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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2012 (22.03.2012)

PCT

(10) International Publication Number
WO 2012/036697 A1

(51) International Patent Classification:
A61B 5/04 (2006.01) *A61K 50/00* (2006.01)
A61B 19/00 (2006.01) *A61K 9/00* (2006.01)
A61K 49/00 (2006.01)

(21) International Application Number:
PCT/US2010/049298

(22) International Filing Date:
17 September 2010 (17.09.2010)

(25) Filing Language: English

(26) Publication Language: English

(72) Inventors; and
(71) Applicants : **YU, Chris, Chang** [US/US]; 4369 State Highway 198, Conneautville, PA 16406 (US). **YU, He** [US/US]; 141 Towpath Lane, Cheshire, CT 06410 (US).

(74) Agent: **RAO, Weisun**; Miller, Canfield, Paddock and Stone, 225 W. Washington, Suite 2600, Chicago, IL 60606 (US).

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

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

Published:
— *with international search report (Art. 21(3))*

(54) **Title**: MICRO DEVICES BIOMEDICAL APPLICATIONS AND USES OF THE SAME

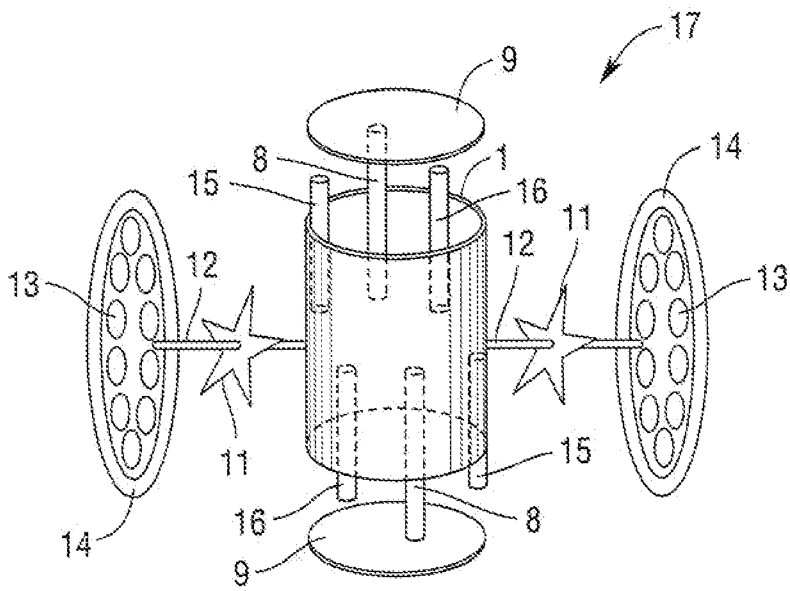


Fig.3

(57) **Abstract**: The present invention provide micro devices for biological applications and methods of using them, wherein each micro device comprises an oater membrane and a property and has a size ranging from approximately 1 angstrom to no greater than approximately millimeters.

WO 2012/036697 A1

MICRO DEVICES FOR BIOMEDICAL APPLICATIONS AND USES OF THE SAME

Background of the Invention

While in the last one to two decades, noted progresses have been made in the area of medicine and biology, particularly in genomics, the conventional approach to modern medicine, including prevention, diagnosis and treatment of diseases such as cancer, has fundamentally remained the same, and it is still mainly focused on macroscopic methodologies. For example, current diagnosis of disease techniques use macroscopic data and information such as temperature, blood pressure, scanned images, measured chemical component levels in the body, etc. Even the effectiveness of newly emerged DNA tests in diagnosing a wide range of diseases in a real-time, reliable, accurate, rapid, and cost efficient manner has not been established. Many diseases with great morbidity and mortality, including cancer and heart disease, are very difficult to diagnose early and accurately. Further, most of the existing diagnosis techniques are invasive.

Relating to disease treatment, the situation is even worse. To date, many operations are still highly invasive, have a high cost, carry a high risk of complications and require a long recuperation time. Some treatments are even destructive of healthy cells or tissue. One such example would be cancer treatment using radiation, which kills not only cancer cells; but normal, healthy cells. Another example would be blood related disease treatment which is often intrusive, risky (e.g., open heart surgery), highly expensive and in many cases, post surgical patients will not be able to return to a normal active life style.

On the prevention side of the equation, beside the general guidelines of eating healthy and exercising regularly, the cause of many diseases, such as cancer, are still unknown at this point. This lack of knowledge relating to disease etiologies directly leads to a lack of preventative drug development.

Most of the above stated issues in prevention, diagnosis, and treatment in modern medicine are, to a large extent, due to, e.g., lack of understanding of pathology at the microscopic level (cell biology level), lack of effective drug delivery and efficient reaction mechanisms, lack of non-invasive monitoring at the microscopic level as well as preventive mechanisms and approaches, and lack of non invasive, effective, targeted disease treatment approaches and technologies.

In recent years, there have been some efforts in the areas of using nano technologies for biological applications, mostly for use *in vitro* (outside the body). This in vitro work has lead to moderate developments in the field. Pantel et al. discussed the use of a micro electromechanical (MEMS) sensor for detecting cancer cells in blood and bone marrow in vitro. See Klaus Pantel et al., *Nature Reviews*, 2008, 8, 329. Wozniak and Chen used laser tweezers and micro needles for measuring forces generated by sample cells. See M.A. Wozniak et al., *Nature Reviews*, 2009, 10, 34. Kubena et al. discussed in US Patent No. 6,922,118, the deployment of MEMS for detecting biological agents, while Weissman et al. discussed in US Patent No. 6,330,885, utilizing MEMS sensor for detecting accretion of biological matter.

Due to the above stated limitations, at the fundamental level, many issues facing modern medicine remain unsolved, including sensing at the microscopic level *in vivo* targeted treatments, cancer prevention, early detection and non invasive treatment with minimum damage to normal tissues and organs. However, to date, most of the publications have been limited to isolated examples for sensing *in vitro*, using systems of relatively simple constructions and large dimensions and often with limited functions. There is no report of highly integrated, multi functional, micro devices (less than or equal to 5 millimeters) for advanced biomedical applications, particularly for applications *in vivo* (inside the body) and at the microscopic level.

Summary of the Invention

The present invention generally relates to novel micro devices, and use thereof, for carrying out disease prevention, diagnosis, or treatment at microscopic levels, using a wide range of novel functions achieved through their functionality integration at the microscopic level and using the state of the art micro device fabrication techniques such as integrated circuit fabrication techniques. Other fabrication techniques that may be suitable include, but are not limited to, mechanical, chemical, chemical mechanical, electro-chemical-mechanical, electro-bio-chemical-mechanical, bio-chemical, bio-chemical mechanical, optical, opto-electrical, opto-electro-mechanical, thermal chemical, thermal mechanical, thermal chemical mechanical, and integrated circuit and semiconductor manufacturing techniques and processes.

In one class of applications, a micro device includes multiple components, with each component typically of miniaturized sizes on the order of sub-biological cell to typical full biological cell sizes (or from one micron to a few hundred microns). Multiple components of diverse functions can be integrated onto a single micro device to perform a range of functions including, e.g., disease detection, treatment, and cleaning, typically at a microscopic level.

Depending upon the intended application, the micro device of or used in the present invention can have a size ranging from 1 angstrom to 5 millimeters. Micro device functionalities would include sensing, detecting, measuring, diagnosing, monitoring, analyzing, drug delivering, selective absorption, selective adsorption, carrying out preventive procedures and surgical intervention, or any of their combinations.

In one aspect, the present invention provides micro devices for medical applications or applications in live biological systems.

In some embodiments, each device comprising an outer membrane and a property selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro-bio-chemical, micro-bio-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro-electro-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, and micro superconducting mechanical properties; and the micro device has a size ranging from approximately 1 angstrom to approximately 5 millimeters. For instance, a micro device with a micro mechanical property can also be called a mechanical device and generally means that the micro device performs an intended function due to this mechanical property. In some examples of these embodiments, the micro devices includes two properties selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, and micro superconducting mechanical properties. In some other examples, the micro devices may further include a property selected from the group consisting of charged surface, chemical potential, geometrical matching, electro-magnetic, and electro-chemical potential related attraction. The one or more additional properties may allow for adsorption of the micro device onto a targeted biological organ or cell structure surfaces.

In some embodiments, the micro devices may be capable of differentiating cancer cells from normal cells. They may perform this function, e.g., by measuring microscopic properties of cells, including but not limited to, biochemical, physical, electrical, electro-magnetic, bio-chemical, mechanical, acoustical, thermal, and optical properties.

In some embodiments, the micro devices may be capable of measuring microscopic properties of organ and cell structures (e.g., for having a detection probe), diagnosing organ and cell structures at a microscopic level, delivering desired chemistry to organ and cell structures at a microscopic level (e.g., for having a micro-injector or micro-container with delivery capabilities), delivering desired drug to organ and cell structures at a microscopic level, and manipulating selected organ and cell structure at a microscopic level. The micro devices may perform an intended function in a non invasive manner, or in real time.

In some embodiments, the micro devices may be capable of measuring at least one property selected from the group consisting of surface charge, resting potential, electro-chemical potential, electrical potential, surface wettability, contact angle, adhesion, temperature, density, friction, hardness, surface tension, trace chemical concentration, hydrophobic level, hydrophilic level, pH, liquid flow rate, pressure, optical properties, absorption, adsorption, and composition.

The micro devices of this invention may include a GPS, a signal transmitter, a signal receiver, a micro-motorizer, a micro-propeller, or a radio frequency (RF) communication chip. As such, the micro devices may be capable of local positioning, location identification, location information communication and location positioning.

In some other embodiments, the micro devices may further comprises a function selected from the group consisting of chemistry delivery function, controlled chemistry delivery function, mechanical action, controlled mechanical action, selective absorption, selective adsorption, detection at microscopic level, timed electro mechanical action, controlled electro mechanical action, controlled electro-chemical-mechanical action, controlled electro-biological action, controlled electro-chemical-biological action, controlled electro-chemical-biological action, controlled electro-chemical-biological-mechanical action, triggered action based upon detected signal and triggered action based upon external instruction. Such function may be a result of a property possessed by the micro device or a specific subunit of the micro device.

