NEK1	4750	-	4q33	NIMA (never in mitosis gene a)-related kinase 1

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NEK3	Other,NEK,SK252,NEK3	4752	-	13q14.13	NIMA (never in mitosis gene a)-related kinase 3
NEK5	Other,NEK,SK558,NEK5	341676	-	13q14.3	similar to Serine/threonine-protein kinase Nek1 (NimA-related protein kinase 1)
NEK10	Other,NEK,SK645,NEK10	152110	-	3p24.1	hypothetical protein FLJ32685
NEK11	Other,NEK,SK574,NEK11	79858	-	3q21.3	NIMA (never in mitosis gene a)-related kinase 11
NEK2	Other,NEK,SK251,NEK2	4751	-	1q32.2-q41	NIMA (never in mitosis gene a)-related kinase 2
NEK4	Other,NEK,SK256,NEK4	6787	2.7.11.1	3p21.1	NIMA (never in mitosis gene a)-related kinase 4
NEK6	Other,NEK,SK420,NEK6	10783	-	9q33.3-q34.11	NIMA (never in mitosis gene a)-related kinase 6
NEK7	Other,NEK,SK421,NEK7	140609	-	1q31.3	NIMA (never in mitosis gene a)-related kinase 7
NEK9	Other,NEK,SK470,NEK9	91754	-	14q24.3	NIMA (never in mitosis gene a)-related kinase 9
NEK8	Other,NEK,SK476,NEK8	284086	-	17q11.1	NIMA (never in mitosis gene a)-related kinase 8
SBK	Other,NKF1,SK650,SBK	388228	-	16p11.2	SH3-binding domain kinase 1
SgK069	Other,NKF1,SK581,SgK069	646643	-	-	-
PINK1	Other,NKF2,SK456,PINK1	65018	-	1p36	PTEN induced putative kinase 1
SgK269	Other,NKF3,SK649,SgK269	79834	-	15q24.3	KIAA2002 protein
SgK223	Other,NKF3,SK643,SgK223	157285	-	8p23.1	hypothetical protein DKFZp761P0423
CLIK1	Other,NKF4,SK493,CLIK1	140901	-	20p13	serine/threonine kinase 35
CLIK1L	Other,NKF4,SK452,CLIK1L	149420	-	1p36.11	PDLIM1 interacting kinase 1 like
SgK307	Other,NKF5,SK699,SgK307	56155	-	17q23.2	testis expressed sequence 14
NRBP1	Other,NRBP,SK479,NRBP1	29959	-	2p23	nuclear receptor binding protein
NRBP2	Other,NRBP,SK520,NRBP2	340371	-	8q24.3	nuclear receptor binding protein 2
RNAseL	Other,Other-Unique,SK729,RNAseL	6041	-	1q25	ribonuclease L (2',5'-oligoisoadenylate synthetase-dependent)
SgK396	Other,Other-Unique,SK652,SgK396	56164	-	7p15.3	serine/threonine kinase 31
SgK196	Other,Other-Unique,SK628,SgK196	84197	-	8p11.21	hypothetical protein FLJ23356
GCN2	Other,PEK,GCN2,SK490,GCN2	440275	-	15q15.1	similar to GCN2 eIF2alpha kinase
HRI	Other,PEK,SK496,HRI	27102	-	7p22	eukaryotic translation initiation factor 2-alpha kinase 1

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PEK	Other,PEK,PEK,SK281,PEK	9451	-	2p12	eukaryotic translation initiation factor 2-alpha kinase 3
PKR	Other,PEK,SK119,PKR	5610	-	2p22-p21	eukaryotic translation initiation factor 2-alpha kinase 2
PLK1	Other,PLK,SK315,PLK1	5347	-	16p12.1	polo-like kinase 1 (Drosophila)
PLK3	Other,PLK,SK316,PLK3	1263	-	1p34.1	polo-like kinase 3 (Drosophila)
PLK2	Other,PLK,SK353,PLK2	10769	-	5q12.1-q13.2	polo-like kinase 2 (Drosophila)
PLK4	Other,PLK,SK341,PLK4	10733	-	4q27-q28	polo-like kinase 4 (Drosophila)
SCYL2	Other,SCY1,SK475,SCYL2	55681	-	12q23.1	SCY1-like 2 (S. cerevisiae)
SCYL3	Other,SCY1,SK468,SCYL3	57147	-	1q24.2	ezrin-binding partner PACE-1
SCYL1	Other,SCY1,SK454,SCYL1	57410	-	11q13	SCY1-like 1 (S. cerevisiae)
SgK071	Other,Other-Unique,SK521,SgK071	169436	-	9q34.2	chromosome 9 open reading frame 96
SgK493	Other,Other-Unique,SK460,SgK493	91461	-	2p21	hypothetical protein BC007901
SgK496	Other,Other-Unique,SK516,SgK496	25778	-	1q32.1	receptor interacting protein kinase 5
Slob	Other,Slob,SK528,Slob	54899	-	3p14.3	PX domain containing serine/threonine kinase
TBCK	Other,TBCK,SK664,TBCK	93627	-	4q24	hypothetical protein MGC16169
TLK1	Other,TLK,SK373,TLK1	9874	-	2q31.1	tousled-like kinase 1
TLK2	Other,TLK,SK374,TLK2	11011	-	17q23	tousled-like kinase 2
PBK	Other,TOPK,SK529,PBK	55872	-	8p21.2	PDZ binding kinase
TTK	Other,TTK,SK383,TTK	7272	-	6q13-q21	TTK protein kinase
Fused	Other,ULK,SK199,Fused	27148	-	2q35	serine/threonine kinase 36 (fused homolog, Drosophila)
ULK1	Other,ULK,SK387,ULK1	8408	-	12q24.3	unc-51-like kinase 1 (C. elegans)
ULK2	Other,ULK,SK388,ULK2	9706	-	17p11.2	unc-51-like kinase 2 (C. elegans)
ULK3	Other,ULK,SK450,ULK3	25989	-	15q24.1	unc-51-like kinase 3 (C. elegans)
ULK4	Other,ULK,SK457,ULK4	54986	-	3p22.1	unc-51-like kinase 4 (C. elegans)
PIK3R4	Other,VPS15,SK262,PIK3R4	30849	-	3q21.3	phosphoinositide-3-kinase, regulatory subunit 4, p150
Wee1	Other,WEE,SK391,Wee1	7465	-	11p15.3-p15.1	WEE1 homolog (S. pombe)
PKMYT1	Other,WEE,SK248	9088	-	16p13.3	protein kinase, membrane

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	,MYT1				associated tyrosine/threonine 1
Wee1B	Other,WEE,SK723,Wee1B	285962	-	7q34	hypothetical protein FLJ40852
Wnk1	Other,Wnk,SK508,Wnk1	65125	-	12p13.3	WNK lysine deficient protein kinase 1
Wnk4	Other,Wnk,SK588,Wnk4	65266	-	17q21-q22	WNK lysine deficient protein kinase 4
Wnk3	Other,Wnk,SK641,Wnk3	65267	-	xp11.23-p11.21	WNK lysine deficient protein kinase 3
Wnk2	Other,Wnk,SK016,Wnk2	65268	-	9q22.3	WNK lysine deficient protein kinase 2
HSER	RGC,RGC,SK171,HSER	2984	-	12p12	guanylate cyclase 2C (heat stable enterotoxin receptor)
CYGF	RGC,RGC,SK099,CYGF	2986	-	xq22	guanylate cyclase 2F, retinal
CYGD	RGC,RGC,SK097,CYGD	3000	-	17p13.1	guanylate cyclase 2D, membrane (retina-specific)
ANPa	RGC,RGC,SK034,ANPa	4881	-	1q21-q22	natriuretic peptide receptor A/guanylate cyclase A (atrionatriuretic peptide receptor A)
ANPb	RGC,RGC,SK035,ANPb	4882	-	9p21-p12	natriuretic peptide receptor B/guanylate cyclase B (atrionatriuretic peptide receptor B)
MAP3K5	STE,STE11,SK225,MAP3K5	4217	-	6q22.33	mitogen-activated protein kinase kinase kinase 5
MAP3K6	STE,STE11,SK503,MAP3K6	9064	-	1p36.11	mitogen-activated protein kinase kinase kinase 6
MAP3K7	STE,STE11,SK681,MAP3K7	389840	-	xp22.12	mitogen-activated protein kinase kinase kinase 15
MAP3K1	STE,STE11,SK221,MAP3K1	4214	-	5q11.2	mitogen-activated protein kinase kinase kinase 1
MAP3K8	STE,STE11,SK573,MAP3K8	80122	-	2q21.3	hypothetical protein FLJ23074
MAP3K3	STE,STE11,SK223,MAP3K3	4215	-	17q23.3	mitogen-activated protein kinase kinase kinase 3
MAP3K2	STE,STE11,SK222,MAP3K2	10746	-	2q14.3	mitogen-activated protein kinase kinase kinase 2
MAP3K4	STE,STE11,SK224,MAP3K4	4216	-	6q26	mitogen-activated protein kinase kinase kinase 4
OXSR1	STE,STE20,FRAY,SK428,OSR1	9943	-	3p22-p21.3	oxidative-stress responsive 1
STLK3	STE,STE20,FRAY,SK432,STLK3	27347	-	2q24.3	serine threonine kinase 39 (STE20/SPS1 homolog, yeast)
MAP4K2	STE,STE20,KHS,SK048,GCK	5871	-	11q13	mitogen-activated protein kinase kinase kinase kinase 2
KHS2	STE,STE20,KHS,SK427,KHS2	8491	-	2p22.1	mitogen-activated protein kinase kinase kinase kinase 3
KHS1	STE,STE20,KHS,SK191,KHS1	11183	-	14q11.2-q21	mitogen-activated protein kinase kinase kinase kinase 5
HPK1	STE,STE20,KHS,SK170,HPK1	11184	-	19q13.1-q13.4	mitogen-activated protein kinase kinase kinase kinase 1
HGK	STE,STE20,MSN,SK437,ZC1	9448	-	2q11.2-q12	mitogen-activated protein kinase kinase kinase kinase 4

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TNIK	STE,STE20,MSN, SK438,ZC2	23043	-	3q26.2	TRAF2 and NCK interacting kinase
NRK	STE,STE20,MSN, SK440,ZC4	203447	-	xq22.3	Nik related kinase
MINK	STE,STE20,MSN, SK439,ZC3	50488	-	17p13.2	misshapen-like kinase 1 (zebrafish)
MST2	STE,STE20,MST, SK245,MST2	6788	-	8q22.2	serine/threonine kinase 3 (STE20 homolog, yeast)
MST1	STE,STE20,MST, SK244,MST1	6789	-	20q11.2-q13.2	serine/threonine kinase 4
MYO3A	STE,STE20,NinaC ,SK636,MYO3A	53904	-	10p11.1	myosin IIIA
MYO3B	STE,STE20,NinaC ,SK583,MYO3B	140469	-	2q31.1-q31.2	myosin IIIB
PAK1	STE,STE20,PAKA ,SK267,PAK1	5058	-	11q13-q14	p21/Cdc42/Rac1-activated kinase 1 (STE20 homolog, yeast)
PAK2	STE,STE20,PAKA ,SK268,PAK2	5062	2.7.11.1	3q29	p21 (CDKN1A)-activated kinase 2
PAK3	STE,STE20,PAKA ,SK269,PAK3	5063	-	xq22.3-q23	p21 (CDKN1A)-activated kinase 3
PAK4	STE,STE20,PAKB ,SK430,PAK4	10298	-	19q13.2	p21(CDKN1A)-activated kinase 4
PAK6	STE,STE20,PAKB ,SK429,PAK6	56924	-	15q14	p21(CDKN1A)-activated kinase 6
PAK5	STE,STE20,PAKB ,SK510,PAK5	57144	-	20p12	p21(CDKN1A)-activated kinase 7
LOK	STE,STE20,SLK,S K426,LOK	6793	-	5q35.1	serine/threonine kinase 10
SLK	STE,STE20,SLK,S K348,SLK	9748	-	10q25.1	STE20-like kinase (yeast)
STLK6	STE,STE20,STLK ,SK434,STLK6	55437	-	2q33-q34	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 2
STLK5	STE,STE20,STLK ,SK433,STLK5	92335	-	17q23.3	protein kinase LYK5
TAO2	STE,STE20,TAO, SK362,TAO2	9344	-	16p11.2	TAO kinase 2
TAO3	STE,STE20,TAO, SK435,TAO3	51347	-	12q	TAO kinase 3
TAO1	STE,STE20,TAO, SK436,TAO1	57551	-	17q11.2	TAO kinase 1
MST3	STE,STE20,YSK, SK246,MST3	8428	-	13q31.2-q32.3	serine/threonine kinase 24 (STE20 homolog, yeast)
YSK1	STE,STE20,YSK, SK395,YSK1	10494	-	2q37.3	serine/threonine kinase 25 (STE20 homolog, yeast)
MST4	STE,STE20,YSK, SK431,MST4	51765	-	xq26.2	Mst3 and SOK1-related kinase
MAP2K1	STE,STE7,SK217, MAP2K1	5604	2.7.12.2	15q22.1-q22.33	mitogen-activated protein kinase kinase 1
MAP2K2	STE,STE7,SK218, MAP2K2	5605	2.7.12.2	19p13.3	mitogen-activated protein kinase kinase 2
MAP2K3	STE,STE7,SK238, MAP2K3	5606	-	17q11.2	mitogen-activated protein kinase kinase 3
MAP2K6	STE,STE7,SK220,	5608	-	17q24.3	mitogen-activated protein kinase

