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PROVISIONAL APPLICATION COVER SHEET

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TITLE OF THE INVENTION (280 characters max)
MEDICAL DEVICE FOR REAL-TIME DIAGNOSIS AND DRUG DELIVERY

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒	Specification	*Number of pages* [28]	☒	Small Entity Statement	
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

☒ Applicant is entitled to Small Entity Status.

Respectfully submitted,

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Medical Device for Real-Time Diagnosis and Drug Delivery

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(35738-0011)

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BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the fields of diagnosis and drug delivery. More particularly it relates to medical devices and methods capable of real-time detection of biological activity and the controlled and localized release of appropriate therapeutic agents.

2. Background

One of the most valuable aspects of modern microarray technology is the ability to detect biological macromolecular dysfunction, malformation or mutation resulting in disease. However, this capability has not been fully exploited. Modern microarray technology is limited to characterization of biological macromolecules and their metabolites by analysis of immobilized analytes stabilized on slides to be inserted into a machine or analyzed manually outside of living organisms. Additionally, the use of systemic biological samples such as blood, urine or stool, cannot provide adequate information as to subtle molecular changes at the situs of disease. Alternatively, even if the clinician could pinpoint the exact situs of an ailment, obtaining a biological sample for analysis comes only at great risk, pain and expense for the patient. As such, there is a specific need for the real-time detection of biological macromolecular activity to obtain real-time diagnoses.

The systemic administration of drug agents, such as by transdermal or intravenous means, treats the body as a whole even though the disease to be treated may be localized. In such a case, systemic administration may not be desirable because the drug agents often have unwanted effects on parts of the body that are not intended to be treated, or because treatment of the diseased part of the body requires a high concentration of drug agent that may not be achievable by systemic administration. For example, when administered to a patient systemically, some drugs (e.g., chemotherapeutic drugs such as those used to treat cancer and other proliferative disorders) may cause undesirable side

effects. It is therefore often desirable to administer drug agents at a localized site within the body.

Therefore, it would be particularly desirable to have a medical device that provides real-time detection of biological macromolecular activity to obtain real-time diagnoses, while locally addressing that diagnosis through a controlled release of a therapeutic agent(s).

SUMMARY OF THE INVENTION

One aspect of the invention relates to a coated medical device comprising a microarray which comprises a bioactive agent capable of interacting with a disease marker biological analyte; a reservoir which comprises at least one therapeutic agent and is capable of releasing the therapeutic agent(s) from the medical device; and a plurality of microchips comprising a microarray scanning device capable of obtaining physical parameter data of an interaction between the disease marker biological analyte with the bioactive agent; a biometric recognition device capable of comparing the physical parameter data with an analyte interaction profile; a therapeutic agent releasing device capable of controlling release of the therapeutic agent from the reservoirs; an interface device capable of facilitating communications between the microarray scanning device, biometric recognition device and the therapeutic agent releasing device; and an energy source to power the medical device.

In one embodiment of this aspect of the invention the coating is a biostable polymer which may have channels. In another embodiment of this aspect of the invention, the polymer is porous.

In a different embodiment bodily fluids are transported through microfluidic lanes which move molecules by means of pressure differences over the microarray. In one embodiment, an osmotic pump is used to propel the fluids through the top portion of the device. In another embodiment fluid transport is powered by natural electric currents in the body conducted through Personal Area Network technology.

In yet another embodiment of this aspect of the invention, the microarray comprises microbeads. In another embodiment, the bioactive agent is a nucleic acid. In

yet another embodiment, the bioactive agent is a polypeptide. In yet another embodiment, the bioactive agent is an immunoglobulin.

In an additional embodiment of the medical devices of the invention, the bioactive agent is fluorescently labeled. In another embodiment, the bioactive agent is fluorescently labeled with a nanocrystal.

In yet another embodiment, the disease marker biological analyte is a nucleic acid. In a further embodiment, the disease marker biological analyte is a polypeptide. In another embodiment, the disease marker biological analyte is an immunoglobulin.

In yet a further embodiment, the plurality of microchips comprise silicon germanium.

In another embodiment, the microarray scanning device comprises fiber optic elements.

In an additional embodiment, the analyte interaction profile is stored in the biometric recognition device. In an alternative embodiment, the analyte interaction profile is stored externally from the medical device.

In another embodiment, the medical device has a plurality of reservoirs. In an additional embodiment, the interface device comprises a personal area network.

In an additional embodiment, the energy source is a battery. In an alternate embodiment, the energy source is provided by a personal area network.