In some other embodiments, the micro devices may have a pre-programmed trigger function for actions selected from the group consisting of: chemistry delivery, mechanical force action, charge injection, light emitting, voltage application, cooling and heating onto organic structures. Such function may be programmed into an on-device chip which has memory and logic functions and may be triggered, e.g., when a sensed signal or a response has reached a pre-set value, an action or set of actions are initiated and taken. In some instance, the trigger function may be achieved by the employment from a group of parameters selected from the group consisting: charge, resting potential, electrical potential, electro-chemical potential, surface current, bulk current, surface wettability, adhesion property, hydrophobic level, hydrophilic level, flow property, electrical field, magnetic field, acoustic field, temperature, light wavelength and/or intensity, frictional force and coefficient, hardness, pressure, and external signal detected by the device.

In some embodiments, the micro devices may has a dissolution capability at a targeted pH range (e.g., from 6 to 8 or from 6.8 to 7.4) between 30 seconds and three (3) days. It means that the micro devices may dissolve in that targeted pH range within that time period.

In some embodiments, the micro device includes a material selected from the group consisting of polymer, organic, and inorganic materials relatively compatible with organic systems. The term "relatively compatible" means that the material is generally biocompatible with a mammal body and does not cause infection, disorder, discomfort, and other negative effects (such as immunogenic effect). The micro devices can be fabricated using a biomaterial, or a biomaterial in combination with another material, or they can be interfaced or coated with a biomaterial. Biomaterials can include naturally occurring materials, synthesized materials, or composite of naturally occurring materials (including autograft, allograft or xenograft) and synthesized materials. Examples of such materials include, but are not limited to, silicon and silicon dioxide, polysilicon, silicon nitride, silicon oxynitride, carbon oxide, and carbon nitride, polymers used in IC device packaging (which are expected to be compatible due to their inertness), lipids, peptides, hydroxyapatite (HA), calcium phosphate, calcium carbonate, magnesium phosphate, ammonium phosphate, silicates, and nautilus shell.

In some embodiments, the micro devices can have a size ranging from about 1 angstrom to about 100 millimeters (e.g., for cell structure, DNA, or bacteria related applications, for human cell tests and analysis), from about 1 angstrom to about 100 microns (e.g., for selective attachment applications), from about 0.01 micron to about 5 millimeters, from about 10 microns to about 2 millimeters, or from about 100 microns to about 1.5 millimeters.

In some embodiments, the micro devices include one material with multiple sub-devices integrated onto one unit with one or more functionalities. Examples of a suitable material include, but are not limited to, organic polymers, organic materials, biological materials, biochemical materials, inorganic conductors, inorganic semi conductors, inorganic insulators and ceramics. Examples of a suitable biological material include, but are not limited to, artificial biological materials, natural biological materials, cultured biological materials, and combinations of natural biological materials and artificial biological materials.

In some embodiments, the micro device is an integrated micro device including at least one function selected from the group consisting of: sensing, detecting, measuring, calculating, analyzing, diagnosing, logic processing (decision making), transmitting, and operating or surgical functions.

In some other embodiments, the micro devices further include a hardware selected from a group consisting of voltage comparator, four point probe, calculator, logic circuitry, memory unit, micro cutter, micro hammer, micro shield, micro dye, micro pin, micro knife, micro needle, micro thread holder, micro tweezers, micro optical absorber, micro mirror, micro shield, micro wheeler, micro filter, micro chopper, micro shredder, micro pumps, micro absorber, micro signal detector, micro driller, micro sucker, micro tester, micro container, micro-puller, signal transmitter, signal generator, friction sensor, electrical charge sensor, temperature sensor, hardness detector, acoustic wave generator, optical wave generator, heat generator, micro refrigerator, and charge generator. These terms are well known in the art and their general definitions apply to this invention. For instance, a filter can be a micro device (or sub micro device) which can separate various components by their sizes; a cleaner can be a micro device capable of washing, polishing, rubbing, and brushing an intended surface; a pump can be a micro device that can transport intended item from one location from the other; and a shredder can be a micro device with blades and sharp edges capable of making a larger item into smaller pieces. In some further embodiments, the micro devices include a cleaner, a filter, a shredder, an injector, and a pump; a cleaner, a filter, a shredder, and an injector; a polishing unit with a polishing pad; or a sensor, a micro tip for sample collection, a micro array for testing collected sample, a data analysis unit, and a signal transmitter.

In some embodiments, the micro devices can function be micro testers for continued scan and analysis of live biological system for early disease detection and prevention.

Alternatively, the micro devices can be for *in vitro* applications outside a biological system, include an outer membrane and one or more properties selected from the group consisting of: micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, and micro superconducting mechanical properties; and have a size ranging from approximately 1 angstrom to approximately 5 millimeters.

The micro devices can also be used for medical applications such as artery cleaning and early cancer detection and prevention *in vivo*.

Accordingly, the invention also provides methods of using a micro device of this invention for cleaning a biological material. Each method include rising the step of contacting the micro device with the biological material, wherein the micro device comprises an outer membrane and a property selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro-bio-chemical, micro-bio-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro-electro-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, and micro superconducting mechanical properties; and the micro device has a size ranging from approximately 1 angstrom to approximately 5 millimeters. Examples of the biological material to be cleaned include, but are not limited to a vein or artery in a mammal. The cleaning can be carried out, e.g., by mechanical polishing, mechanical rubbing, chemical mechanical polishing, chemical dissolution, chemical passivation, chemical treatments, biological treatments, polishing with chemical dissolution, laser oblation, or a combination thereof.

In some embodiments, the method of claim 38 further include the steps of delivering the micro device to the general area of the biological material; optionally measuring the local temperature, local pressure, local frictional force, local surface charge, local resting potential, local electrical potential, local surface property, local composition, or local fluid flow rate; optionally triggering the cleaning function; performing cleaning; optionally collecting debris from cleaning by a micro collector and transporting the debris away; and optionally collecting debris by a micro-filter and transporting the debris away.

In some other embodiments, the method further include the steps of delivering a micro device into the veins; optionally sensing and analyzing data being collected, for instance local pressure; optionally triggering cleaning functions when the targeted blood vein location is reached; cleaning plaque and deposits from the vein wall at the targeted location; optionally injecting desired chemistry into the blockage to be cleaned to soften the plaque being cleaned, avoid formation of large debris from breakage from plaque, and minimize possible damage to the veins; optionally dissolving the micro device following completion of cleaning or filtered out via blood filtration; optionally filtering of the micro device and debris via blood filtration during and following completion of cleaning; and optionally carrying out post-cleaning treatments by the micro device.

Still another aspect of this invention provides methods for delivering multiple doses of drug to a target location *in vivo*, each including the steps of transportation of a micro device to the target location; delivering the first drug to the target location; and delivering a second dose of the drug to the target location within a desired time interval from the delivery time of the initial delivery, wherein the micro device comprises an outer membrane and a property selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro-bio-chemical, micro-bio-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro-electro-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, and micro superconducting mechanical properties; and the micro device has a size ranging from approximately 1 angstrom to approximately 5 millimeters.

In some embodiments, each dose delivers a different drug from another dose. In some other embodiments, the drugs are of different chemistries and delivering of a first drug enhances the attachment selectivity to the second drug.

Alternatively, the invention also provides methods of using a micro device for a medical purpose, wherein the micro device comprises an outer membrane and a property selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro-bio-chemical, micro-bio-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro-electro-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, and micro superconducting mechanical properties; the micro device has a size ranging from approximately 1 angstrom to approximately 5 millimeters; and the medical purpose is selected from the group consisting of: drug delivery, cutting, removing, polishing, transporting, jointing, diagnosing, sensing, selective protection, targeted removing, measuring, treatment of cancer or blood related diseases, and assisting medical treatment functions at cell structure or micro-organ level in a target area (up to about 500 micron scale).

In some embodiments, the method is for cancer treatment and includes the steps of: selectively attaching micro devices with drug delivery functions onto cancer cells; triggering injection function in the micro devices; and injecting drug into cancer cells. Alternatively, the method can include the steps of: selectively attaching micro devices with high optical reflectivity onto healthy cells; carrying out laser treatment to destroy unhealthy cells; and removing unhealthy cells in the treatment due to exposure to the laser.

In some embodiments, the micro device used for these methods can include a property selected from the group consisting of signal sensing unit, memory unit, logic processing unit, signal transmitter, and micro surgery; the micro device performs the function of diagnosing, sensing, or measuring; and the method can include the steps of delivering the micro device to a targeted measuring site; performing measurement on the targeted site; recording data in memory unit; optionally triggering operations using the logic processing function; optionally carrying out surgery using the micro device; retrieving the micro device; and analyzing the recorded data.

In some other embodiments, the micro device can perform the function of diagnosing, sensing, or measuring a target site; the micro device includes a signal sensing unit, a memory unit, a signal transmitter, a logic unit for on site decision making and micro surgery; and the method includes the steps of delivering the micro device to the target site and performing the diagnosing, sensing, or measuring function on the target site; recording data in memory unit; analyzing the data performed by the micro device; deciding the course and type of micro operations based on data analysis and pre programmed logic decisions by the micro device; and performing micro operations on the target site.

In still some other embodiments, the micro devices include an electric property measurement unit and is capable of detecting cancer cells in a target site; and the method comprises the steps of: delivering the micro device to the target site; measuring on the target site one or more properties selected from the group consisting of: surface charge, charge density, resting potential, electrical potential, electro-chemical potential, surface current, bulk current, and current density. They may further include a voltage comparator, which, e.g., has voltage measurement sensitivity better than 1 mV.