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	MAP2K6				kinase 6
MAP2K4	STE,STE7,SK239, MAP2K4	6416	2.7.12.2	17p11.2	mitogen-activated protein kinase kinase 4
MAP2K5	STE,STE7,SK219, MAP2K5	5607	-	15q23	mitogen-activated protein kinase kinase 5
MAP2K7	STE,STE7,SK230, MAP2K7	5609	2.7.12.2	19p13.3-p13.2	mitogen-activated protein kinase kinase 7
COT	STE,STE-Unique,SK093,COT	1326	-	10p11.23	mitogen-activated protein kinase kinase kinase 8
NIK	STE,STE-Unique,SK253,NIK	9020	-	17q21	mitogen-activated protein kinase kinase kinase 14
ABL1	TK,Abl,SK006,ABL	25	-	9q34.1	v-abl Abelson murine leukemia viral oncogene homolog 1
ABL2	TK,Abl,SK037,ARG	27	-	1q24-q25	v-abl Abelson murine leukemia viral oncogene homolog 2 (arg, Abelson-related gene)
ACK	TK,Ack,SK009,ACK	10188	-	3q29	tyrosine kinase, non-receptor, 2
TNK1	TK,Ack,SK375,TNK1	8711	-	17p13.1	tyrosine kinase, non-receptor, 1
ALK	TK,Alk,SK024,ALK	238	-	2p23	anaplastic lymphoma kinase (Ki-1)
LTK	TK,Alk,SK209,LTK	4058	2.7.1.112	15q15.1-q21.1	leukocyte tyrosine kinase
AXL	TK,Axl,SK044,AXL	558	2.7.1.112	19q13.1	AXL receptor tyrosine kinase
TYRO3	TK,Axl,SK386,TYRO3	7301	2.7.1.112	15q15.1-q21.1	TYRO3 protein tyrosine kinase
MER	TK,Axl,SK226,MER	10461	-	2q14.1	c-mer proto-oncogene tyrosine kinase
CCK4	TK,CCK4,SK411, CCK4	5754	2.7.1.112	6p21.1-p12.2	PTK7 protein tyrosine kinase 7
CSK	TK,Csk,SK095,CSK	1445	2.7.10.1	15q23-q25	c-src tyrosine kinase
CTK	TK,Csk,SK418,CTK	4145	-	19p13.3	megakaryocyte-associated tyrosine kinase
DDR1	TK,DDR,SK400,DDR1	780	2.7.1.112	6p21.3	discoidin domain receptor family, member 1
DDR2	TK,DDR,SK410,DDR2	4921	2.7.1.112	1q12-q23	discoidin domain receptor family, member 2
EGFR	TK,EGFR,SK118, EGFR	1956	-	7p12	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)
ErbB2	TK,EGFR,SK166, HER2	2064	-	17q21.1	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)
ErbB3	TK,EGFR,SK167, HER3	2065	-	12q13	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)
ErbB4	TK,EGFR,SK168, HER4	2066	-	2q33.3-q34	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)
EphA2	TK,Eph,SK122,Ep	1969	2.7.1.112	1p36	EPH receptor A2

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	hA2				
EphA1	TK,Eph,SK121,EphA1	2041	2.7.1.112	7q34	EPH receptor A1
EphA3	TK,Eph,SK123,EphA3	2042	2.7.1.112	3p11.2	EPH receptor A3
EphA4	TK,Eph,SK124,EphA4	2043	2.7.1.112	2q36.1	EPH receptor A4
EphA5	TK,Eph,SK125,EphA5	2044	-	4q13.1	EPH receptor A5
EphA7	TK,Eph,SK416,EphA7	2045	-	6q16.1	EPH receptor A7
EphA8	TK,Eph,SK126,EphA8	2046	2.7.1.112	1p36.12	EPH receptor A8
EphB1	TK,Eph,SK127,EphB1	2047	-	3q21-q23	EPH receptor B1
EphB2	TK,Eph,SK128,EphB2	2048	2.7.1.112	1p36.1-p35	EPH receptor B2
EphB3	TK,Eph,SK129,EphB3	2049	-	3q21-qter	EPH receptor B3
EphB4	TK,Eph,SK130,EphB4	2050	-	7q22	EPH receptor B4
EphB6	TK,Eph,SK132,EphB6	2051	-	7q33-q35	EPH receptor B6
EphA10	TK,Eph,SK627,EphA10	284656	-	1p34.3	EPH receptor A10
EphA6	TK,Eph,SK646,EphA6	285220	-	3q11.2	EPH receptor A6
PYK2	TK,FAK,SK424,PYK2	2185	-	8p21.1	PTK2B protein tyrosine kinase 2 beta
FAK	TK,FAK,SK138,FAK	5747	2.7.1.112	8q24-qter	PTK2 protein tyrosine kinase 2
FER	TK,Fer,SK140,FER	2241	2.7.1.112	5q21	fer (fps/fes related) tyrosine kinase (phosphoprotein NCP94)
FES	TK,Fer,SK142,FES	2242	-	15q26.1	feline sarcoma oncogene
FGFR1	TK,FGFR,SK143, FGFR1	2260	2.7.1.112	8p11.2-p11.1	fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome)
FGFR3	TK,FGFR,SK145, FGFR3	2261	-	4p16.3	fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)
FGFR2	TK,FGFR,SK144, FGFR2	2263	-	10q26	fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome)
FGFR4	TK,FGFR,SK147, FGFR4	2264	-	5q35.1-qter	fibroblast growth factor receptor 4
IGF1R	TK,InsR,SK174,IGF1R	3480	-	15q26.3	insulin-like growth factor 1 receptor
INSR	TK,InsR,SK178,INSR	3643	-	19p13.3-p13.2	insulin receptor

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IRR	TK,InsR,SK183,IR R	3645	-	1q21-q23	insulin receptor-related receptor
JAK1	TK,JakA,SK185,J AK1	3716	2.7.1.112	1p32.3-p31.3	Janus kinase 1 (a protein tyrosine kinase)
JAK2	TK,JakA,SK186,J AK2	3717	2.7.1.112	9p24	Janus kinase 2 (a protein tyrosine kinase)
JAK3	TK,JakA,SK187,J AK3	3718	-	19p13.1	Janus kinase 3 (a protein tyrosine kinase, leukocyte)
TYK2	TK,JakA,SK385,T YK2	7297	2.7.1.112	19p13.2	tyrosine kinase 2
LMR1	TK,Lmr,SK413,L MR1	9625	-	17q25.3	apoptosis-associated tyrosine kinase
LMR2	TK,Lmr,SK414,L MR2	22853	-	7q21.3	lemur tyrosine kinase 2
LMR3	TK,Lmr,SK415,L MR3	114783	-	19q13.32	lemur tyrosine kinase 3
MET	TK,Met,SK227,M ET	4233	-	7q31	met proto-oncogene (hepatocyte growth factor receptor)
RON	TK,Met,SK332,R ON	4486	-	3p21.3	macrophage stimulating 1 receptor (c-met-related tyrosine kinase)
MUSK	TK,Musk,SK247, MUSK	4593	-	9q31.3-q32	muscle, skeletal, receptor tyrosine kinase
FMS	TK,PDGFR,SK09 4,FMS	1436	-	5q33-q35	colony stimulating factor 1 receptor, formerly McDonough feline sarcoma viral (v-fms) oncogene homolog
FLT3	TK,PDGFR,SK14 9,FLT3	2322	2.7.1.112	13q12	fms-related tyrosine kinase 3
KIT	TK,PDGFR,SK20 1,KIT	3815	-	4q11-q12	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
PDGFRa	TK,PDGFR,SK27 4,PDGFRa	5156	-	4q11-q13	platelet-derived growth factor receptor, alpha polypeptide
PDGFRb	TK,PDGFR,SK27 5,PDGFRb	5159	-	5q31-q32	platelet-derived growth factor receptor, beta polypeptide
RET	TK,Ret,SK326,RE T	5979	-	10q11.2	ret proto-oncogene (multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease)
ROR1	TK,Ror,SK333,RO R1	4919	-	1p32-p31	receptor tyrosine kinase-like orphan receptor 1
ROR2	TK,Ror,SK334,RO R2	4920	-	9q22	receptor tyrosine kinase-like orphan receptor 2
RYK	TK,Ryk,SK340,R YK	6259	2.7.1.112	3q22	RYK receptor-like tyrosine kinase
ROS	TK,Sev,SK335,RO S	6098	-	6q22	v-ros UR2 sarcoma virus oncogene homolog 1 (avian)
FRK	TK,Src,SK419,FR K	2444	2.7.1.112	6q21-q22.3	fyn-related kinase
FGR	TK,Src,SK148,FG R	2268	-	1p36.2-p36.1	Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog
FYN	TK,Src,SK153,FY N	2534	-	6q21	FYN oncogene related to SRC, FGR, YES
SRC	TK,Src,SK357,SR C	6714	-	20q12-q13	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)

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YES	TK,Src,SK393,YES	7525	-	18p11.31-p11.21	v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1
BLK	TK,Src,SK049,BLK	640	-	8p23-p22	B lymphoid tyrosine kinase
HCK	TK,Src,SK164,HCK	3055	-	20q11-q12	hemopoietic cell kinase
LCK	TK,Src,SK206,LCK	3932	2.7.1.112	1p34.3	lymphocyte-specific protein tyrosine kinase
LYN	TK,Src,SK210,LYN	4067	-	8q13	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog
BRK	TK,Src,SK051,BRK	5753	2.7.1.112	20q13.3	PTK6 protein tyrosine kinase 6
SRM	TK,Src,SK425,SRM	6725	-	20q13.33	src-related kinase lacking C-terminal regulatory tyrosine and N-terminal myristylation sites
SYK	TK,Syk,SK363,SYK	6850	-	9q22	spleen tyrosine kinase
ZAP70	TK,Syk,SK397,ZAP70	7535	-	2q12	zeta-chain (TCR) associated protein kinase 70kDa
BMX	TK,Tec,SK417,BMX	660	-	xp22.2	BMX non-receptor tyrosine kinase
BTK	TK,Tec,SK052,BTK	695	2.7.1.112	xq21.33-q22	Bruton agammaglobulinemia tyrosine kinase
ITK	TK,Tec,SK184,ITK	3702	-	5q31-q32	IL2-inducible T-cell kinase
TEC	TK,Tec,SK366,TEC	7006	-	4p12	tec protein tyrosine kinase
TXK	TK,Tec,SK384,TXK	7294	2.7.1.112	4p12	TXK tyrosine kinase
TIE2	TK,Tie,SK367,TIE2	7010	-	9p21	TEK tyrosine kinase, endothelial (venous malformations, multiple cutaneous and mucosal)
TIE1	TK,Tie,SK370,TIE1	7075	2.7.1.112	1p34-p33	tyrosine kinase with immunoglobulin-like and EGF-like domains 1
SuRTK106	TK,TK-Unique,SK530,SuRTK106	55359	-	12p13.2	serine/threonine/tyrosine kinase 1
TRKA	TK,Trk,SK377,TRKA	4914	2.7.1.112	1q21-q22	neurotrophic tyrosine kinase, receptor, type 1
TRKB	TK,Trk,SK378,TRKB	4915	2.7.1.112	9q22.1	neurotrophic tyrosine kinase, receptor, type 2
TRKC	TK,Trk,SK379,TRKC	4916	2.7.1.112	15q25	neurotrophic tyrosine kinase, receptor, type 3
FLT1	TK,VEGFR,SK150,FLT1	2321	2.7.1.112	13q12	fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)
FLT4	TK,VEGFR,SK151,FLT4	2324	2.7.1.112	5q34-q35	fms-related tyrosine kinase 4
KDR	TK,VEGFR,SK402,KDR	3791	2.7.1.112	4q11-q12	kinase insert domain receptor (a type III receptor tyrosine kinase)
IRAK1	TKL,IRAK,SK179,IRAK1	3654	-	xq28	interleukin-1 receptor-associated kinase 1

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IRAK2	TKL,IRAK,SK180 ,IRAK2	3656	-	3p25.3	interleukin-1 receptor-associated kinase 2
IRAK3	TKL,IRAK,SK181 ,IRAK3	11213	-	12q14.3	interleukin-1 receptor-associated kinase 3
IRAK4	TKL,IRAK,SK257 ,IRAK4	51135	-	12q12	interleukin-1 receptor-associated kinase 4
LIMK1	TKL,LISK,LIMK, SK412,LIMK1	3984	-	7q11.23	LIM domain kinase 1
LIMK2	TKL,LISK,LIMK, SK207,LIMK2	3985	-	22q12.2	LIM domain kinase 2
TESK1	TKL,LISK,TESK, SK368,TESK1	7016	EC, 2.7.12.1	9p13	testis-specific kinase 1
TESK2	TKL,LISK,TESK, SK532,TESK2	10420	-	1p32	testis-specific kinase 2
LRRK1	TKL,LRRK,SK69 8,LRRK1	79705	-	15q26.3	leucine-rich repeat kinase 1
LRRK2	TKL,LRRK,SK69 0,LRRK2	120892	-	12q12	leucine-rich repeat kinase 2
HH498	TKL,MLK,HH498 ,SK494,HH498	51086	-	1p31.1	TNNI3 interacting kinase
ILK	TKL,MLK,ILK,S K177,ILK	3611	-	11p15.5-p15.4	integrin-linked kinase
DLK	TKL,MLK,LZK,S K110,DLK	7786	-	12q13	mitogen-activated protein kinase kinase kinase 12
LZK	TKL,MLK,LZK,S K398,LZK	9175	-	3q27	mitogen-activated protein kinase kinase kinase 13
MLK1	TKL,MLK,MLK,S K232,MLK1	4293	-	14q24.3-q31	mitogen-activated protein kinase kinase kinase 9
MLK2	TKL,MLK,MLK,S K233,MLK2	4294	-	19q13.2	mitogen-activated protein kinase kinase kinase 10
MLK3	TKL,MLK,MLK,S K356,MLK3	4296	2.7.10.1	11q13.1-q13.3	mitogen-activated protein kinase kinase kinase 11
MLK4	TKL,MLK,MLK,S K691,MLK4	84451	-	1q42	mixed lineage kinase 4
TAK1	TKL,MLK,TAK1, SK364,TAK1	6885	-	6q16.1-q16.3	mitogen-activated protein kinase kinase kinase 7
ZAK	TKL,MLK,MLK,S K504,ZAK	51776	-	2q24.2	sterile alpha motif and leucine zipper containing kinase AZK
KSR1	TKL,RAF,SK205, KSR1	8844	-	17q11.2	kinase suppressor of ras
KSR2	TKL,RAF,SK605, KSR2	283455	-	12q24.22-q24.23	kinase suppressor of ras 2
ARAF	TKL,RAF,SK036, ARAF	369	-	xp11.4-p11.2	v-raf murine sarcoma 3611 viral oncogene homolog
BRAF	TKL,RAF,SK050, BRAF	673	-	7q34	v-raf murine sarcoma viral oncogene homolog B1
RAF1	TKL,RAF,SK324, RAF1	5894	-	3p25	v-raf-1 murine leukemia viral oncogene homolog 1
RIPK1	TKL,RIPK,SK328, RIPK1	8737	-	6p25.2	receptor (TNFRSF)-interacting serine-threonine kinase 1
RIPK2	TKL,RIPK,SK329, RIPK2	8767	-	8q21	receptor-interacting serine-threonine kinase 2
RIPK3	TKL,RIPK,SK330, RIPK3	11035	-	14q11.2	receptor-interacting serine-threonine kinase 3