Another aspect of the invention relates to a method of detecting and treating a disease in a patient comprising administering to the patient a coated medical device comprising a microarray comprising a bioactive agent capable of interacting with a disease marker biological analyte; at least one reservoir comprising at least one therapeutic agent and capable of releasing the at least one therapeutic agent from the medical device; a plurality of microchips comprising a microarray scanning device capable of obtaining physical parameter data of an interaction between the disease marker biological analyte with the bioactive agent; a biometric recognition device capable of comparing the physical parameter data with an analyte interaction profile; a therapeutic agent releasing device capable of controlling release of the therapeutic agent from the reservoir; and an interface device capable of facilitating communications between the microarray scanning device, the biometric recognition device and the therapeutic agent

releasing device; an energy source to power the medical device; and biocompatible coating enabling the medical device to be swallowed, pass through the patient's intestinal tract and be naturally excreted.

In one embodiment of the method the coating is a biostable polymer which may have channels. In another embodiment, the polymer is porous.

In yet another embodiment of the method, the microarray comprises microbeads. In another embodiment, the bioactive agent is a nucleic acid. In yet another embodiment, the bioactive agent is a polypeptide. In yet another embodiment, the bioactive agent is an immunoglobulin.

In an additional embodiment of the method of the invention, the bioactive agent is fluorescently labeled. In another embodiment, the bioactive agent is a fluorescently labeled with a nanocrystal.

In yet another embodiment of the method, the disease marker biological analyte is a nucleic acid. In a further embodiment, the disease marker biological analyte is a polypeptide. In another embodiment, the disease marker biological analyte is an immunoglobulin.

In yet a further embodiment of the method, the plurality of microchips comprise silicon germanium.

In another embodiment of the method, the microarray scanning device comprises fiber optic elements.

In an additional embodiment of the method, the analyte interaction profile is stored in the biometric recognition device. In an alternative embodiment, the analyte interaction profile is stored externally from the medical device.

In another embodiment of the method utilizes a plurality of reservoirs.
In an additional embodiment of the method, the interface device comprises a personal area network.

In an additional embodiment of the method, the energy source is a battery. In an alternate embodiment, the energy source is provided by a personal area network.

In an additional embodiment of the method, the communications are monitored by an external computer. In another embodiment, the external computer directs release of the therapeutic agent.

Additional advantages of the present invention will become readily apparent to those skilled in this art from the following detailed description, wherein only the preferred embodiment of the invention is shown and described, simply by way of illustration of the best mode contemplated of carrying out the invention. As will be realized, the invention is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the invention. The present invention may be practiced without some or all of these specific details. In other instances, well known process operations have not been described in detail, in order not to unnecessarily obscure the present invention. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is schematic drawing of an exemplary medical device of the invention. The device has a biostable polymer coating **1** as well as an osmotic pump in this preferred embodiment **2** to facilitate fluid movement through the device's porous coating **3**. The device comprises a microarray **4** comprising a bioactive agent capable of interacting with a disease marker biological analyte; a reservoir **10** comprising a therapeutic agent and capable of releasing therapeutic agent from the medical device; and a plurality of microchips **5, 7, 8, 9, 6,10, 12, 13 & 14** comprising; a microarray scanning device **7** capable of obtaining physical parameter data of an interaction between the disease marker biological analyte with the bioactive agent(s); a biometric recognition device **9** capable of comparing the physical parameter data with an analyte interaction profile; a therapeutic agent releasing device **10** capable of controlling release of therapeutic agent(s) from a plurality of reservoirs and checkpoints **13 & 14**; and an interface device **8** capable of facilitating communications between the microarray scanning device **7**, biometric recognition device **9** and the therapeutic agent releasing device **10**; and an energy source to power the medical device **15**. Additionally, the exemplary device contains transmitters

for a personal area network **5 &6** and transmission pathways for communication between the PAN and a hand-held computer monitor **15** or external computer network **16**. Additionally, the exemplary device contains a compartment **11** for the mixing of therapeutic agents prior to release.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to a medical device which acts as a real time sensor within the body to detect biological analytes indicative of disease or defective proteins and is capable of releasing therapeutic agent(s) to address the disease. It further provides for real-time diagnosis and medication by combining biological microarray and microchip technologies.

Bodily fluid drawn into the medical device is brought into contact with the microarray within the medical device, which samples biological analytes in bodily fluids. Fluid released from the medical device can contain therapeutic agent(s) released in response to the presence of a disease marker biological analyte. Most preferably, bodily fluid movement into and out of the medical device is facilitated by a pump, such as a microfluidic or osmotic pump. In another embodiment, molecular transport is conducted through pressurized microfluidc lanes which cause fluids to flow over the microarray beads and through the porous membrane in the top portion of the device. In yet another embodiment molecules are transported by natural electric currents conducted by PAN transmitters.