In some other embodiments, the methods can be used for cancer cell detection in a target site and include the steps of: delivering the micro device to the target site; and measuring on the target site one or more parameters selected from the group consisting of: surface charge, resting potential, electro-chemical potential, electrical potential, surface current, bulk current, surface wettability, contact angle, adhesion properties, temperature, density, friction, hardness, surface tension, trace chemical concentration, pH, liquid flow rate, pressure, optical properties, absorption, adsorption, and composition.

The micro devices of this invention can be fabricated by methods known in the art, e.g., one or more methods selected from the group consisting of integrated circuit manufacturing method, semiconductor manufacturing method, mechanical manufacturing method, chemistry processing method, synthesis method, electro chemistry processing method, biological processing method, bio-chemical processing method, mechanical manufacturing method, and laser processing method.

Thus, another aspect of the present invention is the use of micro devices for obtaining real time data and information at the cell structure level in a non-invasive manner, such as using a micro voltage comparator, four-point probe and other circuitry designs to measure cell surface charge. The cell surface charge differentiation can be an important factor in deciding the healthy or unhealthy status of a cell and, if necessary, the proper treatment thereof. One example would be the use of such devices for measuring surface and/or bulk electrical properties including resting potential and surface charge for differentiating normal cells and cancer cells.

Yet another aspect of the present invention is the use of a micro device to deliver drugs to targeted locations within the human body and with differentiation between healthy cells and unhealthy (cancer, for instance) cells. This can be achieved through selective absorption or adsorption of a micro device onto healthy or unhealthy cells (such as cancer cells). For example, to remove a part of an unhealthy organ with laser surgery, micro devices with high optical reflectivity can be used to selectively adsorb onto healthy cells, thereby protecting good cells from being removed and/or ablated via laser treatment.

As used herein, the term "or" is meant to include both "and" and "or."

As used herein, a term consisting of the word "a" or "one" and a single noun, includes the meaning of the noun in its plurality.

As used herein, a "micro device" or "micro device" can be any of a wide range of materials, properties, shapes, degree of complexity and integration, or their combination as appropriate. The term has a general meaning for an application from a single material to a very complex device comprising multiple materials with multiple sub units and multiple functions.

The complexity contemplated in the present invention ranges from a very small, single particle with a set of desired properties to a fairly complicated, integrated unit with various functional units contained therein. For example, a simple micro device could be a single spherical article of manufacture of a diameter as small as 100 angstroms with a desired hardness, a desired surface charge, or a desired organic chemistry absorbed on its surface. A more complex micro device could be a 1 millimeter device with a sensor, a simple calculator, a memory unit, a logic unit, and a cutter all integrated onto it. In the former case, the particle can be formed via a fumed or colloidal precipitation process, while the device with various components integrated onto it can be fabricated using various integrated circuit manufacturing processes.

A micro device of or used in the present invention can range in size (e.g., diameter) from on the order of about 1 angstrom to on the order of about 5 millimeters. For instance, a micro device ranging in size from on the order of about 10 angstroms to on the order of 100 microns can be used in this invention for targeting biological molecules, entities or compositions of small sizes such as cell structures, DNA, and bacteria. Or, a micro device ranging in size from on the order of about one micron to the order of about 5 millimeters can be used in the present invention for targeting relatively large biological matters such as a portion of a human organ. As an example, a simple micro device defined in the present application can be a single particle of a diameter less than 100 angstroms, with desired surface properties (e.g., with surface charge or a chemical coating) for preferential absorption or adsorption into a targeted type of cell.

The word "absorption" typically means a physical bonding between the surface and the material attached to it (absorbed onto it, in this case). On the other hand, the word "adsorption" generally means a stronger, chemical bonding between the two. These properties are very important for the present invention as they can be effectively used for targeted attachment by desired micro devices for (a) measurement at the microscopic level, (b) targeted removal of unhealthy cells, and (c) protection of healthy cells during a treatment such as laser surgery.

As used herein, the term "chemistry" generally refers to a chemical material of certain activities(e.g., a large or small compound) or a compound that may react with a substance in the target delivery area).

Through novel micro devices, their novel combinations and integrations, and integrated operating process flow, many issues in today's medicine can be solved. In particular, with the present invention, a micro device can be used in "cleaning" biological organs, e.g., cleaning veins to prevent heart attack, strokes and blood clogging due to plaques and fatty deposits in the veins.

Brief Description of the Drawings

Fig. 1 is a perspective view of a micro device that can act as a micro injector showing the micro device before and then after the injection process has completed.

Fig. 2 is a perspective view of a micro device that acts as a micro polisher.

Fig. 3 is a perspective view of a micro device that acts as a micro polisher, a micro-filter, a micro injector, a micro sensor and micro shredder.

Fig. 4 is a perspective view of a micro device that acts as a micro knife.

Fig. 5 is a perspective view of a micro device that acts as a micro filter.

Fig. 6 is a perspective view of a micro device that acts as a micro shield.

Fig. 7 is a perspective view of a micro device in a blood vessel as it nears a plaque in the vessel wall.

Fig. 8 is a perspective view of a micro device in a blood vessel as it senses a change in pressure around a plaque, triggering the micro device's cleaning function.

Fig. 9 is a perspective view of a micro device in a blood vessel after the device has cleaned a plaque from the vessel wall.

Fig. 10 is a perspective close up view of a group of healthy cells and a group of unhealthy, cancerous cells.

Fig. 11 is a perspective close up view of a group of healthy cells and a group of unhealthy, cancerous cells with micro devices acting as a voltage comparator on both sets of cells.

Fig. 12 is a perspective close up view of a group of healthy cells and a group of unhealthy, cancerous cells.

Fig. 13 is a perspective close up view of a group of healthy cells and a group of unhealthy, cancerous cells with micro devices either adsorbed or absorbed onto the healthy cells only.

Fig. 14 is a perspective close up view of an integrated micro device with various sub-units being a micro-cutter, a micro-needle, a memory unit, a unit for analysis and logic processing, a micro-sensor and a signal transmitter.

Fig. 15 is a perspective view of a micro device with a sensing unit, logic unit and micro-injector.

Detailed Description of the Invention

The present invention provides novel micro devices for biological applications, which are expected to resolve a number of critical issues in the modern approach to medicine. These issues include lacks of, e.g., understanding in pathology and prevention for a number of deadly diseases; non invasive, microscopic and effective diagnosis of various disease states; and an effective and targeted drug delivery system and treatment for deadly diseases such as cancer.

A micro device of the present invention can range in size from about 1 angstrom to about 5 millimeters (e.g., from about 1 angstrom to about 100 microns; or from about 100 microns to 5 millimeters). A smaller micro device (e.g., from about 1 angstrom to about 100 microns) can be used for sensing, measuring, and diagnostic purposes, particularly for obtaining information and data at the cell structure level or molecular (e.g., DNA, RNA, or protein) level; whereas a larger micro device (e.g., from about 100 microns to about 5 millimeters) can be used in mechanical or surgical operations of a human organ or a human tissue except for manipulation at the cell structure level.

As stated herein, the general term "micro device" can mean a wide range of materials, properties, shapes, degree of complexity and integration, or combination thereof. The complexity contemplated in the present invention ranges from a very small, single particle with a set of desired properties to a fairly complicated, integrated unit comprising various functional subunits. For example, a simple micro device could be a single spherical article of manufacture of a diameter as small as 100 angstroms with a desired hardness, a desired surface charge, or a desired organic chemistry absorbed on its surface. A more complex micro device could be a 1 millimeter device with a sensor, a simple calculator, a memory unit, a logic unit, and a cutter all integrated onto it. In the former case, the particle can be formed, e.g., by a fumed or colloidal precipitation process, while the device with various components integrated onto it can be fabricated using various integrated circuit manufacturing processes.

The micro devices of the present invention can have a wide range of designs, structures and functionalities. They include, e.g., a voltage comparator, a four point probe, a calculator, a logic circuitry, a memory unit, a micro cutter, a micro hammer, a micro shield, a micro dye, a micro pin, a micro knife, a micro needle, a micro thread holder, micro tweezers, a micro optical absorber, a micro mirror, a micro wheeler, a micro filter, a micro chopper, a micro shredder, micro pumps, a micro absorber, a micro signal detector, a micro driller, a micro sucker, a micro tester, a micro container, a signal transmitter, a signal generator, a friction sensor, an electrical charge sensor, a temperature sensor, a hardness detector, an acoustic wave generator, an optical wave generator, a heat generator, a micro refrigerator, and a charge generator.

As disclosed herein, the range of functionalities and applications using the micro devices can be made extremely powerful due to their diverse properties, high degree of flexibility, and ability of integration and miniaturization.

Further, it should be noted that advancements in manufacturing technologies have now made it highly feasible and cost effective to fabricate a wide range of micro devices and integrate various functions onto a micro device. The typical human cell size is about 10 microns. Using the state of the art integrated circuit fabrication techniques, the minimum feature size defined on a micro device can be as small as 0.1 micron. Thus, the micro devices of this invention are ideal for biological applications.

In terms of materials for the micro devices, the general principle will be a material's compatibility with biological materials. Since the time in contact with a biological material (e.g., biological molecules such as DNA, RNA, or protein; cell; a group of cells; tissue; or organ) may vary, depending on its applications, different materials may be selected for fabricating the micro devices of this invention or any subunits thereof. In some cases, the materials may dissolve in a given pH in a controlled manner and thus may be selected as an appropriate material. Other considerations include cost, simplicity, ease of use, and practicality. With the significant advancements in micro fabrication technologies such as integrated circuit manufacturing technology, highly integrated devices with minimum feature size as small as 0.1 micron can now be made cost effectively and commercially. One example is the design and fabrication of micro electro mechanical devices (MEMS), which now are being used in a wide variety of applications in the integrated circuit industry.

The following sections include several examples of the use of various types of micro devices of the present invention that can be used for novel biological applications.

Sensing, Measuring, and Diagnosis

It is believed that before the present invention, there had been no probe to measure microscopic properties, in real time, at the cellular level in living organs (*in vivo*). The novel micro devices provided by the present invention can measure cell properties in living organs. It is expected that the information from the measurement can be retrieved in real time for use as a diagnostic tool.