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ANKRD3	TKL,RIPK,SK546, ANKRD3	54101	-	21q22.3	receptor-interacting serine-threonine kinase 4
SgK288	TKL,RIPK,SK658, SgK288	255239	-	11q23.2	ankyrin repeat and kinase domain containing 1
ALK2	TKL,STKR,Type1 ,SK026,ALK2	90	-	2q23-q24	activin A receptor, type I
ALK4	TKL,STKR,Type1 ,SK028,ALK4	91	-	12q13	activin A receptor, type IB
ALK1	TKL,STKR,Type1 ,SK025,ALK1	94	-	12q11-q14	activin A receptor type II-like 1
BMPR1A	TKL,STKR,Type1 ,SK027,BMPR1A	657	-	10q22.3	bone morphogenetic protein receptor, type IA
BMPR1B	TKL,STKR,Type1 ,SK030,BMPR1B	658	-	4q22-q24	bone morphogenetic protein receptor, type IB
TGFbR1	TKL,STKR,Type1 ,SK029,TGFbR1	7046	-	9q22	transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kDa)
ALK7	TKL,STKR,Type1 ,SK405,ALK7	130399	-	2q24.1	activin A receptor, type IC
ACVR2A	TKL,STKR,Type2 ,SK010,ACTR2	92	-	2q22.2-q23.3	activin A receptor, type II
ACTR2B	TKL,STKR,Type2 ,SK011,ACTR2B	93	-	3p22	activin A receptor, type IIB
MISR2	TKL,STKR,Type2 ,SK228,MISR2	269	-	12q13	anti-Mullerian hormone receptor, type II
BMPR2	TKL,STKR,Type2 ,SK365,BMPR2	659	-	2q33-q34	bone morphogenetic protein receptor, type II (serine/threonine kinase)
TGFbR2	TKL,STKR,Type2 ,SK369,TGFbR2	7048	-	3p22	transforming growth factor, beta receptor II (70/80kDa)
MLKL	TKL,TKL-Unique,SK458,MLKL	197259	-	16q22.3	mixed lineage kinase domain-like
ABCB10	others	23456	-	1q42	ATP-binding cassette, sub-family B (MDR/TAP), member 10
ABCB8	others	11194	-	7q36	ATP-binding cassette, sub-family B (MDR/TAP), member 8
ABCG1	others	9619	-	21q22.3	ATP-binding cassette, sub-family G (WHITE), member 1
ACTR2	others	10097	-	2p14	ARP2 actin-related protein 2 homolog (yeast)
ADCY3	others	109	4.6.1.1	2p24-p22	adenylate cyclase 3
ADCY6	others	112	4.6.1.1	12q12-q13	adenylate cyclase 6
ADCY7	others	113	4.6.1.1	16q12-q13	adenylate cyclase 7
ADCY8	others	114	4.6.1.1	8q24	adenylate cyclase 8 (brain)
ADCY9	others	115	4.6.1.1	16p13.3	adenylate cyclase 9
ADK	others	132	2.7.1.20	10q22	adenosine kinase
AK3L1	others	205	2.7.4.10	1p31.3	adenylate kinase 3
ALDH18A1	others	5832	-	10q24.3	aldehyde dehydrogenase 18 family, member A1
ALS2CR11	others	151254	-	2q33.1	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 11
ALS2CR12	others	130540	-	2q33.1	amyotrophic lateral sclerosis 2

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					(juvenile) chromosome region, candidate 12
ALS2CR13	others	150864	-	2q33.2	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 13
ICA1L	others	130026	-	2q33.2	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 15
PARD3B	others	117583	-	2q33.3	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 19
TRAK2	others	66008	-	2q33	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 3
ALS2CR4	others	65062	-	2q33.2	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 4
ALS2CR8	others	79800	-	2q33.2	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 8
DBF4	others	10926	-	7q21.3	activator of S phase kinase
MAGI1	others	9223	-	3p14.1	BAI1-associated protein 1
BUB3	others	9184	-	10q26	BUB3 budding uninhibited by benzimidazoles 3 homolog (yeast)
IPPK	others	64768	-	9q21.33-q22.31	chromosome 9 open reading frame 12
CARD11	others	84433	-	7p22	caspase recruitment domain family, member 11
CARD14	others	79092	-	17q25	caspase recruitment domain family, member 14
CARKL	others	23729	2.7.1.14	17p13	carbohydrate kinase-like
CHKB	others	1120	-	22q13.33	choline kinase beta
CINP	others	51550	-	14q32.32	cyclin-dependent kinase 2-interacting protein
CKB	others	1152	2.7.3.2	14q32	creatine kinase, brain
CKM	others	1158	2.7.3.2	19q13.2-q13.3	creatine kinase, muscle
CKMT1A	others	548596	2.7.3.2	15q15	creatine kinase, mitochondrial 1A
CKMT1B	others	1159	2.7.3.2	15q15	creatine kinase, mitochondrial 1 (ubiquitous)
CKMT2	others	1160	2.7.3.2	5q13.3	creatine kinase, mitochondrial 2 (sarcomeric)
CKS1B	others	1163	-	1q21.2	CDC28 protein kinase regulatory subunit 1B
CKS2	others	1164	-	9q22	CDC28 protein kinase regulatory subunit 2
CMPK	others	51727	2.7.4.14	1p34.1-p33	UMP-CMP kinase
CNKSR2	others	22866	-	xp22.12	connector enhancer of kinase suppressor of Ras 2
COASY	others	80347	2.7.7.3	17q12-q21	Coenzyme A synthase
COL4A3BP	others	10087	-	5q13.3	collagen, type IV, alpha 3 (Goodpasture antigen) binding protein
COPB1	others	1315	-	11p15.2	coatomer protein complex, subunit beta

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
COPB2	others	9276	-	3q23	coatomer protein complex, subunit beta 2 (beta prime)
DCK	others	1633	2.7.1.74	4q13.3-q21.1	deoxycytidine kinase
DDX1	others	1653	-	2p24	DEAD (Asp-Glu-Ala-Asp) box polypeptide 1
DGKA	others	1606	2.7.1.107	12q13.3	diacylglycerol kinase, alpha 80kDa
DGKB	others	1607	2.7.1.107	7p21.3	diacylglycerol kinase, beta 90kDa
DGKD	others	8527	-	2q37.1	diacylglycerol kinase, delta 130kDa
DGKE	others	8526	-	17q22	diacylglycerol kinase, epsilon 64kDa
DGKH	others	160851	-	13q14.11	diacylglycerol kinase, eta
DGKG	others	1608	2.7.1.107	3q27-q28	diacylglycerol kinase, gamma 90kDa
DGKI	others	9162	-	7q32.3-q33	diacylglycerol kinase, iota
DGKQ	others	1609	-	4p16.3	diacylglycerol kinase, theta 110kDa
DGKZ	others	8525	-	11p11.2	diacylglycerol kinase, zeta 104kDa
DGUOK	others	1716	2.7.1.113	2p13	deoxyguanosine kinase
DLG1	others	1739	-	3q29	discs, large homolog 1 (Drosophila)
DLG2	others	1740	-	11q21	discs, large homolog 2, chapsyn-110 (Drosophila)
DLG3	others	1741	-	xq13.1	discs, large homolog 3 (neuroendocrine-dlg, Drosophila)
DLG4	others	1742	-	17p13.1	discs, large homolog 4 (Drosophila)
DLG5	others	9231	-	10q23	discs, large homolog 5 (Drosophila)
DTYMK	others	1841	2.7.4.9	2q37.3	deoxythymidylate kinase (thymidylate kinase)
ETNK1	others	55500	-	12p12.1	ethanolamine kinase 1
EVI1	others	2122	-	3q24-q28	ecotropic viral integration site 1
ETNK2	others	55224	-	1q32.1	ethanolamine kinase 2
OXSM	others	54995	2.3.1.41	3p24.2	hypothetical protein FLJ20604
FN3K	others	64122	-	17q25.3	fructosamine 3 kinase
FXN	others	2395	-	9q13-q21.1	frataxin
GALK2	others	2585	2.7.1.6	15q21.1	galactokinase 2
GK	others	2710	2.7.1.30	xp21.3	glycerol kinase
GK2	others	2712	-	4q13	glycerol kinase 2
GNE	others	10020	-	9p13.2	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase
GUCY1A2	others	2977	4.6.1.2	11q21-q22	guanylate cyclase 1, soluble, alpha 2
GUCY1A3	others	2982	4.6.1.2	4q31.1-q31.2	guanylate cyclase 1, soluble, alpha 3
GUCY1B3	others	2983	4.6.1.2	4q31.3-q33	guanylate cyclase 1, soluble, beta 3
GUK1	others	2987	2.7.4.8	1q32-q41	guanylate kinase 1
IHPK2	others	51447	-	3p21.31	inositol hexaphosphate kinase 2
IKBKAP	others	8518	-	9q31	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein
CNKSR1	others	10256	-	1p36.11	connector enhancer of kinase

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
					suppressor of Ras 1
MBIP	others	51562	-	14q13.3	MAP3K12 binding inhibitory protein 1
KCNE1	others	3753	-	21q22.12	potassium voltage-gated channel, Isk-related family, member 1
MPP1	others	4354	-	xq28	membrane protein, palmitoylated 1, 55kDa
MPP2	others	4355	-	17q12-q21	membrane protein, palmitoylated 2 (MAGUK p55 subfamily member 2)
MPP3	others	4356	-	17q12-q21	membrane protein, palmitoylated 3 (MAGUK p55 subfamily member 3)
MPP4	others	58538	-	2q33.2	membrane protein, palmitoylated 4 (MAGUK p55 subfamily member 4)
MPP5	others	64398	-	14q23.3	membrane protein, palmitoylated 5 (MAGUK p55 subfamily member 5)
MPP6	others	51678	-	7p15	membrane protein, palmitoylated 6 (MAGUK p55 subfamily member 6)
MPP7	others	143098	-	10p12.1	membrane protein, palmitoylated 7 (MAGUK p55 subfamily member 7)
MVK	others	4598	2.7.1.36	12q24	mevalonate kinase (mevalonic aciduria)
NAGK	others	55577	2.7.1.59	2p13.3	N-acetylglucosamine kinase
NDUFA10	others	4705	-	2q37.3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42kDa
NME1	others	4830	-	17q21.3	non-metastatic cells 1, protein (NM23A) expressed in
NME2	others	4831	-	17q21.3	non-metastatic cells 2, protein (NM23B) expressed in
NME3	others	4832	-	16q13	non-metastatic cells 3, protein expressed in
NME4	others	4833	-	16p13.3	non-metastatic cells 4, protein expressed in
NME5	others	8382	-	5q31	non-metastatic cells 5, protein expressed in (nucleoside-diphosphate kinase)
NME6	others	10201	-	3p21	non-metastatic cells 6, protein expressed in (nucleoside-diphosphate kinase)
NME7	others	29922	-	1q24	non-metastatic cells 7, protein expressed in (nucleoside-diphosphate kinase)
NPR3	others	4883	-	5p14-p13	natriuretic peptide receptor C/guanylate cyclase C (atrionatriuretic peptide receptor C)
NSF	others	4905	-	17q21	N-ethylmaleimide-sensitive factor
NUBP1	others	4682	-	16p13.13	nucleotide binding protein 1 (MinD homolog, E. coli)

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
NUBP2	others	10101	-	16p13.3	nucleotide binding protein 2 (MinD homolog, E. coli)
PACSIN1	others	29993	-	6p21.3	protein kinase C and casein kinase substrate in neurons 1
PANK1	others	53354	-	10q23.31	pantothenate kinase 1
PANK2	others	80025	-	20p13	pantothenate kinase 2 (Hallervorden-Spatz syndrome)
PANK3	others	79646	-	5q34	pantothenate kinase 3
PANK4	others	55229	-	1p36.32	pantothenate kinase 4
PAPSS1	others	9061	2.7.7.4, 2.7	4q24	3'-phosphoadenosine 5'-phosphosulfate synthase 1
PAPSS2	others	9060	2.7.7.4, 2.7.1.25	10q23-q24	3'-phosphoadenosine 5'-phosphosulfate synthase 2
PCK1	others	5105	4.1.1.32	20q13.31	phosphoenolpyruvate carboxykinase 1 (soluble)
PCK2	others	5106	4.1.1.32	14q11.2	phosphoenolpyruvate carboxykinase 2 (mitochondrial)
PDXK	others	8566	2.7.1.35	21q22.3	pyridoxal (pyridoxine, vitamin B6) kinase
PFKL	others	5211	2.7.1.11	21q22.3	phosphofructokinase, liver
PFKM	others	5213	2.7.1.11	12q13.3	phosphofructokinase, muscle
PFKP	others	5214	2.7.1.11	10p15.3-p15.2	phosphofructokinase, platelet
PI4K2B	others	55300	-	4p15.2	phosphatidylinositol 4-kinase type-II beta
PI4K2A	others	55361	-	10q24	phosphatidylinositol 4-kinase type II
PIK3C2A	others	5286	2.7.1.137	11p15.5-p14	phosphoinositide-3-kinase, class 2, alpha polypeptide
PIK3C2B	others	5287	2.7.1.137	1q32	phosphoinositide-3-kinase, class 2, beta polypeptide
PIK3C2G	others	5288	2.7.1.137	12p12	phosphoinositide-3-kinase, class 2, gamma polypeptide
PIK3C3	others	5289	-	18q12.3	phosphoinositide-3-kinase, class 3
PIK3CA	others	5290	2.7.1.137	3q26.3	phosphoinositide-3-kinase, catalytic, alpha polypeptide
PIK3CB	others	5291	2.7.1.137	3q22.3	phosphoinositide-3-kinase, catalytic, beta polypeptide
PIK3CD	others	5293	-	1p36.2	phosphoinositide-3-kinase, catalytic, delta polypeptide
PIK3CG	others	5294	2.7.1.137	7q22.3	phosphoinositide-3-kinase, catalytic, gamma polypeptide
PIK3R2	others	5296	-	19q13.2-q13.4	phosphoinositide-3-kinase, regulatory subunit 2 (p85 beta)
PIK4CA	others	5297	-	22q11.21	phosphatidylinositol 4-kinase, catalytic, alpha polypeptide
PIK4CB	others	5298	-	1q21	phosphatidylinositol 4-kinase, catalytic, beta polypeptide
PIP5K1A	others	8394	-	1q22-q24	phosphatidylinositol-4-phosphate 5-kinase, type I, alpha
PIP5K1B	others	8395	-	9q13	phosphatidylinositol-4-phosphate 5-kinase, type I, beta
PIP5K2A	others	5305	-	10p12.32	phosphatidylinositol-4-phosphate 5-kinase, type II, alpha
PIP5K2B	others	8396	2.7.1.149	17q12	phosphatidylinositol-4-phosphate