One aspect of the invention relates to a "biostable polymer," which refers to those materials that do not undergo significant degradation upon prolonged exposure (e.g., up to one week, six months, a year, or longer) to bodily fluids, tissues, and the like and thus enables the device to pass through the entirety of the intestinal tract. It is preferred that fluid is drawn into and released from the medical device either through pores or channels in the polymer.

The biostable coating materials of certain embodiments of this aspect of the invention are porous polymer materials that are characterized by interconnected pores of sufficient size to allow for the flow of bodily fluids into the medical device and the

release therefrom, of therapeutic agents. The porous polymer materials are preferably characterized by an average pore diameter of at least about 5 microns, more preferably at least about 8 microns, and more preferably at least about 10 microns. Suitable polymers for use in embodiments wherein a porous structure is obtained by freeze-drying include any suitable biostable polymer, such as polyurethanes (including polyurethane dispersions), ethylene vinylacetate polymers, hydrogels such as crosslinked gelatin, dextran, polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, acrylic latex dispersions, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, and blends and copolymers thereof.

The term "disease marker" as referred to herein is a detectable biological analyte, e.g., antibodies, serum proteins, cholesterol, polysaccharides, nulceic acids, drugs and drug metabolites, etc., found in bodily fluids and tissues which is present in the body and known to be correlated with disease. Biological analytes, which allow for the detection of certain physiological conditions, can also be indicative of normal healthy physiology. These are referred to herein as "normal" or "healthy" biological analytes. Preferably, the biorecognition device of the invention detects a disease marker based on physical parameter data discerning between the physical characteristics of an interaction between 1) a disease marker biological analyte and a bioactive agent on the microarray and 2) a normal biological analyte with a bioactive agent on the microarray. Disease marker biological analytes allow for the detection of certain physiological conditions, e.g., infection, inflammation, autoimmune disease, cancer, etc. Disease markers presently known to those of skill and disease markers that will be known in the future are encompassed by this invention. The presence of a disease marker indicates the presence of disease and warrants the release of a therapeutic agent.

The disease marker biological analytes may be genes or their products which are over-expressed or over-active in cells under going unwanted proliferation. If the invention detects increased concentrations of such biological analytes or mutated over-active forms of such analytes, as disease markers, a release of therapeutic agent(s) such as a cytotoxic agent is warranted. These disease marker biological analytes can be indicative of unwanted cellular proliferation such as cancer, neointimal proliferation

resulting in arterial stenosis, psoriasis, etc. Disease marker biological analytes may be detected by analyzing gene expression in tissues and matching it to known tumor-gene expression patterns or comparing them to known normal expression patterns. In a preferred embodiment, the microarrays are used to detect the presence of a disease marker biological analyte as defined by the presence, absence or over-abundance of a particular nucleotide sequence, including a single nucleotide polymorphism (SNP), mRNA or a particular protein, such as an enzyme, an antibody or an antigen.

In one embodiment, the disease marker biological analytes are tumor specific antigen. For example, such antigen are expressed on the surface of or released from cancer cells, for example the tumor specific antigen MUC-1. Detection of MUC-1 expression through nucleic acid detection or by protein activity, can constitute a disease marker and can warrant the release of cytotoxic agents as therapeutic agents.

Another example relates to receptor tyrosine kinases (RTKs), which are important in the transduction of mitogenic signals. RTKs are large membrane spanning proteins which possess an extracellular ligand binding domain for growth factors such as epidermal growth factor (EGF), an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acid residues on cytosol proteins thereby mediating cell proliferation. Various classes of receptor tyrosine kinases are known based on families of growth factors which bind to different receptor tyrosine kinases. Class I kinases such as the EGF-R family of receptor tyrosine kinases include the EGF, HER2-neu, erbB, Xmrk, DER and let23 receptors. These receptors are frequently present in common human cancers such as breast cancer, squamous cell cancer of the lung, bladder cancer, oesophageal cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukaemia and ovarian, bronchial or pancreatic cancer. As further human tumor tissues are tested for the EGF family of receptor tyrosine kinases it is expected that its widespread prevalence will be established in other cancers such as thyroid and uterine cancer. Specifically, EGFR tyrosine kinase activity is rarely detected in normal cells whereas it is more frequently detectable in malignant cells. It has been more recently shown that EGFR is overexpressed in many human cancers such as brain, lung squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynaecological and thyroid tumours. Receptor tyrosine kinases are also important in other cell-proliferation diseases