For example, a micro device of this invention can be utilized to detect a cancer cell in a living organ in a non invasive manner. Fig. 10 illustrates an area in the human body with a number of healthy (or normal) cells "**a**" **39** and a number of unhealthy (or abnormal) cells "**b**" **40**. The electrical properties such as electrical charge and resting potential of healthy cells "**a**" **39** are different from those of unhealthy cells "**b**" **40**. First, the micro device with a voltage comparator is calibrated by measuring surface charge (or voltage) at known healthy cells. Next, as shown in Fig. 11, for an area containing both healthy cells **39** and unhealthy cells **40**, a micro device **41** with voltage comparators **42** is used to scan the area. By comparing voltages at the cell surface (the difference in charges or potential), unhealthy cells **40** can readily be differentiated from the healthy cells **39**. Such micro devices **41** can be easily extended to perform functions of identifying, measuring and treating of cancer cell by integrating a voltage comparator, a logic circuitry unit, and a micro injector (needle) which can deliver, e.g., cancer killing agents specifically to a cancer cell.

Drug Delivery

To date, many cancer treatment drugs have not shown their expected promising results in human trials, even though laboratory tests on mice may have been successful. It is believed that there may be major problems relating to the successful and effective drug delivery to the targeted cancer cells. Since such drugs are often taken in pill form or by injection into the body, there may be serious issues in the drug reaching the targeted cancer sites. Even if a drug can reach its targeted site, its strength (concentration) and chemical composition may have been altered, rendering it either partially or entirely ineffective. An increase in the amount of drug delivered in this fashion will increase side effects and possibly cause an increase in mortality.

In the present invention, the novel, effective and targeted drug delivery system hopes to correct the above stated problems. As shown in Fig. 15, a micro device **64** with a sensing unit **62**, a logic unit **63** and a micro injector **61** is utilized. The micro device **64** is designed in a way that it will preferentially absorb (or adsorb) only onto unhealthy cells. Alternatively, the sensor **62** can detect unhealthy cells through measurements of desired physical, chemical, electrical and biological properties of cells being scanned and attached onto detected unhealthy cells. Once the micro device **64** is attached to the unhealthy cell, it will inject one or more cancer killing agents into the cancer cell through a micro-injector **61**. To make sure that healthy cells are not injected due to error in attachment, a logic unit **63** may be used to make a correct decision based on the sensor data received by the sensing unit **62** from the attached cell. Since this approach is a targeted approach with a cancer killing drug directly delivered to the unhealthy cells, it is expected that its effectiveness can be greatly improved over the standard therapies that are used conventionally for the current treatment of cancer.

Cleaning

Another major area of focus for this invention is a novel type of micro device for biological "cleaning" purposes, in particular, for the "cleaning" of human arteries and veins. Fig. 7 illustrates a blood vessel wall **30**, a micro device **32** traveling in a direction **33**, a blood clot **36**, lower blood pressure P1 **34** and a lower blood pressure P2 **35**. In this type of applications, the present invention is a micro device **32** with at least one cleaner attached thereto. A more complete micro device will be comprised of at least one sensor, one cleaner, one micro filter, one injector, one shredder and one pump.

As shown in Fig. 8, a micro device **32** with integrated functions of sensing (for local pressure measurement) and cleaning **37** can be used for arteries and vein cleaning applications. In this case, local pressure is higher where a plaque **36** is located at P2 **35** within the blood vessel wall **30**. The device is moving within the vessel walls **30** in direction **33** toward the plaque **36**. The device **32** senses this increase in local pressure as it approaches the plaque, triggering the cleaning function **37** to be deployed.

Fig. 9 illustrates the blood vessel wall **30** after the micro device **32** with cleaning function **37** has cleaned the plaque from an area **38** within the blood vessel wall **30**. This is just one of the many examples where a micro device disclosed in this application can be used as a "smart" device for biological applications in a non invasive, real time manner.

In Fig. 3, a more refined micro device **17** is disclosed, which is comprised of cleaner arms **8** and cleaners **9**, sensors **15**, micro filters **13** and 14, micro shredders **11**, and micro injectors **16**. This design is aimed to facilitate the cleaning process and to make sure that cleaning debris is reduced to much smaller pieces so that it is completely removed and will not cause a clot in other areas of the human body. The cleaner typically has a polishing or rubbing capability, while filters are used to filter debris from cleaning and prevent them from moving to other parts of the body and cause clogging problems. The injector is used to dispense a dissolution agent to dissolve the debris from the cleaner portion of the micro device; it can also deliver agents to facilitate the "cleaning" (polishing) process. A micro shredder **11** can be used to shred the relatively large debris from the cleaning (if any) activity. More specifically, the cleaning unit can be a polishing pad **9** made of polymer material(s) with desired roughness for polishing or rubbing. To reduce mechanical force and avoid breakage of the plaque into large pieces, a polishing solution can be applied at the point of micro polishing, with the use of an injector **16**. In a preferred method, the plaque is polished off in a layer-by-layer (a few mono layers of about 10 angstroms in thickness) process, with a controlled removal rate. A balanced chemical mechanical polishing process is preferred where both surface chemical reaction and mechanical abrasion is present, with the mechanical abrasion controlled to a low enough level not to cause breakage in plaque. In the meantime, micro filters **13** and **14** are used to insure that no large debris can leave the area of cleaning and causing damage to other portions of the human body. For patients with a propensity for deposits building up in their veins, cleaning using the disclosed method should be carried out on a regular basis to reduce the risks of heart attack and stroke, and to reduce the degree of difficulty in subsequent cleaning processes.

Since the diameter for major arteries is typically a few millimeters (about 2 mm to 4 mm in diameters), the size for a micro device for this type of cleaning application (for cleaning of major arteries) can range from about 10 microns to less than 2 millimeters, e.g., from about 100 microns to about 1.5 millimeters.

Targeted Treatment

The micro devices disclosed in this invention are ideally suited for targeted medical treatment to remove or destroy unhealthy cells or organ portions while minimizing damage to healthy cells or organ parts. This can be carried out with a high degree of selectivity, can be non invasive and can be done in a microscopic manner.

Fig. 12 illustrates an area in the human body with a number of healthy cells **39** and a number of unhealthy cells **40**. In Fig. 13, for use in laser surgery using an optical oblation process, healthy cells **39** are first covered with micro devices **43** (called micro shields) with a high optical reflectivity. Next, unhealthy cells 40 such as cancer cells are removed via optical oblation, while healthy cells **39** are protected by the micro shields **43**. This selective attachment of the micro-shields 43 to healthy cells is made possible through surface adsorption (or absorption) between the micro devices and healthy cells through micro device sensing process and/or desired micro device properties such as charge attraction. For example, micro devices can be designed or programmed such that they only attach to healthy cells through surface charge measurement and subsequent logic decision and action as set forth in Fig. 11 described above.

Another embodiment of the present invention for targeted treatment is the use of an integrated micro device with sensing, logic processing, and injection functions. The micro device first uses a sensing function to locate its target. The micro device then attaches itself to the target. Finally, the micro device injects cancer killing agent(s) into the cancer cell.

Micro Surgery

As disclosed herein, various micro devices capable of performing a wide range of surgical functions can be employed to accomplish specific goals. Some examples of the micro devices capable of carrying out micro surgeries are shown in Figs. 1 through 6.

Fig. 1 illustrates a micro device **6** before it is triggered and a micro device **7** after it is triggered. The device **6** is comprised of an outer membrane **1**, a sensing unit **2**, a floor **3** and an area **4** in which various agents can be held prior to triggering. The triggered device **7** has an area **5** which is empty once the floor **3** is pushed vertically to expel the contents of the area **4**. Fig. 2 illustrates a micro device **10** with a polisher/scrubber function **9** attached to an extension arm **8** outside of the outer membrane **1**. Fig. 4 illustrates a micro device **20** with an outer membrane **1**, a vertical attachment **19** with a cutting knife end **18**. Fig. 5 illustrates a micro device **25** with a top side **24**, an outer membrane **21**, a series of openings **22** in the top side **24** with the openings **22** extending through passage **23** entirely through micro device **25** to the bottom side **26**. Fig. 6 illustrates a micro device **29** having a body **27** with a reflective portion **28** attached to the top of the body **27**.

It should be emphasized that for practical surgical applications, integrated micro devices with multiple functional components and functionalities will be the preferred choices, and they will be the most effective and versatile instruments for surgeries. The clear advantages of those "smart" devices disclosed in this invention will be to carry out surgery in a minimally invasive and at a microscopic level with high precision, high selectivity, with minimum damage to healthy cells and organs.

One example of an integrated micro device includes at least one sensor, one memory unit, one logic processing unit, one signal transmitter, one signal receiver, at least one micro injector, multiple micro knives, multiple micro needles, at least one pair of micro tweezers, and at least one micro thread holder. Such integrated micro device will be capable of performing some basic surgical operations. One such example of integrated micro devices is shown in Figure 14. Fig. 14 illustrates an integrated micro device **43** with an outer membrane **44**, a sensing unit **47** attached to a sensing arm **48** linked to a memory unit **50** via pathway **49**, the memory unit **50** linked via pathway **51** to an analysis/logic unit **52** attached via pathway **46** to a signal transmitter **45**, the unit **52** attached via pathway **53** to a micro-needle unit **55** reaching externally via a needle **54** extending past the outer membrane **44** and the unit **52** attached via pathway **56** to a micro-cutter unit **57** with an extending arm **58** having a cutting end **59**.

Thus it is apparent that there has been provided, in accordance with the invention disclosed herein, a micro device for biological applications, particularly for disease detection, treatment, and prevention in live biological systems at a microscopic level, that fully meets the needs and advantages set forth herein. Although specific embodiments have been illustrated herein, it will be appreciated by those skilled in the art that any modifications and variations can be made without departing from the spirit of the invention. Therefore, it is not intended that the invention be limited by the description herein. Any combination of the micro devices disclosed in this invention and any obvious extension of the micro devices for biological applications would be covered by this invention. Additionally, any integration of disclosed micro devices for disease detection, prevention and treatment including surgical operations in live human body disclosed herein. Therefore, it is intended that this invention encompass any arrangement, which is calculated to achieve that same purpose, and all such variations and modifications as fall within the scope of the appended claims.