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
					5-kinase, type II, beta
PIP5K2C	others	79837	-	12q13.3	phosphatidylinositol-4-phosphate 5-kinase, type II, gamma
PKD1	others	5310	-	16p13.3	polycystic kidney disease 1 (autosomal dominant)
PKD2	others	5311	-	4q21-q23	polycystic kidney disease 2 (autosomal dominant)
EXOSC10	others	5394	-	1p36.22	exosome component 10
PMVK	others	10654	2.7.4.2	1p13-q23	phosphomevalonate kinase
PRKAG3	others	53632	-	2q35	protein kinase, AMP-activated, gamma 3 non-catalytic subunit
PRPF4	others	9128	-	9q31-q33	PRP4 pre-mRNA processing factor 4 homolog (yeast)
PRPS1	others	5631	2.4.2.17	xq21-q27	phosphoribosyl pyrophosphate synthetase 1
PRPS2	others	5634	2.4.2.17	xp22.3-p22.2	phosphoribosyl pyrophosphate synthetase 2
PRPSAP1	others	5635	-	17q24-q25	phosphoribosyl pyrophosphate synthetase-associated protein 1
PRPSAP2	others	5636	-	17p11.2-p12	phosphoribosyl pyrophosphate synthetase-associated protein 2
LONP1	others	9361	-	19p13.2	protease, serine, 15
TWF1	others	5756	-	12q12	PTK9 protein tyrosine kinase 9
TWF2	others	11344	-	3p21.1	PTK9L protein tyrosine kinase 9-like (A6-related protein)
PTPRN	others	5798	-	2q35-q36.1	protein tyrosine phosphatase, receptor type, N
PTPRT	others	11122	-	20q12-q13	protein tyrosine phosphatase, receptor type, T
RAPGEF4	others	11069	-	2q31-q32	Rap guanine nucleotide exchange factor (GEF) 4
RBM19	others	9904	-	12q24.13-q24.21	RNA binding motif protein 19
RBKS	others	64080	2.7.1.15	2p23.3	ribokinase
RCE1	others	9986	-	11q13	RCE1 homolog, prenyl protein protease (S. cerevisiae)
RECQL5	others	9400	-	17q25.2-q25.3	RecQ protein-like 5
RFK	others	55312	-	9q21.13	riboflavin kinase
SLC6A14	others	11254	-	xq23-q24	solute carrier family 6 (amino acid transporter), member 14
SPHK1	others	8877	-	17q25.2	sphingosine kinase 1
SPHK2	others	56848	-	19q13.2	sphingosine kinase 2
SEPHS1	others	22929	-	10p14	selenophosphate synthetase 1
SEPHS2	others	22928	-	16p11.2	selenophosphate synthetase 2
MAP3K7IP 1	others	10454	-	22q13.1	mitogen-activated protein kinase kinase kinase 7 interacting protein 1
MAP3K7IP 2	others	23118	-	6q25.1-q25.3	mitogen-activated protein kinase kinase kinase 7 interacting protein 2
TAS2R14	others	50840	-	12p13	taste receptor, type 2, member 14
TJP1	others	7082	-	15q13	tight junction protein 1 (zona occludens 1)
TJP2	others	9414	-	9q13-q21	tight junction protein 2 (zona occludens 2)

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
TJP3	others	27134	-	19p13.3	tight junction protein 3 (zona occludens 3)
TK1	others	7083	2.7.1.21	17q23.2-q25.3	thymidine kinase 1, soluble
TK2	others	7084	2.7.1.21	16q22-q23.1	thymidine kinase 2, mitochondrial
TPK1	others	27010	-	7q34-q35	thiamin pyrophosphokinase 1
TRIP13	others	9319	-	5p15.33	thyroid hormone receptor interactor 13
UCK2	others	7371	2.7.4.-	1q23	uridine-cytidine kinase 2
UCKL1	others	54963	-	20q13.33	uridine-cytidine kinase 1-like 1
XYLB	others	9942	-	3p22-p21.3	xylulokinase homolog (H. influenzae)
MAGI2	others	9863	-	7q21	atrophin-1 interacting protein 1
ADPGK	others	83440	-	15q24.1	ADP-dependent glucokinase
AGK	others	55750	2.7.1.94	7q34	multiple substrate lipid kinase
AK1	others	203	2.7.4.3	9q34.1	adenylate kinase 1
AK2	others	204	2.7.4.3	1p34	adenylate kinase 2
AK3	others	50808	-	9p24.1-p24.3	adenylate kinase 3 like 1
AK5	others	26289	-	1p31	adenylate kinase 5
AK7	others	122481	-	14q32.2	adenylate kinase 7
CALM2	others	805	-	2p21	calmodulin 2 (phosphorylase kinase, delta)
CDK5R1	others	8851	-	17q11.2	cyclin-dependent kinase 5, regulatory subunit 1 (p35)
CDK5R2	others	8941	-	2q35	cyclin-dependent kinase 5, regulatory subunit 2 (p39)
CDKN3	others	1033	-	14q22	cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)
CERK	others	64781	-	22q13.31	ceramide kinase
CERKL	others	375298	-	2q31.3	ceramide kinase-like
CHKA	others	1119	2.7.1.32	11q13.2	choline kinase alpha
DAK	others	26007	-	11q12.2	DKFZP586B1621 protein
DCAKD	others	79877	-	17q21.31	hypothetical protein FLJ22955
DGKK	others	139189	-	xp11.22	similar to C130007D14 protein
DOLK	others	22845	-	9q34.11	transmembrane protein 15
FASTKD1	others	79675	-	2q31	hypothetical protein FLJ21901
FASTKD2	others	22868	-	2q33.3	KIAA0971
FASTKD3	others	79072	-	5p15.3-p15.2	hypothetical protein MGC5297
FASTKD5	others	60493	-	20p13	hypothetical protein FLJ13149
FUK	others	197258	2.7.1.52	16q22.1	fucokinase
GCK	others	2645	2.7.1.2, 2.7.1.1	7p15.3-p15.1	glucokinase (hexokinase 4, maturity onset diabetes of the young 2)
HK1	others	3098	2.7.1.1	10q22	hexokinase 1
HK2	others	3099	2.7.1.1	2p13	hexokinase 2
HK3	others	3101	2.7.1.1	5q35.2	hexokinase 3 (white cell)
HKDC1	others	80201	-	10q22.1	hypothetical protein FLJ22761
IHPK1	others	9807	-	3p21.31	inositol hexaphosphate kinase 1
IHPK3	others	117283	-	6p21.31	inositol hexaphosphate kinase 3
IPMK	others	253430	-	10q21.1	inositol polyphosphate multikinase
ITPK1	others	3705	-	14q31	inositol 1,3,4-triphosphate 5/6 kinase
ITPKA	others	3706	2.7.1.-	15q14-q21	inositol 1,4,5-trisphosphate 3-

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
					kinase A
ITPKB	others	3707	2.7.1.-	1q42.13	inositol 1,4,5-trisphosphate 3-kinase B
ITPKC	others	80271	-	19q13.1	inositol 1,4,5-trisphosphate 3-kinase C
NADK	others	65220	-	1p36.33-p36.21	NAD kinase
PHKB	others	5257	2.7.1.38	16q12-q13	phosphorylase kinase, beta
PIP5K1C	others	23396	-	19p13.3	phosphatidylinositol-4-phosphate 5-kinase, type I, gamma
PIP5KL1	others	138429	-	9q34.11	phosphatidylinositol-4-phosphate 5-kinase-like 1
PKLR	others	5313	2.7.1.40	1q21	pyruvate kinase, liver and RBC
PKM2	others	5315	2.7.1.40	15q22	pyruvate kinase, muscle
PLAU	others	5328	3.4.21.31	10q24	plasminogen activator, urokinase
PSTK	others	118672	-	10q26.13	chromosome 10 open reading frame 89
UCK1	others	83549	2.7.1.48	9q34.13	uridine-cytidine kinase 1
CALM1	others	801	2.7.1.38	14q24-q31	calmodulin 1 (phosphorylase kinase, delta)
CALM3	others	808	-	19q13.2-q13.3	calmodulin 3 (phosphorylase kinase, delta)
CSNK2B	others	1460	2.7.1.37	6p21.3	casein kinase 2, beta polypeptide
GALK1	others	2584	2.7.1.6	17q24	galactokinase 1
KHK	others	3795	2.7.1.3	2p23.3-p23.2	ketohexokinase (fructokinase)
MAGI3	others	260425	-	1p12-p11.2	membrane-associated guanylate kinase-related (MAGI-3)
PFKFB1	others	5207	2.7.1.105, 3.1.-.-	xp11.21	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1
PFKFB2	others	5208	2.7.1.105, 3.1.-.-	1q31	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2
PFKFB3	others	5209	-	10p14-p15	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3
PFKFB4	others	5210	-	3p22-p21	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4
PGK1	others	5230	2.7.2.3	xq13	phosphoglycerate kinase 1
PGK2	others	5232	-	6p12.3	phosphoglycerate kinase 2
PHKA1	others	5255	2.7.1.38	xq12-q13	phosphorylase kinase, alpha 1 (muscle)
PHKA2	others	5256	2.7.1.38	xp22.2-p22.1	phosphorylase kinase, alpha 2 (liver)
PRKAB1	others	5564	-	12q24.1	protein kinase, AMP-activated, beta 1 non-catalytic subunit
PRKAB2	others	5565	-	1q21.1	protein kinase, AMP-activated, beta 2 non-catalytic subunit
PRKAG1	others	5571	-	12q12-q14	protein kinase, AMP-activated, gamma 1 non-catalytic subunit
PRKAG2	others	51422	-	7q35-q36	protein kinase, AMP-activated, gamma 2 non-catalytic subunit
PRKAR1A	others	5573	2.7.1.37	17q23-q24	protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)
PRKAR2A	others	5576	2.7.1.37	3p21.3-p21.2	protein kinase, cAMP-dependent, regulatory, type II, alpha
PRKAR2B	others	5577	2.7.1.37	7q22	protein kinase, cAMP-dependent,

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
					regulatory, type II, beta
PRKRA	others	11108	-	12q23-q24.1	PR domain containing 4
PRKRIR	others	5612	-	11q13.5	protein-kinase, interferon-inducible double stranded RNA dependent inhibitor, repressor of (P58 repressor)
CDC2L2	others	728642	-	1p36.33	cell division cycle 2-like 2 (PITSLRE proteins)
PIP5K3	others	200576	-	2q33.3	phosphatidylinositol-3-phosphate/phosphatidylinositol 5-kinase, type III
PRKAR1B	others	645590	-	-	similar to cAMP-dependent protein kinase type I-beta regulatory subunit
CKS1A	others	137529	-	8q21.13	CDC28 protein kinase regulatory subunit 1A
FCGR3A	others	2214	-	1q23	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)
BCAT2	others	587	2.6.1.26	19q13	branched chain aminotransferase 2, mitochondrial
CCNA2	others	890	-	4q25-q31	cyclin A2
CCNE1	others	898	-	19q12	cyclin E1
GCKR	others	2646	-	2p23	glucokinase (hexokinase 4) regulator
CCND2	others	894	-	12p13	cyclin D2
MNAT1	others	4331	-	14q23	menage a trois 1 (CAK assembly factor)
RAD17	others	5884	-	5q13	RAD17 homolog (S. pombe)
SHB	others	6461	-	9p12-p11	SHB (Src homology 2 domain containing) adaptor protein B
SHC1	others	6464	-	1q21	SHC (Src homology 2 domain containing) transforming protein 1
SLPI	others	6590	-	20q12	secretory leukocyte protease inhibitor (antileukoproteinase)
CAD	others	790	2.1.3.2, 3.5.2.-	2p22-p21	carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase
MYT1	others	4661	-	20q13.33	myelin transcription factor 1
CRK	others	1398	-	17p13.3	v-crk sarcoma virus CT10 oncogene homolog (avian)
GTH2H1	others	2965	-	11p15.1-p14	general transcription factor IIH, polypeptide 1, 62kDa
ZRANB2	others	9406	-	1p31	zinc finger protein 265
BACE2	others	25825	-	21q22.3	beta-site APP-cleaving enzyme 2
CCNB1	others	891	-	5q12	cyclin B1
OSR1	others	130497	-	2p24.1	odd-skipped related 1 (Drosophila)
MAPKNS	others	AAA74301	-	-	MAP kinase
AAA36585	others	AAA36585	-	-	rac protein kinase-beta
AAB05036	others	AAB05036	-	-	p38B MAP kinase
AAC16273	others	AAC16273	-	-	mitogen-activated protein kinase kinase 7b

Kinase Gene Name	Family	Entrez Gene ID	enzyme ID	Map Location ID (cytogenetic or genetic location)	Descriptive Name (or default name)
AAC24716	others	AAC24716	-	-	p21 activated kinase 1B
AAC98920	others	AAC98920	-	-	cell cycle related kinase
AAH13051	others	AAH13051	-	-	LIM domain kinase 2
AAO12758	others	AAO12758	-	-	casein kinase I gamma 1 isoform
BAB62909	others	BAB62909	-	-	testicular protein kinase 2
BAD18671	others	BAD18671	-	-	-
NME1-NME2	others	654364	-	17q21.3	NME1-NME2
PTPN11	others	5781	-	12q24	protein tyrosine phosphatase, non-receptor type 11 (Noonan syndrome 1)
TSSK1A	others	23752	-	22q11.21	serine/threonine kinase 22A (spermiogenesis associated)

[00179] The preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, *i.e.*, any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims.