such as psoriasis. EGFR disorders are those characterized by EGFR expression by cells normally not expressing EGFR, or increased EGFR activation leading to unwanted cell proliferation, and/or the existence of inappropriate EGFR levels. The EGFR is known to be activated by its ligand EGF as well as transforming growth factor-alpha (TGF-α). The Her2-neu protein is also a member of the class I receptor tyrosine kinase (RTK) family. Her2-neu protein is structurally related to EGFR. These receptors share a common molecular architecture and contain two cysteine-rich regions within their cytoplasmic domains and structurally related enzymatic regions within their cytoplasmic domains. Accordingly, detection of abnormally high levels of RTK expression or signaling activity through nucleic acid detection or by protein activity can constitute a disease marker and can warrant the release of RTK inhibitors or cytotoxic agents as therapeutic agents.

The relatively high expression of genes that directly or indirectly inhibit chemotherapeutics constitute a disease marker for purposes of the invention. For example, high tumor expression of the DNA repair gene ERCC1 warrants release of genotoxic chemotherapeutic agents to a high local yet low systemic concentration. Thus, achieving concentrations that would not be safely sustained systemically. Additionally, high tumor levels of the gene DPD are known to inhibit 5-FU based chemotherapeutic regimen. Similarly, high tumor expression of the DPD warrants release of 5-FU chemotherapeutic agents to a high local yet low systemic concentration. Alternatively, the skilled artisan would also realize that high levels of ERCC1 or DPD may be indicative of chemotherapeutic resistance and that the use of genotoxic agents or 5-FU, respectively, may not be appropriate. In such a case, cytotoxic therapeutic agents other than genotoxic agents or 5-FU should be released from the device, respectively.

Alternatively, the device can be set up as to detect a panel of disease markers indicative of a disease such as cancer and release high local concentrations of cytotoxic agents as a therapeutic agent.

In a further embodiment, disease marker biological analytes can be indicative of inflammation, which plays a crucial role in the etiology of inflammatory bowel disease, multiple sclerosis, childhood-onset diabetes, psoriasis, rheumatoid arthritis, etc. Such diseases previously required regular large systemic doses of potentially harmful steroids to address only localized inflammation. High localized concentrations of biological

analytes such as TNF-alpha, IL-1, IL-8, IL-2, IL-3, MIF (IL-4), GM-CSF, INF-gamma, and TNF-beta are indicative of inflammation. The detection of abnormally high concentration of such biological analytes constitutes a disease marker and warrants localized release of anti-inflammatory drugs or antibodies as therapeutic agents.

In another embodiment, disease marker biological analytes can be indicative of infection by a microorganism. As such, disease markers can include viral or bacterial proteins or nucleic acids or fragments thereof. For example, detection of biological analytes such as bacterial toxins including exotoxins and enterotoxins as well as TSST-1, or other bacterial superantigen, or botulinum toxin, diphtheria toxin, anthrax protective antigen, anthrax edema factor, and anthrax lethal factor, etc., as well as viral proteins such as influenza hemagglutinin or neuraminidase, would constitute a disease marker indicative of infection and warrant localized release of anti-microbial drugs or toxin-specific antibodies as therapeutic agents.

Another aspect of the invention relates to a microarray facilitating the interaction between 1) a disease marker biological analyte and a bioactive agent on the microarray and 2) a normal biological analyte with a bioactive agent on the microarray. A micorarray is a collection of miniaturized test sites arranged on a surface that permits many tests, or assays, to be performed in parallel. The microarray is directly exposed to bodily fluids and/or tissues such that it is able to simultaneously process a plurality of different assays and provide for the interaction of one or more bioactive agents with one or more biological analytes. The physical parameter data of an interaction between biological analytes and the bioactive agents microarray are preferably "read" by a microarray scanning device and transmitted to the biorecognition device to determine the presence of disease markers. Suitable microarrays may be obtained from Illumina, Inc., San Diego, CA.