The reader's attention is directed to all papers and documents which are filed concurrently with this specification and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference. All the features disclosed in this specification (including any accompanying claims, abstract and drawings) may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example of a generic series of equivalent or similar features.

Any element in a claim that does not explicitly state "means for" performing a specific function, or "step for" or "step of" performing a specific function, is not to be interpreted as a "means" or "step" clause as specified in 35 U.S.C. §112 paragraph 6.

All publications referred to above are incorporated herein by reference in their entireties.

What Is Claimed Is:

1. A micro device for applications in a biological system, comprising an outer membrane and a property selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro-bio-chemical, micro-bio-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro-electro-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, micro thermal mechanical, micro thermal electrical, micro thermal electro-mechanical, and micro superconducting mechanical properties; wherein the micro device has a size ranging from approximately 1 angstrom to approximately 5 millimeters.

2. The micro device of claim 1, comprising two properties selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, micro thermal mechanical, micro thermal chemical mechanical, micro thermal electrical, micro thermal electro-mechanical, and micro superconducting mechanical properties.

3. The micro device of claim 1, further comprising a property selected from the group consisting of charged surface, electrical potential, chemical potential, geometrical matching, electro-magnetic, ion gradient, thermal gradient, surface tension, mechanical force, electro-chemical potential, and physical force related attraction.

4. The micro device of claim 1, wherein the micro device is capable of differentiating cancer cells from normal cells.

5. The micro device of claim 1, wherein the micro device is capable of measuring microscopic properties of organ and cell structures, diagnosing organ and cell structures at a microscopic level, delivering desired chemistry to organ and cell structures at a microscopic level, delivering desired drug to organ and cell structures at a microscopic level, and manipulating selected organ and cell structure at a microscopic level.

6. The micro device of claim 5, wherein the micro device performs the function in a non invasive manner.

7. The micro device of claim 5, wherein the micro device performs the function in real time.

8. The micro device of claim 5, wherein the micro device is capable of measuring at least one property selected from the group consisting of surface charge, resting potential, electro-chemical potential, electrical potential, surface wettability, contact angle, adhesion, temperature, density, friction, hardness, surface tension, trace chemical concentration, hydrophobic level, hydrophilic level, pH, liquid flow rate, pressure, optical properties, absorption, adsorption, and composition.

9. The micro device of claim 1, further comprising a global positioning system (GPS), a signal transmitter, a signal receiver, a micro-motorizer, a micro-propeller, an RF communication chip, logic circuits, and memory circuits.

10. The micro device of claim 1, further comprising a function selected from the group consisting of chemistry delivery function, controlled chemistry delivery function, mechanical action, controlled mechanical action, selective absorption, selective adsorption, detection at microscopic level, timed electro mechanical action, controlled electro mechanical action, controlled electro-chemical-mechanical action, controlled electro-biological action, controlled electro-chemical-biological action, controlled electro-chemical-biological action, controlled electro-chemical-biological-mechanical action, triggered action based upon detected signal and triggered action based upon external instruction.

11. The micro device of claim 1, wherein the micro device has a pre-programmed trigger function for actions selected from the group consisting of: chemistry delivery, mechanical force action, charge injection, light emitting, voltage application, cooling and heating onto organic structures.

12. The micro device of claim 11, wherein the trigger function is achieved by the employment from a group of parameters selected from the group consisting of: charge, resting potential, electrical potential, electro-chemical potential, surface current, bulk current, surface wettability, adhesion property, hydrophobic level, hydrophilic level, flow property, electrical field, magnetic field, acoustic field, temperature, light wavelength and/or intensity, frictional force and coefficient, hardness, pressure and external signal detected by the device.

13. The micro device of claim 1, wherein the micro device optionally has a dissolution capability at a targeted pH range between 30 seconds and 3 days.

14. The micro device of claim 1, wherein the micro device comprise a material selected from the group consisting of polymer, organic, and inorganic materials relatively compatible with organic systems.

15. The micro device of claim 1, wherein the micro device has a size ranging from about 1 angstrom to about 100 millimeters.

16. The micro device of claim 1, wherein the micro device has a size ranging from about 1 angstrom to about 100 microns.

17. The micro device of claim 1, wherein the micro device comprises one material with multiple sub-devices integrated onto one unit with at least one functionality.

18. The micro device of claim 1, further comprising a material selected from the group consisting of polymers, organic materials, biological materials, biochemical materials, inorganic conductors, inorganic semi conductors, inorganic insulators and ceramics.

19. The micro device of claim 18, wherein a biological material is selected from the group consisting of: artificial biological materials, natural biological materials, cultured biological materials, and combinations of natural biological materials and artificial biological materials.

20. The micro device of claim 17, wherein the micro device has a size ranging from about 0.01 micron to about 5 millimeters.

21. The micro device of claim 1, wherein the micro device is an integrated micro device comprising one function selected from the group consisting of: sensing, detecting, measuring, calculating, analyzing, diagnosing, logic processing (decision making), transmitting, and operating or surgical functions.

22. The micro device of claim 1, further comprising a hardware selected from a group consisting of voltage comparator, four point probe, calculator, logic circuitry, memory unit, micro cutter, micro hammer, micro shield, micro dye, micro pin, micro knife, micro needle, micro thread holder, micro tweezers, micro optical absorber, micro mirror, micro shield, micro wheeler, micro filter, micro chopper, micro shredder, micro pumps, micro absorber, micro signal detector, micro driller, micro sucker, micro tester, micro container, micro-puller, signal transmitter, signal generator, friction sensor, electrical charge sensor, temperature sensor, hardness detector, acoustic wave generator, optical wave generator, thermal mechanical device, thermal chemical mechanical device, thermal electro-mechanical device, heat generator, micro refrigerator, micro signal transmitter, micro signal receiver, and charge generator.

23. The micro device of claim 1, wherein the micro device is fabricated by a method selected from the group consisting of integrated circuit manufacturing method, semiconductor manufacturing method, mechanical manufacturing method, chemistry processing method, synthesis method, electro chemistry processing method, biological processing method, bio-chemical processing method, mechanical manufacturing method, and laser processing method.

24. The micro device of claim 1, further comprising a cleaner, a filter, a shredder, an injector, or a pump.

25. The micro device of claim 1, further comprising a cleaner, a filter, a shredder, or an injector.

26. The micro device of claim 1, further comprising a polishing unit with a polishing pad.

27. The micro device of claim 1, wherein the micro device has a size ranging from 10 microns to 2 millimeters.

28. The micro device of claim 1, wherein the micro device has a size ranging from 100 microns to 1.5 millimeters.

29. The micro device of claim 1, wherein the micro device is a micro tester for continued scan and analysis of live biological system for early disease detection and prevention.

30. The micro device of claim 1, further comprising a sensor, a micro tip for sample collection, a micro array for testing collected sample, a data analysis unit, or a signal transmitter.

31. The micro device of claim 1, wherein the micro device has a size ranging from about 1 micron to about 100 microns.

32. The micro device of claim 1, wherein the micro device has a size ranging from about 10 microns to about 5 millimeters.

33. The micro device of claim 1, wherein the micro device has a size ranging from about 2 angstroms to about 500 microns.

34. The micro device of claim 1, wherein the micro device is used for artery cleaning.

35. The micro device of claim 1, wherein the micro device is employed for early cancer detection and prevention *in vivo*.

36. A method of using a micro device for cleaning a biological material, comprising the step of contacting the micro device with the biological material, wherein the micro device comprises an outer membrane and a property selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological,

micro-bio-chemical, micro-bio-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro-electro-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, micro thermal mechanical, micro thermal chemical mechanical, micro thermal electrical, micro thermal electro-mechanical, and micro superconducting mechanical properties; and the micro device has a size ranging from approximately 1 angstrom to approximately 5 millimeters.

37. The method of claim 36, wherein the biological material is a vein or artery in a mammal.

38. The method of claim 36, further comprising the steps of: delivering the micro device to the general area of the biological material; optionally measuring the local temperature, local pressure, local frictional force, local surface charge, local resting potential, local electrical potential, local surface property, local composition, or local fluid flow rate; optionally triggering the cleaning function; performing cleaning; optionally collecting debris from cleaning by a micro collector and transporting the debris away; and optionally collecting debris by a micro-filter and transporting the debris away.

39. The method of claim 36, further comprising the steps of: delivering a micro device into the veins; optionally sensing and analyzing data being collected, for instance local pressure; optionally triggering cleaning functions when the targeted blood vein location is reached; cleaning plaque and deposits from the vein wall at the targeted location; optionally injecting desired chemistry into the blockage to be cleaned to soften the plaque being cleaned, avoid formation of large debris from breakage from plaque, and minimize possible damage to the veins; optionally dissolving the micro device following completion of cleaning or filtered out via blood filtration; optionally filtering of the micro device and debris via blood filtration during and following completion of cleaning; and optionally carrying out post-cleaning treatments by the micro device.

40. The method of claim 36, wherein the cleaning is carried out by mechanical polishing, mechanical rubbing, chemical mechanical polishing, chemical dissolution, chemical passivation, chemical treatments, biological treatments, polishing with chemical dissolution, laser oblation, or a combination thereof.

41. A method for delivering multiple doses of drug to a target location *in vivo*, comprising: transportation of a micro device to the target location; delivering the first drug to the target location; and delivering a second dose of the drug to the target location within a desired time

interval from the delivery time of the initial delivery, wherein the micro device comprises an outer membrane and a property selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro-bio-chemical, micro-bio-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro-electro-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, micro thermal mechanical, micro thermal chemical mechanical, micro thermal electrical, micro thermal electro-mechanical, and micro superconducting mechanical properties; and the micro device has a size ranging from approximately 1 angstrom to approximately 5 millimeters.