CLAIMS

That which is claimed is:

1. An apparatus configured for analysis of a sample, the apparatus comprising:

a chamber configured to receive the sample via an inlet port, and to discharge the sample via an outlet port, wherein the inlet and outlet ports are positioned on a first side of the chamber;

a plurality of enzymatic substrate extensions coupled to a surface on the first side of the chamber, the surface having a nanoparticle structure;

an illuminator positioned on a second side of the chamber, the second side being opposite the first side, the illuminator being positioned to provide an excitation beam to a selected one of the plurality of enzymatic substrate extensions; and

an analysis module configured to receive a reflected beam from the selected enzymatic substrate extension, and to determine therefrom whether a modification of the selected enzymatic substrate extension by the sample has occurred.

2. The apparatus of claim 1, further comprising a step control motor configured to position the illuminator and the analysis module relative to the selected enzymatic substrate extension.

3. The apparatus of claim 1, wherein the analysis module comprises a mirror and a spectrometer.

4. The apparatus of claim 3, wherein a waveform peak in the spectrometer indicates modification of the selected enzymatic substrate extension by the sample.

5. The apparatus of claim 1, wherein the nanoparticle structure comprises a metal deposited on a nanopyramid array.

6. The apparatus of claim 1, wherein the excitation beam comprises a laser.

7. The apparatus of claim 1, wherein the analysis module comprises a digital light processor (DLP).

8. The apparatus of claim 1, wherein at least one of the plurality of enzymatic substrate extensions comprises a polypeptide.

9. The apparatus of claim 1, wherein at least one of the plurality of enzymatic substrate extensions comprises a nucleic acid.

10. The apparatus of claim 1, wherein at least one of the plurality of enzymatic substrate extensions comprises a polysaccharide.

11. The apparatus of claim 1, wherein the modification comprises a phosphorylation event between the selected enzymatic substrate extension and the enzyme from the sample.

12. The apparatus of claim 1, wherein the modification comprises a dephsophorylation event between the selected enzymatic substrate extension and the enzyme from the sample.

13. The apparatus of claim 1, wherein the modification comprises a cleavage event between the selected enzymatic substrate extension and the enzyme from the sample.

14. A method of making a microfluidic optical device, comprising:
depositing polycrystalline silicon layers on each side of a silicon wafer;
forming via-holes through the silicon wafer;
patterning a frontside of the silicon wafer;
etching silicon nanostructures in areas formed by the patterning of the frontside;
depositing metal in areas formed by the etched silicon nanostructures;
removing remaining photoresist and annealing the deposited metal; and
integrating a chip separated from the silicon wafer with handling units and a transparent window coupled to a chamber in the microfluidic optical device.

15. The method of claim 14, wherein the forming of the via-holes comprises using chemical etching.

16. The method of claim 14, wherein the forming of the via-holes comprises using laser drilling.

17. The method of claim 14, wherein the integrating of the chip comprises coupling inlet and outlet ports to the via-hole formation.

18. A method of characterizing a liquid sample, comprising:

receiving the liquid sample via an inlet port, and discharging the sample via an outlet port, wherein the inlet and outlet ports are positioned on a first side of the chamber;

providing an excitation beam to a selected one of a plurality of enzymatic substrate extensions, the enzymatic substrate extensions being coupled to a surface on the first side of the chamber, the surface having a nanoparticle structure;

receiving a reflected beam from the selected enzymatic substrate extension in an analysis module; and

determining from the received reflected beam whether a modification of the selected enzymatic substrate extension by the sample has occurred.

19. The method of claim 18, further comprising adjusting a voltage proximate to the selected enzymatic substrate extension.

20. The method of claim 18, further comprising positioning the analysis module relative to the selected enzymatic substrate extension.

21. A method for determining the activity of a target biomolecule using a surface enhanced Raman spectroscopy (SERS) system, comprising:

introducing a fluid sample into a microfluidic optical chamber wherein said optical chamber comprises a Raman active surface with a plurality of substrates extending therefrom;

allowing for specific interaction between a biomolecule in the fluid sample and a plurality of said substrates;

directing a laser at the fluid sample, wherein the interaction of the laser with the fluid sample produces a SERS signal that is specific for the interaction between the biomolecule and the substrate; and

detecting the activity of the biomolecule by detecting a change in the Raman scattering spectrum of the biomolecule as compared to the Raman scattering spectrum of a control sample.

22. The method of claim 21 wherein the target biomolecule is a protein.

23. The method of claim 21 wherein the target biomolecule is an enzyme.

24. The method of claim 21 wherein the target biomolecule is a kinase.

25. The method of claim 21 wherein the target biomolecule is an antibody.

26. The method of claim 21 wherein the target biomolecule is a substrate for an enzymatic reaction.

27. The method of claim 21 wherein the target biomolecule is a DNA binding protein and the substrate is a nucleic acid.

28. The method of claim 21 wherein the interaction between the target biomolecule the plurality of substrates is a protein-ligand binding interaction.

29. The method of claim 21 wherein the interaction between the target biomolecule the plurality of substrates is a protein-protein binding interaction.