42. The method of claim 41, wherein each dose delivers a different drug from another dose.

43. The method of claim 41, wherein the drugs are of different chemistries and delivering of a first drug enhances the attachment selectivity to the second drug.

44. A method of using a micro device for a medical purpose, wherein the micro device comprises an outer membrane and a property selected from the group consisting of micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro-bio-chemical, micro-bio-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro-electro-chemical-mechanical, micro-electro-bio-chemical-mechanical, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, and micro superconducting mechanical properties; the micro device has a size ranging from approximately 1 angstrom to approximately 5 millimeters; and the medical purpose is selected from the group consisting of: drug delivery, cutting, removing, polishing, transporting, jointing, diagnosing, sensing, selective protection, targeted removing, measuring, and assisting medical treatment functions at cell structure or micro-organ level in a target area.

45. The method of claim 44, wherein the method is used for cancer treatment and comprises the steps of: selectively attaching micro devices with drug delivery functions onto cancer cells; triggering injection function in the micro devices; and injecting drug into cancer cells.

46. The method of claim 44, comprising the steps of: selectively attaching micro devices with high optical reflectivity onto healthy cells; carrying out laser treatment to destroy unhealthy cells; and removing unhealthy cells in the treatment due to exposure to the laser.

47. The method of claim 44, wherein the micro device comprises a property selected from the group consisting of: signal sensing unit, memory unit, logic processing unit, signal

transmitter, and micro surgery; the micro device performs the function of diagnosing, sensing, or measuring; and the method comprises the steps of: delivering the micro device to a targeted measuring site; performing measurement on the targeted site; recording data in memory unit; optionally triggering operations using the logic processing function; optionally carrying out surgery using the micro device; retrieving the micro device; and analyzing the recorded data.

48. The method of claim 44, wherein the micro device performs the function of diagnosing, sensing, or measuring a target site; the micro device comprises a signal sensing unit, a memory unit, a signal transmitter, a logic unit for on site decision making and micro surgery; and the method comprise the steps of: delivering the micro device to the target site and performing the diagnosing, sensing, or measuring function on the target site; recording data in memory unit; analyzing the data performed by the micro device; deciding the course and type of micro operations based on data analysis and pre programmed logic decisions by the micro device; and performing micro operations on the target site.

49. The method of claim 44, wherein the micro device comprises an electric property measurement unit and is capable of detecting cancer cells in a target site; and the method comprises the steps of: delivering the micro device to the target site; measuring on the target site one or more properties selected from the group consisting of: surface charge, charge density, resting potential, electrical potential, electro-chemical potential, surface current, bulk current, and current density.

50. The method of claim 49, wherein the micro device further comprises a voltage comparator.

51. The method of claim 50, whereby the voltage comparator has a voltage measurement sensitivity better than 1 mV.

52. The method of claim 44, wherein the method is used for cancer cell detection in a target site and comprises the steps of: delivering the micro device to the target site; and measuring on the target site one or more parameters selected from the group consisting of: surface charge, resting potential, electro-chemical potential, electrical potential, surface current, bulk current, surface wettability, contact angle, adhesion properties, temperature, density, friction, hardness, compressibility, shear modulus, acoustical properties, surface tension, trace chemical concentration, pH, liquid flow rate, pressure, optical properties, absorption, adsorption, and composition.

53. A micro device for application outside a biological system, comprising an outer membrane and one property selected from the group consisting of: micro mechanical, micro chemical, micro chemical mechanical, micro optical, micro acoustical, micro biological, micro electro mechanical, micro electromagnetic mechanical, micro acoustic mechanical, and micro superconducting mechanical properties; wherein the micro device has a size ranging from approximately 1 angstrom to approximately 5 millimeters.

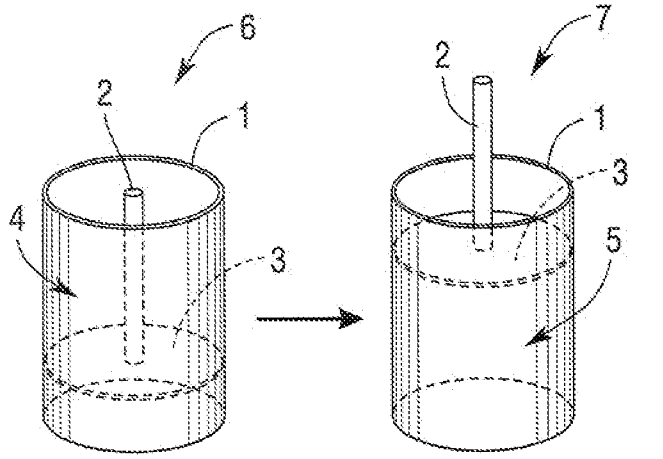


Fig.1

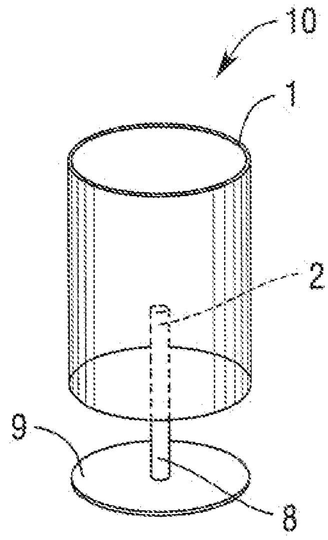


Fig.2

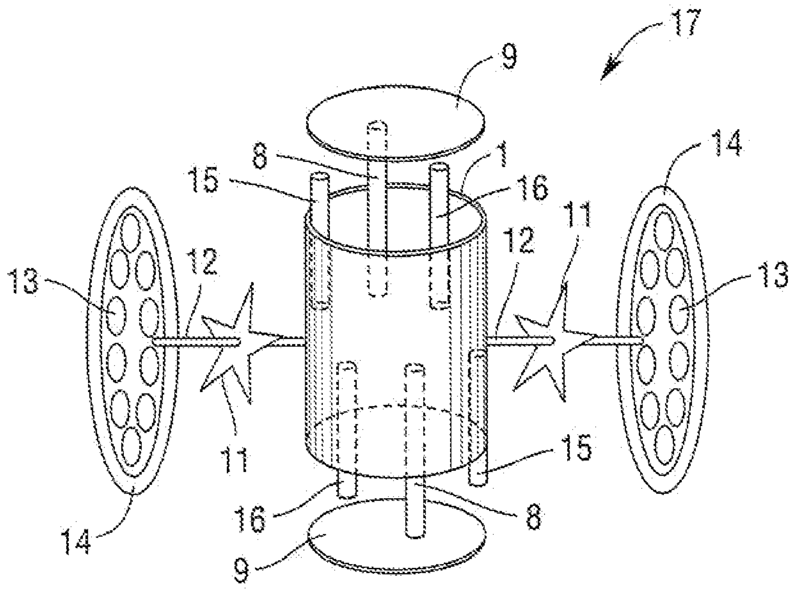


Fig.3

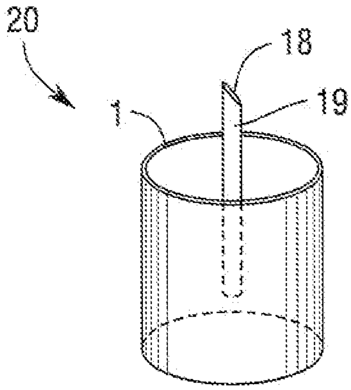


Fig.4

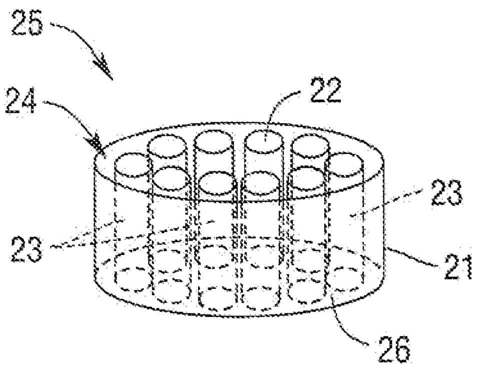


Fig.5

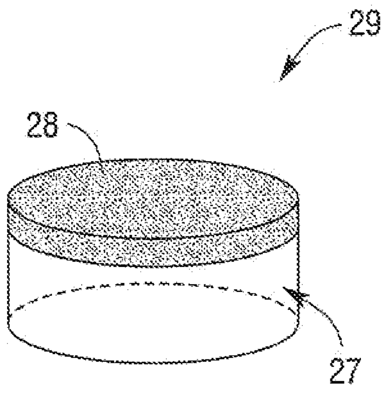


Fig.6

Fig.7

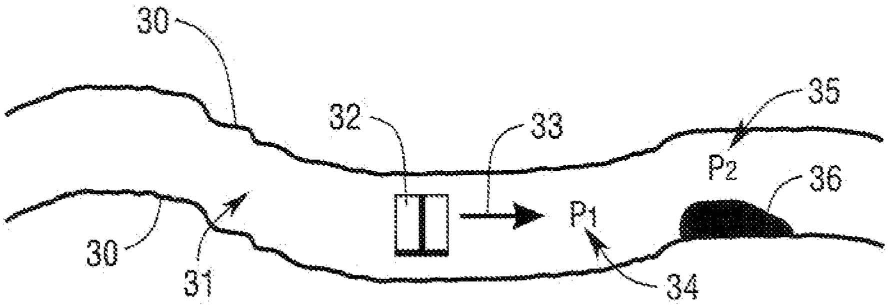


Fig.8

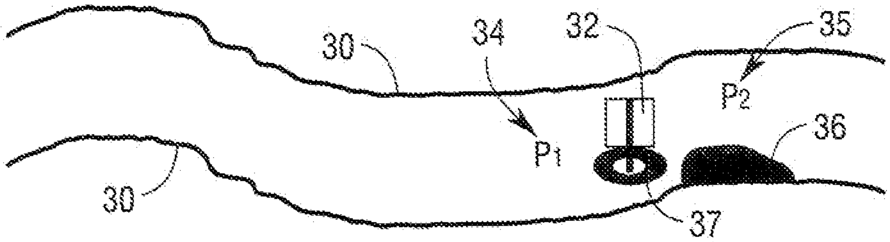
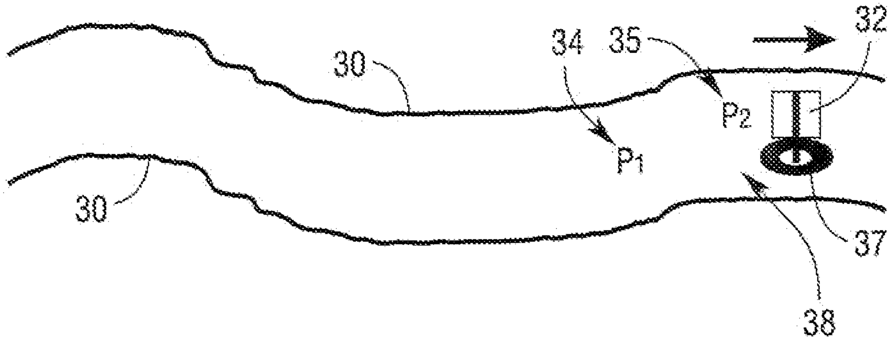


Fig.9



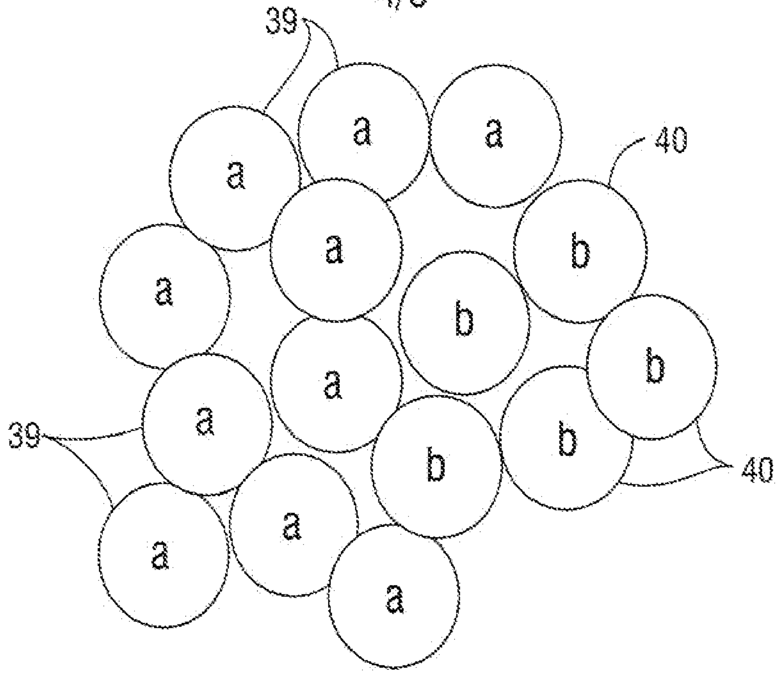

39
a
a
a
40
a
b
a
b
a
b
a
b
39
a
b
40
a
a
a

Fig.10

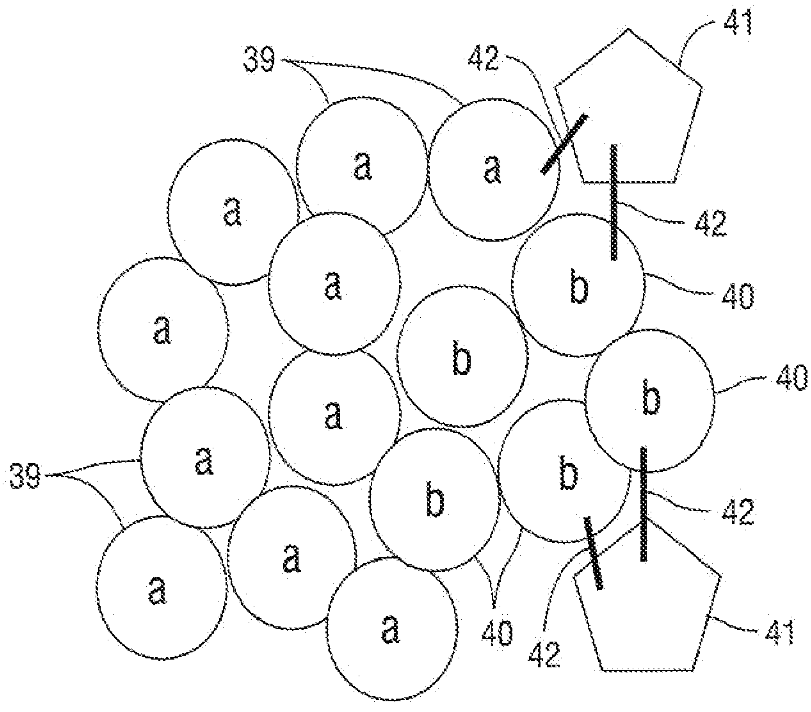

39
42
41
a
a
a
42
a
40
a
b
b
40
b
a
a
39
b
b
42
a
a
a
40
42
41

Fig.11

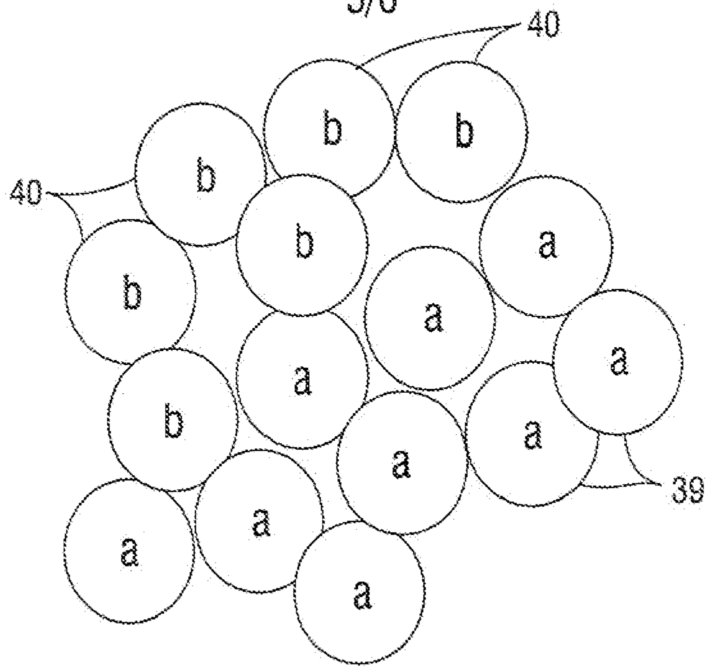


Fig.12

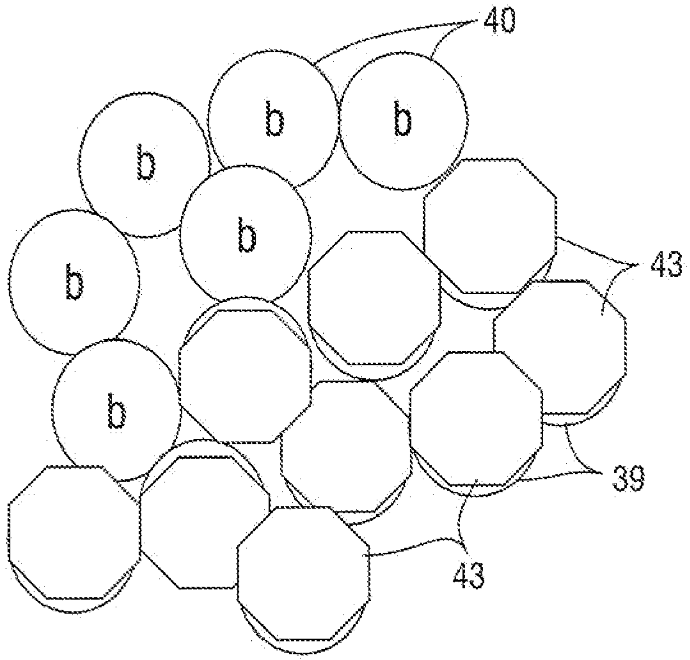


Fig.13

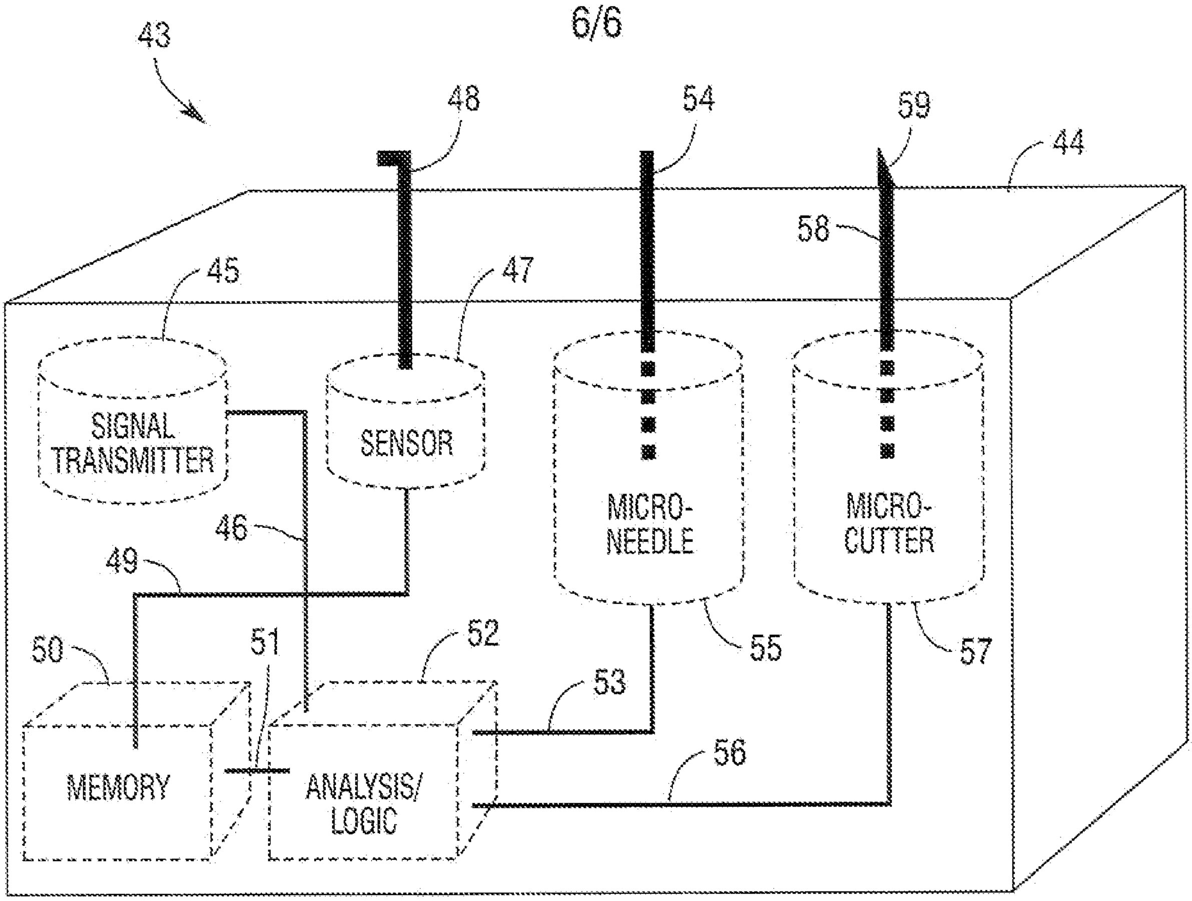

43
48
54
59
44
58
45
47
SIGNAL TRANSMITTER
SENSOR
MICRO-NEEDLE
MICRO-CUTTER
46
49
55
57
50
51
52
53
MEMORY
ANALYSIS/ LOGIC
56

Fig.14

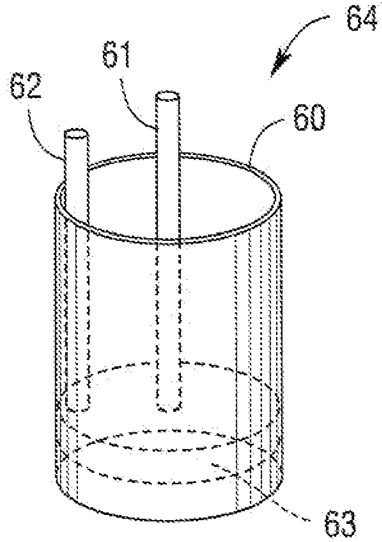

64
61
62
60
63

Fig.15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/049298

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/04(2006.01)i, A61B 19/00(2006.01)i, A61K 49/00(2006.01)i, A61K 50/00(2006.01)i, A61K 9/00(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B 5/04; A61B 5/05; A61K 9/22; A61B 6/00; A61M 1/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: micro device, bio, medical

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 6240312 B1 (ALFANO; ROBERT R. et al.) 29 May 2001 See abstract, column 4 line 27-31, claims 1,3,4,9,10 and figure 2	1,2,3,5,53 4,6-35,41-43
X A	US 2007-0225633 A1 (FERREN, BRAN et al.)27 September 2007 See Abstract, paragraphs [0125],[0136],[0139],[0140], claim 148 and figures 12, 26,27	1,2,3,5,8,22,53 4,6,7,9-21,23-35 ,41-43
X A	US 6663615 B1 (MADOU; MARC J. et al.) 16 December 2003 See abstract, claims 1,8,22,23	1,2,3,5,41,53 4,6-35,42,43

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier 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 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
28 APRIL 2011 (28.04.2011)	**29 APRIL 2011 (29.04.2011)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
KIM Tae Hoon
Telephone No. 82-42-481-5728

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/049298

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

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

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

2. ☒ Claims Nos.: 36-40,44-52
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

As explained below, some of the features in the method claims 36-53 relate to method of using a micro device rather than clearly defining each step of method in terms of its technical features. Therefore, the intended limitations are not clear from these claims, contrary to the requirements of PCT Article 6.

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

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6240312 B1	29.05.2001	None	
US 2007-0225633 A1	27.09.2007	CN 101065077 A0	31.10.2007
		EP 2182874 A1	12.05.2010
		GB 2432537 A	30.05.2007
		GB 2451982 A	18.02.2009
		GB 2453272 A	01.04.2009
		GB 2453273 A	01.04.2009
		GB 2453455 A	08.04.2009
		GB 2453676 A	15.04.2009
		GB 2453677 A	15.04.2009
		GB 2463841 A	31.03.2010
		GB 2463842 A	31.03.2010
		GB 2471598 A	05.01.2011
		JP 2008-514284 A	08.05.2008
		KR 10-2007-0063559 A	19.06.2007
		KR 10-2009-0008436 A	21.01.2009
		KR 10-2009-0009940 A	23.01.2009
		KR 10-2009-0011006 A	30.01.2009
		KR 10-2009-0018084 A	19.02.2009
		KR 10-2009-0026269 A	12.03.2009
		KR 10-2009-0027196 A	16.03.2009
		US 2005-0234393 A1	20.10.2005