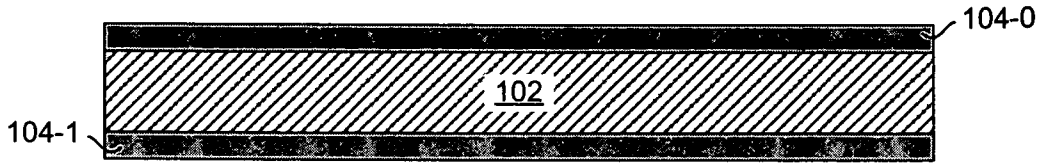


FIG. 1A

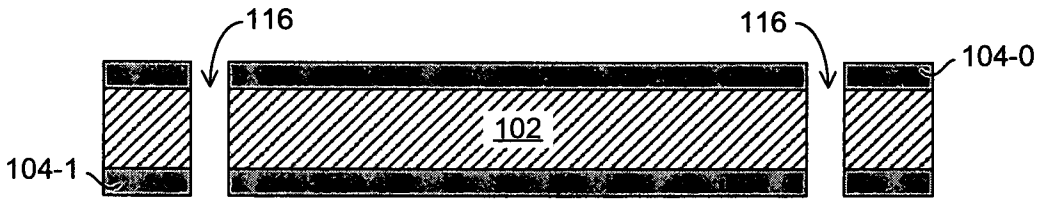


FIG. 1B

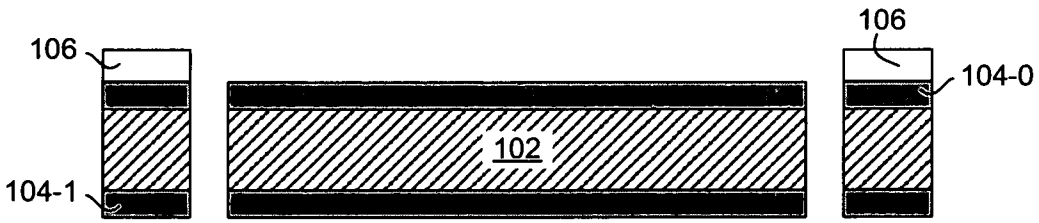


FIG. 1C

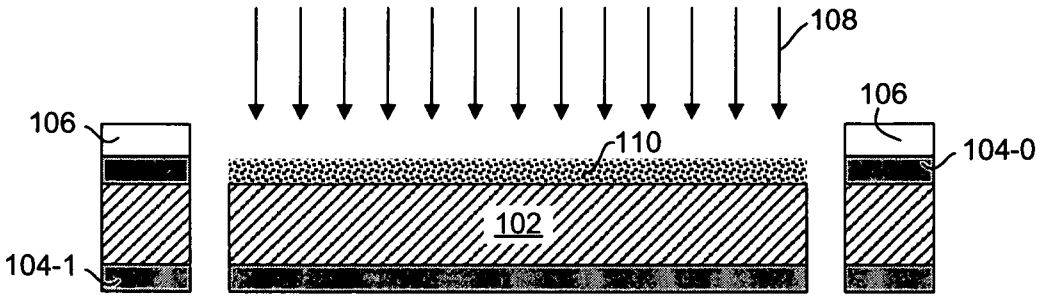


FIG. 1D

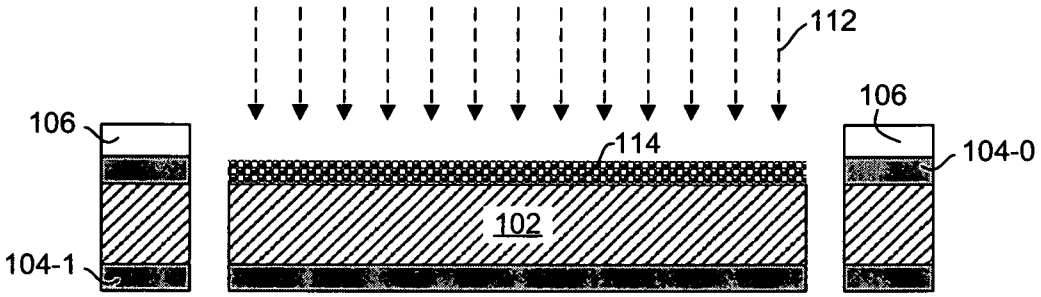


FIG. 1E

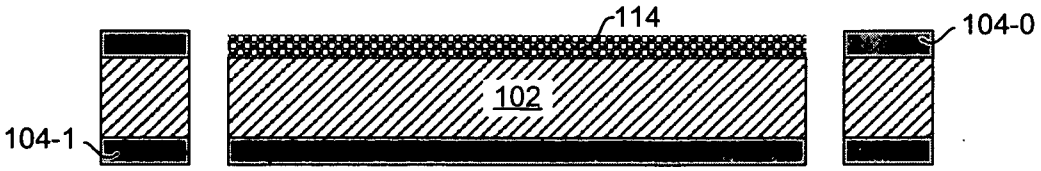


FIG. 1F

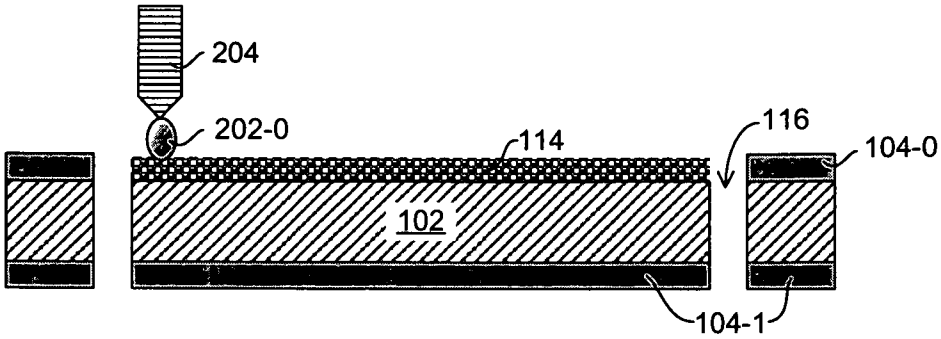


FIG. 2A

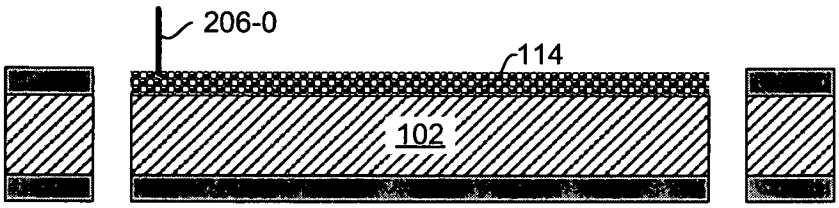


FIG. 2B

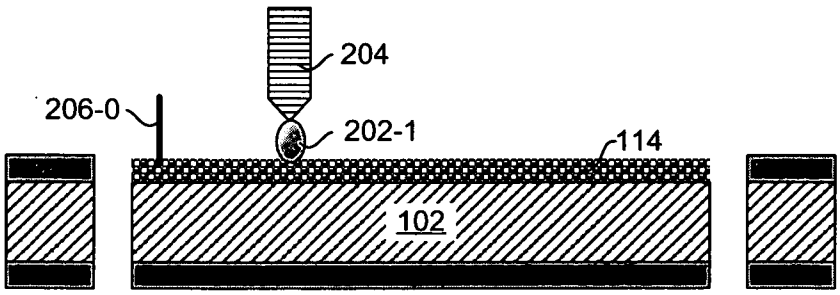


FIG. 2C

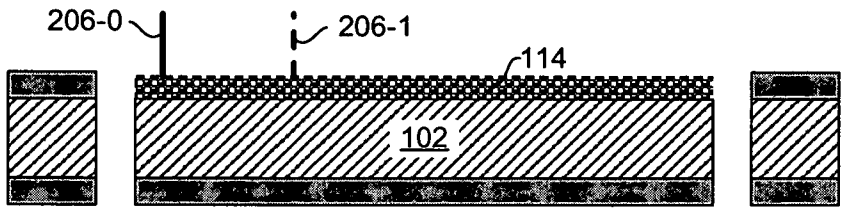


FIG. 2D

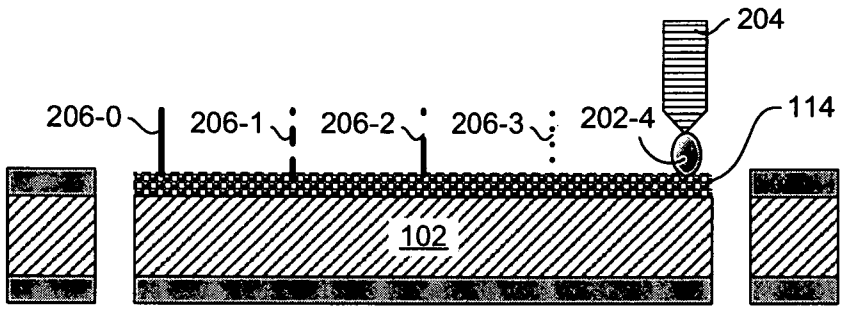


FIG. 2E

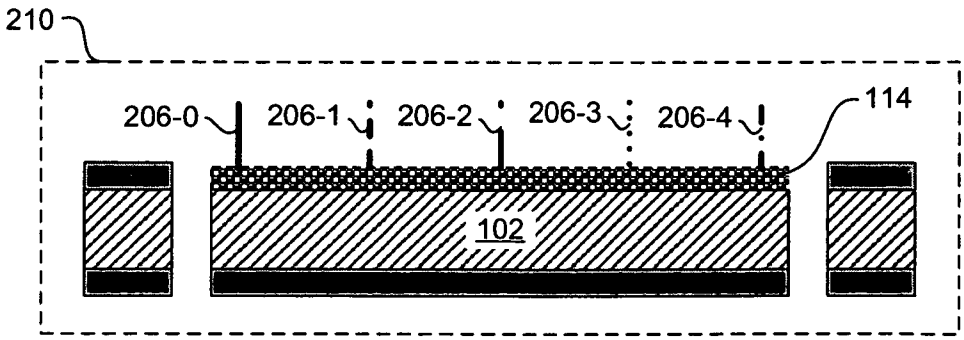


FIG. 2F

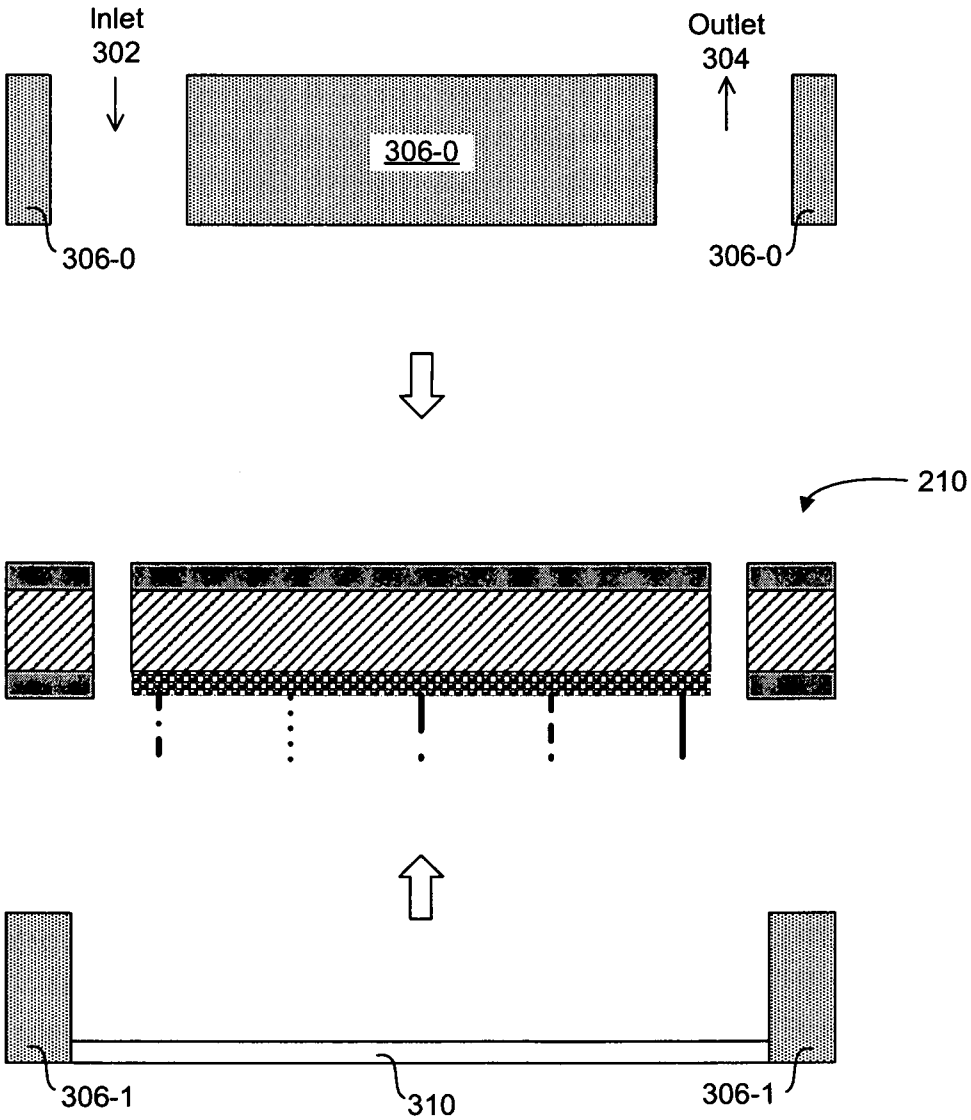
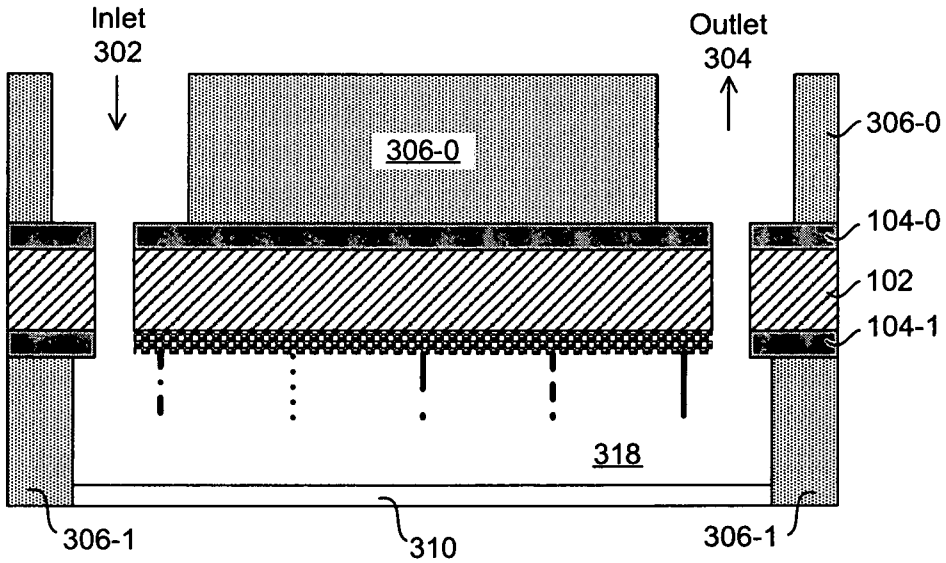


FIG. 3A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Outlet
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306-0
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318
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306-1

FIG. 3B

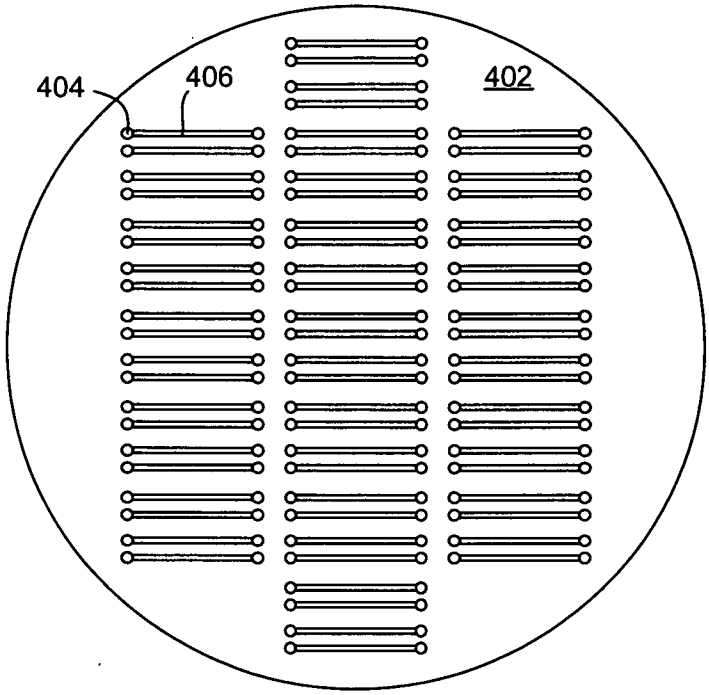


FIG. 4A

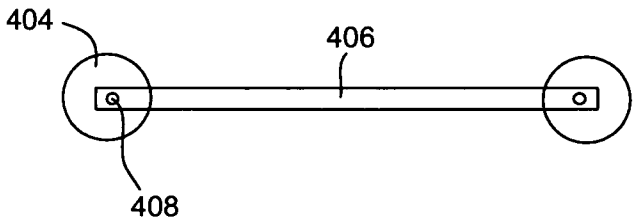
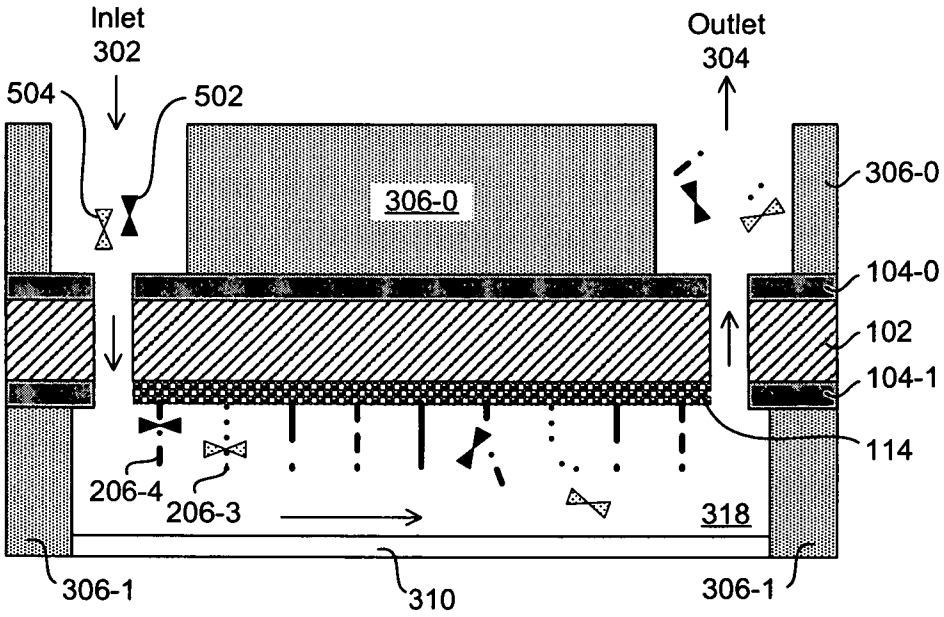


FIG. 4B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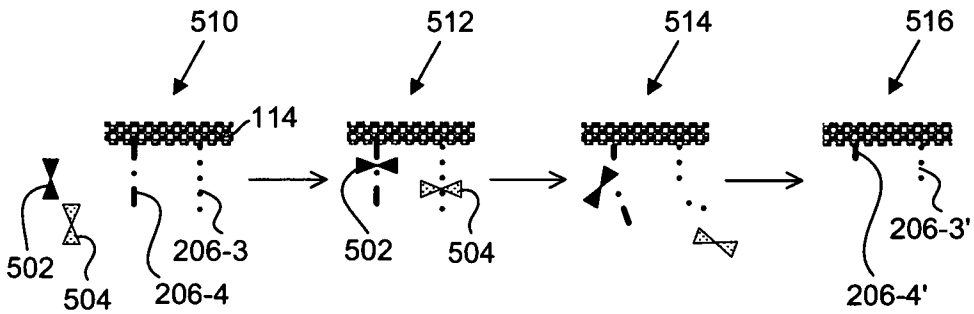
306-1

FIG. 5A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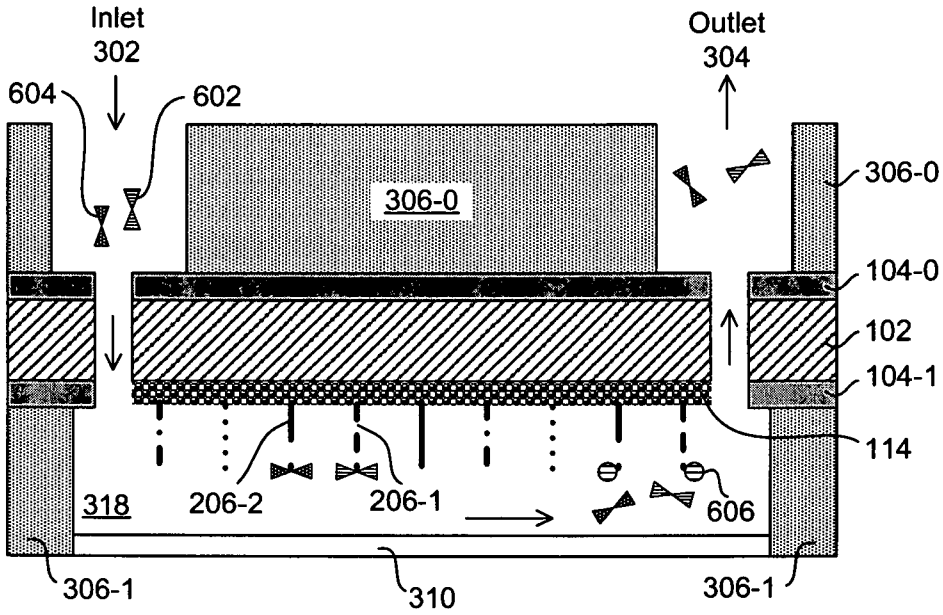
206-4'

FIG. 5B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602
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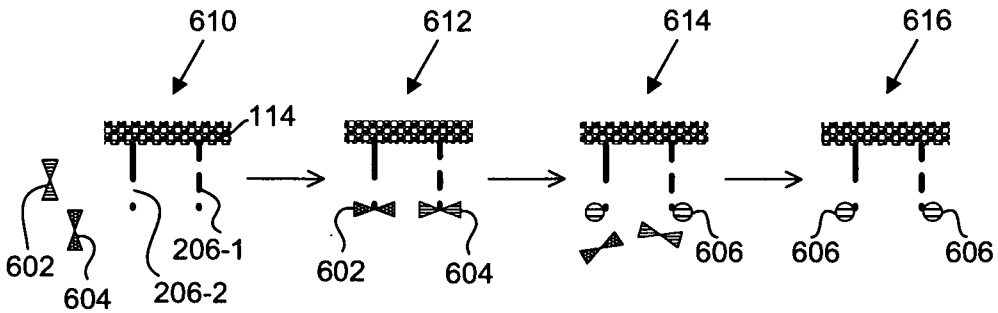
306-1

FIG. 6A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206-2
602
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606
606
606

FIG. 6B

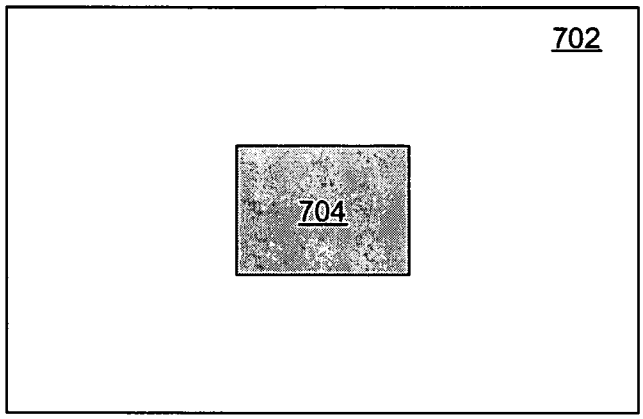


FIG. 7A

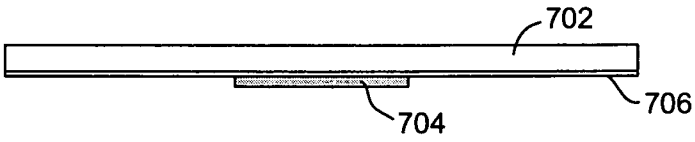
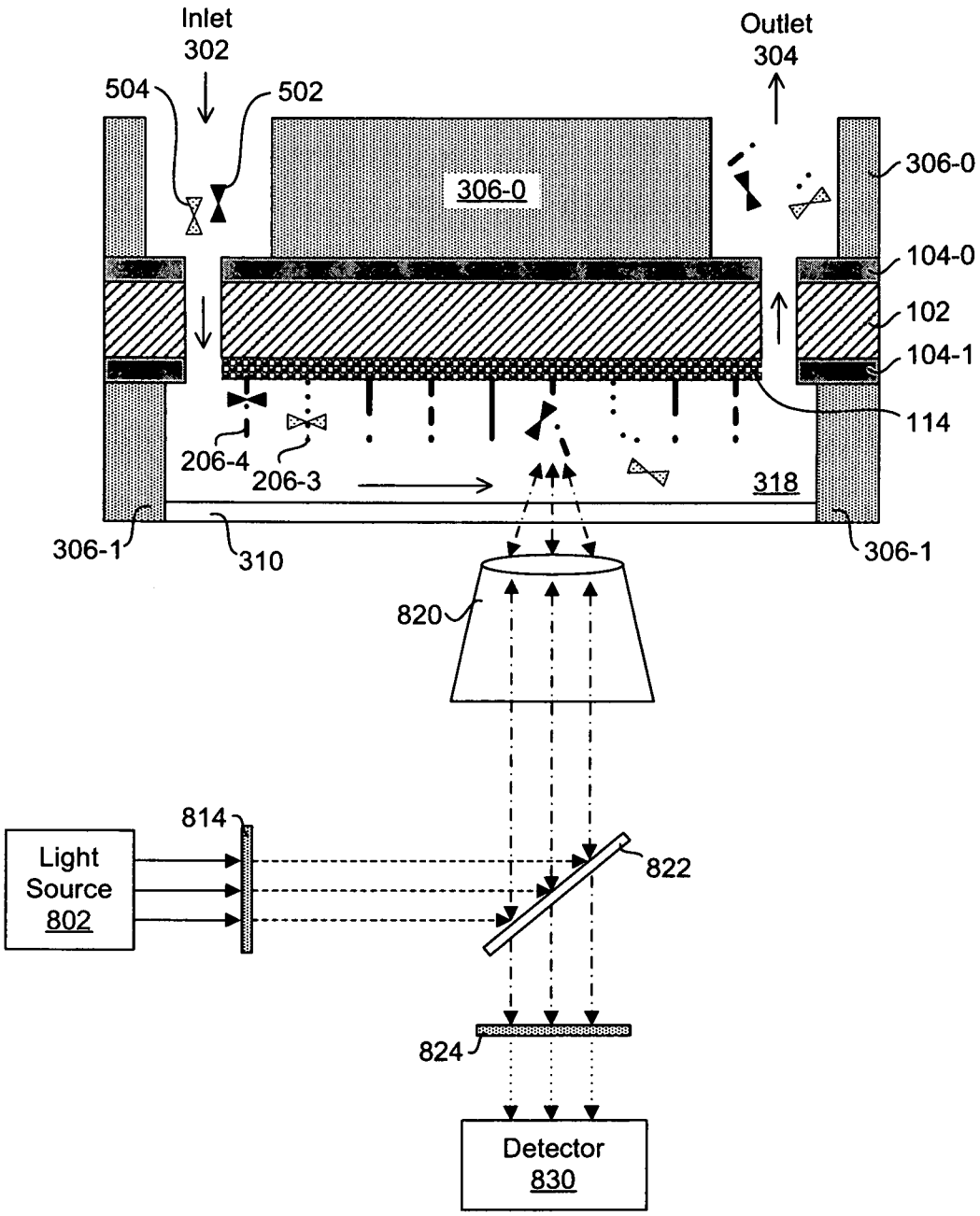


FIG. 7B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102
104-1
114
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206-3
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820
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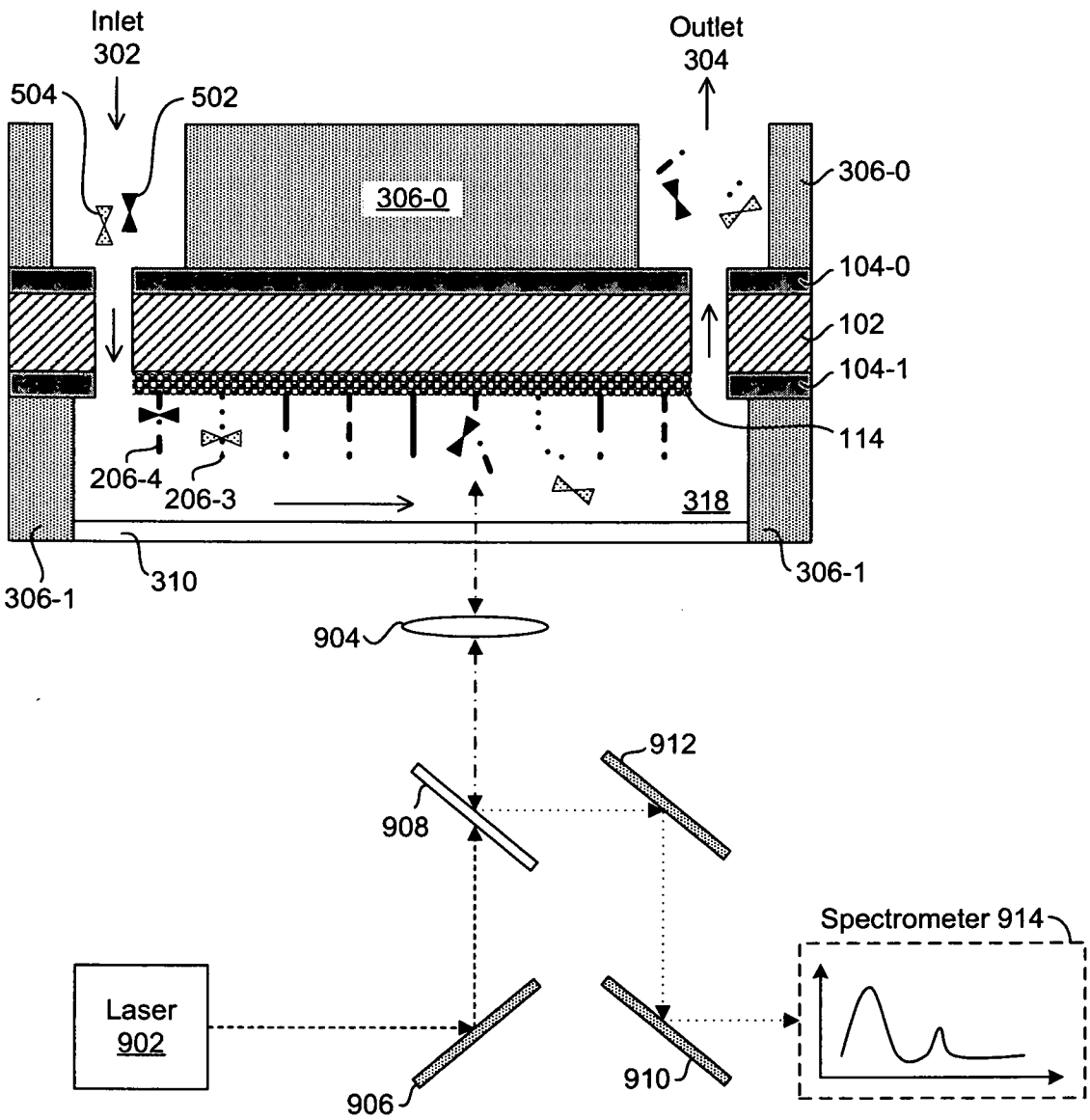
Light
Source
802
822
824
Detector
830

FIG. 8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104-1
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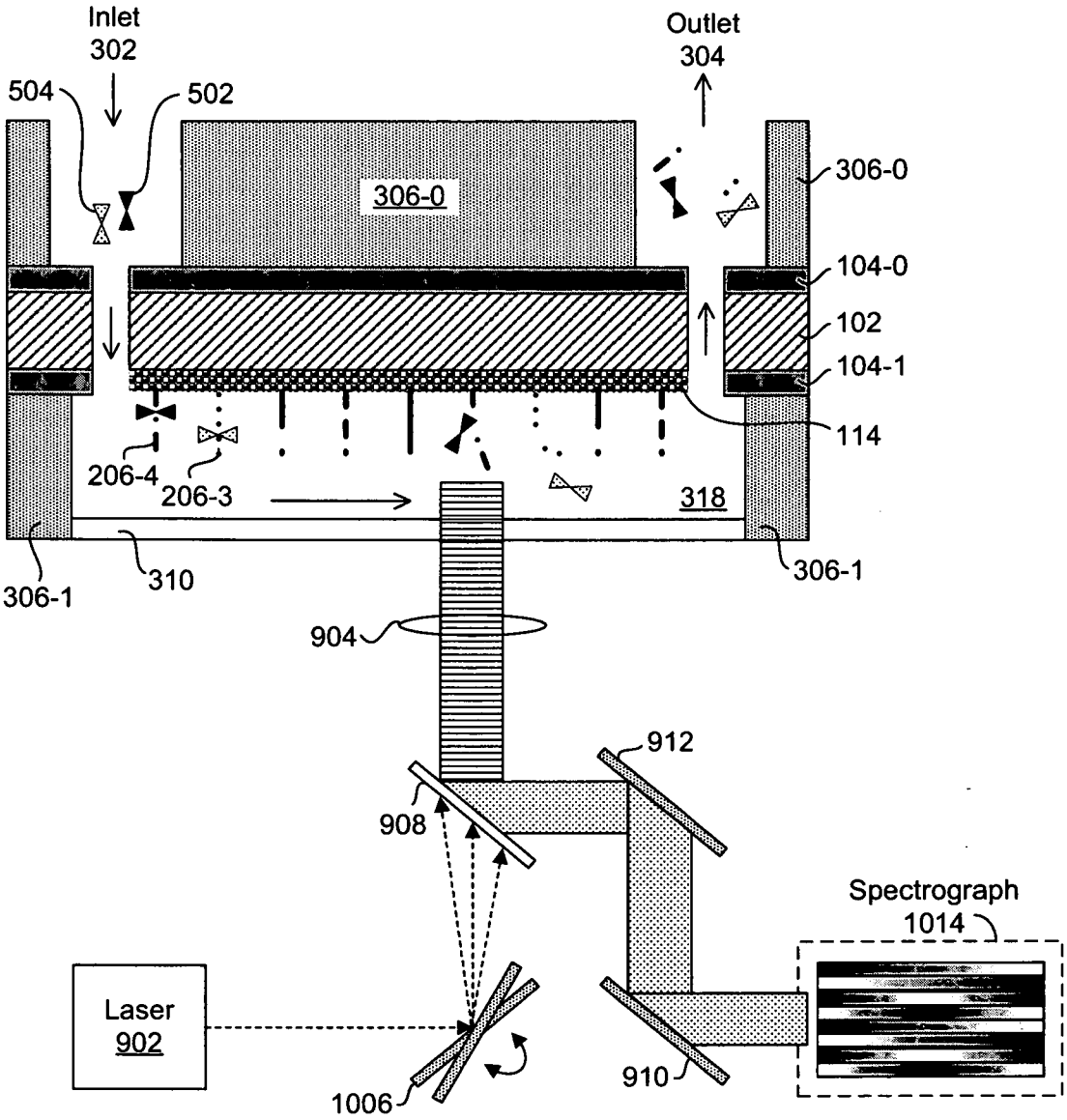
904
912
908
Spectrometer 914
Laser
902
906
910

FIG. 9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908
Spectrograph
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Laser
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910
1006