		US 2005-0234398 A1	20.10.2005
		US 2005-0234399 A1	20.10.2005
		US 2005-0234440 A1	20.10.2005
		US 2006-0069425 A1	30.03.2006
		US 2007-0010868 A1	11.01.2007
		US 2007-0066929 A1	22.03.2007
		US 2007-0088334 A1	19.04.2007
		US 2007-0156211 A1	05.07.2007
		US 2007-0225634 A1	27.09.2007
		US 2007-0244520 A1	18.10.2007
		US 2007-0282260 A1	06.12.2007
		US 2007-0282261 A1	06.12.2007
		US 2007-0293756 A1	20.12.2007
		US 2007-0293963 A1	20.12.2007
		US 2007-0293965 A1	20.12.2007
		US 2007-0293966 A1	20.12.2007
		US 2007-0294150 A1	20.12.2007
		US 2007-0294151 A1	20.12.2007
		US 2007-0294152 A1	20.12.2007
		US 2007-0294210 A1	20.12.2007
		US 2007-0294279 A1	20.12.2007
		US 2007-0294280 A1	20.12.2007
		US 2008-0033569 A1	07.02.2008
		US 2008-0039779 A1	14.02.2008
		US 2008-0039783 A1	14.02.2008
		US 2008-0058587 A1	06.03.2008

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2010/049298

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2008-0058633 A1	06.03.2008
		US 2008-0058649 A1	06.03.2008
		US 2008-0058713 A1	06.03.2008
		US 2008-0058785 A1	06.03.2008
		US 2008-0058786 A1	06.03.2008
		US 2008-0058788 A1	06.03.2008
		US 2008-0058795 A1	06.03.2008
		US 2008-0059070 A1	06.03.2008
		US 2008-0077265 A1	27.03.2008
		US 2008-0082160 A1	03.04.2008
		US 2008-0086119 A1	10.04.2008
		US 2008-0103355 A1	01.05.2008
		US 2008-0103440 A1	01.05.2008
		US 2008-0133040 A1	05.06.2008
		US 2008-0172073 A1	17.07.2008
		US 2008-0201007 A1	21.08.2008
		US 2008-0243056 A1	02.10.2008
		US 2008-0262341 A1	23.10.2008
		US 2009-0024152 A1	22.01.2009
		US 2009-0084844 A1	02.04.2009
		US 2010-0256609 A1	07.10.2010
		US 7769603 B2	03.08.2010
		US 7818084 B2	19.10.2010
		US 7850676 B2	14.12.2010
		US 7857767 B2	28.12.2010
		US 7867217 B2	11.01.2011
		US 7871402 B2	18.01.2011
		US 7879023 B2	01.02.2011
		WO 2005-102408 A2	03.11.2005
		WO 2005-102408 A3	03.11.2005
		WO 2005-102409 A2	03.11.2005
		WO 2005-102409 A3	03.11.2005
		WO 2005-102410 A2	03.11.2005
		WO 2005-102410 A3	03.11.2005
		WO 2005-102411 A2	03.11.2005
		WO 2005-102411 A3	03.11.2005
		WO 2006-036633 A2	06.04.2006
		WO 2006-036633 A3	06.04.2006
		WO 2007-120742 A2	25.10.2007
		WO 2007-120742 A3	25.10.2007
		WO 2007-130564 A2	15.11.2007
		WO 2007-130564 A3	15.11.2007
		WO 2007-130566 A2	15.11.2007
		WO 2007-130566 A3	15.11.2007
		WO 2007-130586 A2	15.11.2007
		WO 2007-130586 A3	15.11.2007
		WO 2007-130634 A2	15.11.2007
		WO 2007-130634 A3	15.11.2007
		WO 2007-130639 A2	15.11.2007
		WO 2007-130639 A3	15.11.2007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2007-130652 A2	15.11.2007
		WO 2007-130652 A3	15.11.2007
		WO 2007-149308 A2	27.12.2007
		WO 2007-149308 A3	27.12.2007
		WO 2007-149428 A2	27.12.2007
		WO 2007-149428 A3	27.12.2007
		WO 2007-149430 A2	27.12.2007
		WO 2007-149430 A3	27.12.2007
		WO 2009-011918 A1	22.01.2009
		WO 2009-011919 A2	22.01.2009
		WO 2009-011919 A3	22.01.2009
		WO 2009-011919 A8	22.01.2009
		WO 2009-025849 A1	26.02.2009
		WO 2009-029215 A1	05.03.2009
		WO 2009-029216 A1	05.03.2009
US 6663615 B1	16.12.2003	AU 2002-343331 A1	18.03.2003
		AU 2002-343331 A8	18.03.2003
		EP 1453486 A2	08.09.2004
		WO 03-020335 A2	13.03.2003
		WO 03-020335 A3	16.10.2003
		WO 03-020335 A3	13.03.2003