FIG. 10

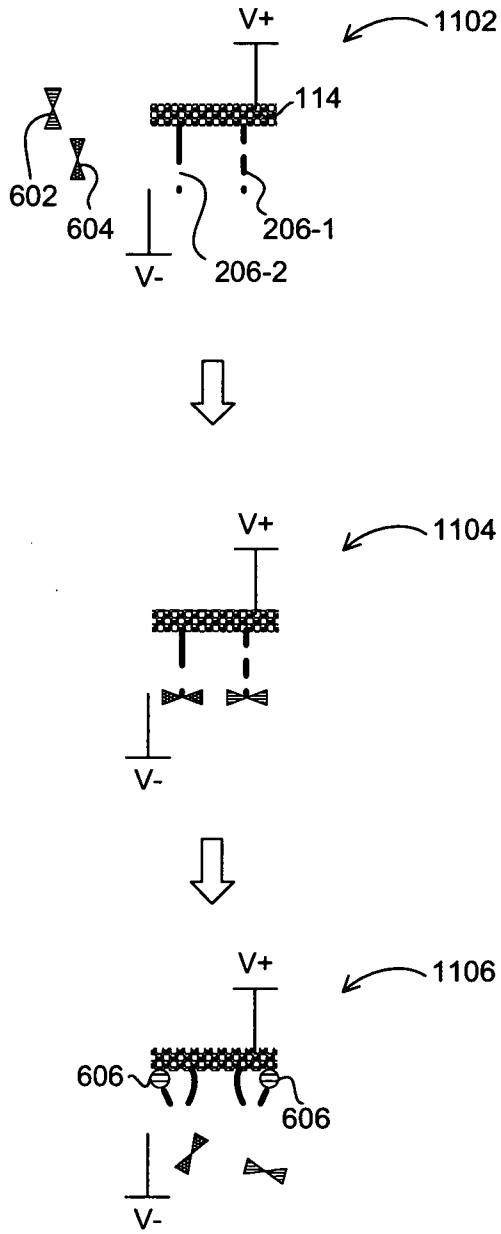

FIG. 11

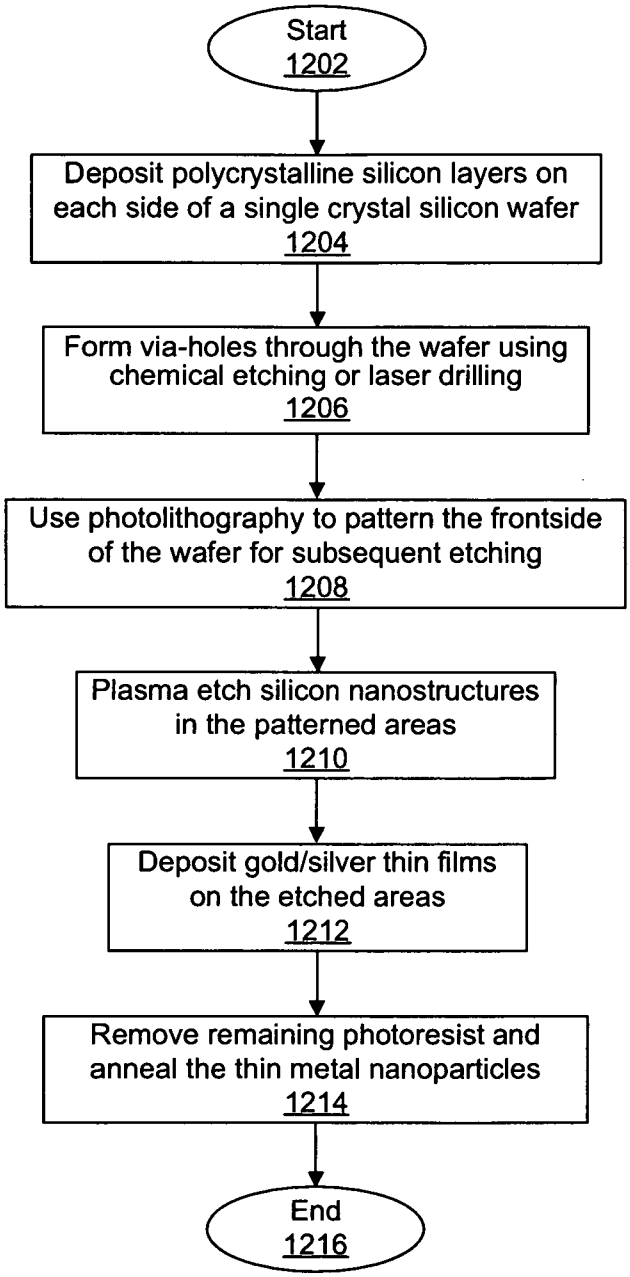
Start
1202
Deposit polycrystalline silicon layers on each side of a single crystal silicon wafer
1204
Form via-holes through the wafer using chemical etching or laser drilling
1206
Use photolithography to pattern the frontside of the wafer for subsequent etching
1208
Plasma etch silicon nanostructures in the patterned areas
1210
Deposit gold/silver thin films on the etched areas
1212
Remove remaining photoresist and anneal the thin metal nanoparticles
1214
End
1216

FIG. 12

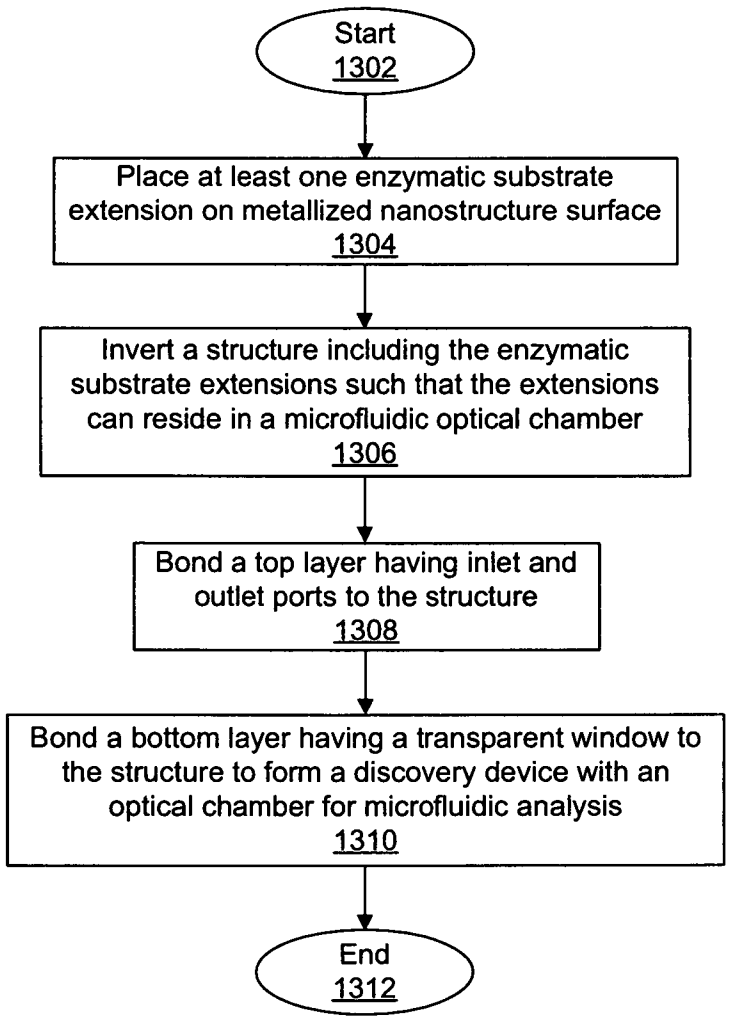
Start
1302
Place at least one enzymatic substrate extension on metallized nanostructure surface
1304
Invert a structure including the enzymatic substrate extensions such that the extensions can reside in a microfluidic optical chamber
1306
Bond a top layer having inlet and outlet ports to the structure
1308
Bond a bottom layer having a transparent window to the structure to form a discovery device with an optical chamber for microfluidic analysis
1310
End
1312

FIG. 13

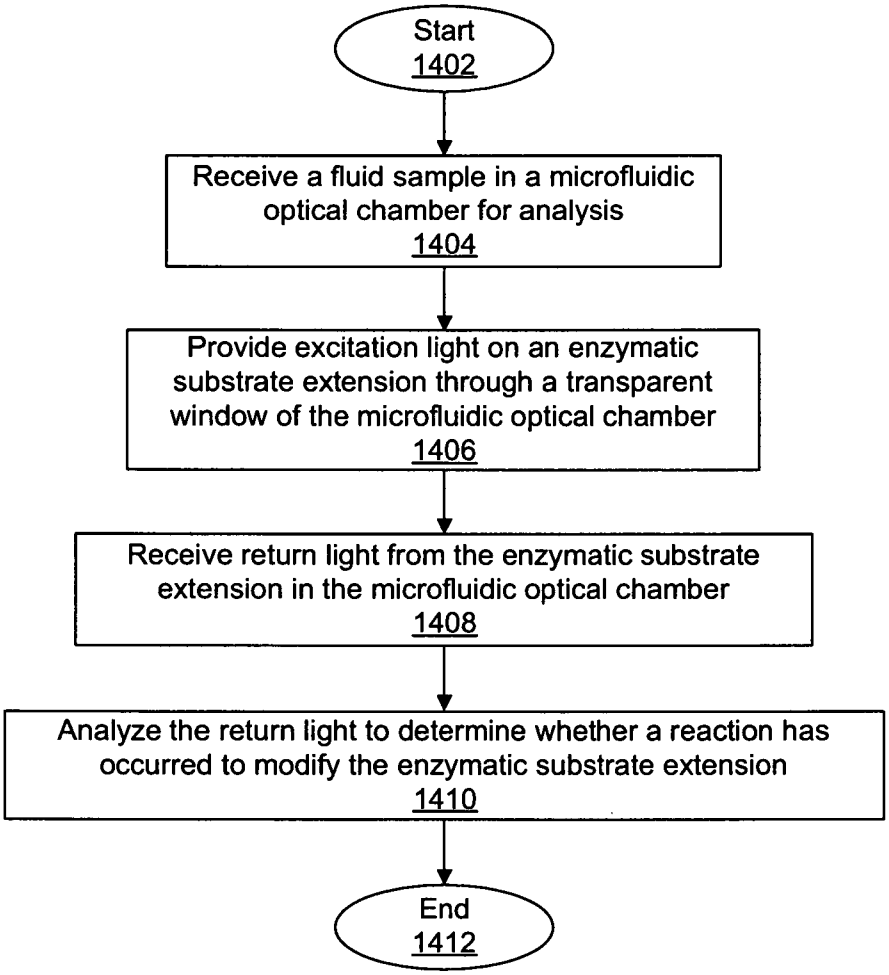
Start
1402
Receive a fluid sample in a microfluidic optical chamber for analysis
1404
Provide excitation light on an enzymatic substrate extension through a transparent window of the microfluidic optical chamber
1406
Receive return light from the enzymatic substrate extension in the microfluidic optical chamber
1408
Analyze the return light to determine whether a reaction has occurred to modify the enzymatic substrate extension
1410
End
1412

FIG. 14

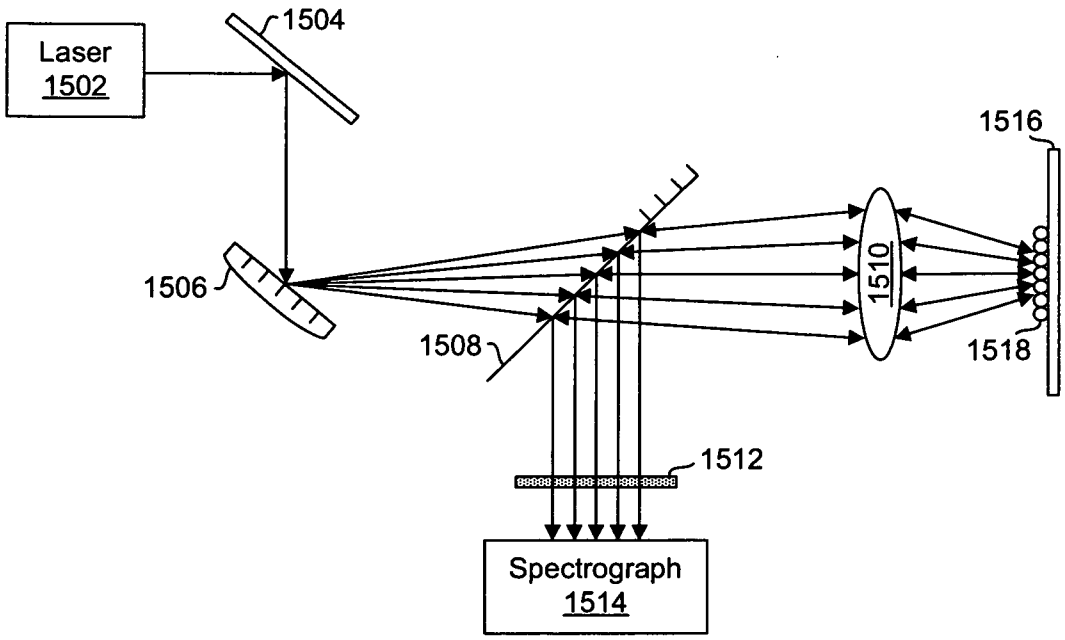
Laser
1502
1504
1506
1508
1510
1512
1514
Spectrograph
1516
1518

FIG. 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/12369

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01J 3/44 (2009.01)
USPC - 356/301
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 356/301

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 356/300, 301, 303, 319, 324; 250/339.7, 336.1; 359/333, 334, 337.2, 346(text searched)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Google Scholar
Search Terms - spectrometer, enzymatic, chamber, laser, step, motor, laser, nanopyramid, nanoparticle, DLP, polypeptide, nucleic acid, polysaccharide, phosphorylation, dephosphorylation, cleavage, SERS, protein, kinase, antibody, polycrystalline, microfluidic, via, photoresist

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2004/0005582 A1 (Shipwash) 08 January 2004 (08.01.2004), entire document, especially Figure 8 and para [0199], [0298], [0421]	1, 3, 4, 6, 8-11, and 18 --- 2, 5, 7, 12, 13, 19, and 20
X -- Y	US 2007/0105339 A1 (Faris) 10 May 2007 (10.05.2007), entire document, especially Abstract, para [0008], [0155], [0180], [0314]	14, 15, and 17 --- 16
X -- Y	US 2005/0244863 A1 (Mir) 03 November 2005 (03.11.2005), entire document, especially Abstract, [0315], [0325], [0545]	21-28 --- 29
Y	US 2004/0095579 A1 (Bisson et al.) 20 May 2004 (20.05.2004), entire document, especially para [0039]	2 and 20
Y	US 2006/0084792 A1 (Paavola et al.) 20 April 2006 (20.04.2006), entire document, especially para [0270] and [0277]	5 and 19
Y	US 2005/0018201 A1 (de Boer et al.) 27 January 2005 (27.01.2005), entire document, especially para [0107]	7
Y	US 2006/0046277 A1 (Belyaev et al.) 02 March 2006 (02.03.2006), entire document, especially para [0099]	12
Y	US 2004/0033525 A1 (Monforte et al.) 19 February 2004 (19.02.2004), entire document, especially para [0126]	13

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
09 January 2009 (09.01.2009)	28 JAN 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/12369

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0189044 A1 (Shah et al.) 24 August 2006 (24.08.2006), entire document, especially para [0026]	16
Y	US 2006/0115536 A1 (Yacaman et al.) 1 June 2006 (1.06.2006), entire document, especially para [0036]	29