In a preferred embodiment of this aspect of the invention, microbead arrays are used. By "microspheres" or "beads" or "particles" or grammatical equivalents herein is meant small discrete particles. The composition of the beads will vary, depending on the class of bioactive agent and the method of synthesis. Suitable bead compositions include those used in peptide, nucleic acid and organic moiety synthesis, including, but not limited to, plastics, ceramics, glass, polystyrene, methylstyrene, acrylic polymers,

paramagnetic materials, thoria sol, carbon graphited, titanium dioxide, latex or cross-linked dextrans such as Sepharose, cellulose, nylon, cross-linked micelles and teflon may all be used. "Microsphere Detection Guide" from Bangs Laboratories, Fishers Ind. is a helpful guide, and is incorporated by reference in its entirety. The beads need not be spherical; irregular particles may be used. In addition, the beads may be porous, thus increasing the surface area of the bead available for either bioactive agent attachment or tag attachment. The bead sizes range from nanometers, e.g. 100 nm, to millimeters, e.g.. 1 mm, with beads from about 0.2 micron to about 200 microns being preferred, and from about 0.5 to about 5 microns being particularly preferred, although in some embodiments smaller or larger beads may be used.

Preferably, each microsphere comprises a bioactive agent. A "bioactive agent" is used herein to describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc. which can be attached to the microspheres of the microarray and can interact with a disease marker biological analyte or differentially interact with normal and disease marker biological analytes present in bodily fluids or tissues. Bioactive agents are labeled in such a way as to allow the microarray scanning device to ascertain certain physical parameters specific to the bioactive agent that are altered upon interaction with biological analytes.

In one embodiment, bioactive agents are fluorescently labeled and their fluorescence is altered upon interaction with biological analytes. Most preferably, the bioactive agents are labeled with fluorescent nanocrystals. In comparison to organic dyes such as rhodamine, nanocrystals are approximately at least 20 times as bright, approximately at least 100 times as stable against photobleaching, and are approximately one-third as wide in the emission spectral linewidth. See, for example, Bruchez, et al., Science, 281:2013-2016 (1998); Chan and Nie, Science, 281:2016-2018 (1998); Bawendi et al., Annu. Rev. Phys. Chem. 41:477-496 (1990), and references cited therein, all of which are expressly incorporated by reference. The brightness, stability and narrowness of emission bandwidth all contribute to the ability to use a relatively large number of different colors as further described below (i.e. different size nanocrystals) while preserving the ability to resolve them from each other, and to resolve different quantities

of each nanocrystal. In addition, the broad excitation spectrum allows many different nanocrystals to be excited by a common light source.

Bioactive agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, and preferably at least two of the functional chemical groups. The bioactive agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Bioactive agents are also found among biomolecules including peptides, nucleic acids, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof. Particularly preferred are nucleic acids and proteins.

"Interact with," as used herein refers to the ionic, covalent or hydrogen bonding, protein binding, nucleic acid hybridization, magnetic or hydrophobic attraction or other detectable and/or quantifiable association of a biological analyte with a bioactive agent on the microarray. "Differentially interact with," refers to the fact that a disease marker biological analyte will interact with a bioactive agent differently than a biological analyte indicative of normal physiology.

The physical differences in interaction between 1) a disease marker biological analyte and a bioactive agent and 2) a normal biological analyte with a bioactive agent, are detectable by comparing the physical characteristics of the bioactive agent before, during or after interaction with the biological analyte. The detectable and/or quantifiable changes in bioactive agents upon interaction with a biological analyte are measurable through a series of physical parameters that depend on the nature of the bioactive agent employed. For example a detectable and/or quantifiable association may be evidenced by a shift in fluorescence intensity or wavelength due to binding or hybridization of the bioactive agent with a biological analyte.

In another embodiment, the binding (interaction), of a fluorescence-associated antibody on a microarray (bioactive agent), specific for a particular tumor-specifc protein (disease marker biological analyte), results in a detectable shift in the intensity of the fluorescence of the bioactive agent. This stereotyped shift is indicative of the presence of a particular disease marker and is empirically determined while selecting the appropriate

bioactive agent and target disease marker. Whereas non-specific binding may alter the fluorescence of the bioactive agent, it will not do so in a predicable and stereotyped way consistent with empirically determined results, and as such, will not be indicative of the presence of a disease marker biological analyte.

A "therapeutic agent," as used herein refers to compounds that are useful in or appropriate for locally treating a disease associated with a particular biological anomaly indicative of disease, i.e., disease marker. Therapeutic agents of the invention are any therapeutic substance for the treatment of diseases including for example: pharmaceutical compounds that are preferably delivered locally such as chemotherapeutics, steroids, therapeutic nucleic acids including DNA, RNA, double stranded RNA (by means of RNA interface) and antisense RNA, or proteins such as immunoglobulins, growth factors, anti-inflammatory agents, or enzyme inhibitors, etc. By release of therapeutic agent from the device, it is preferable to establish an effective local concentration of the drug. The local concentration can substantially exceed the safe systemic concentration for the same drug, thus sparing the patient substantial discomfort yet maximizing efficacy. For example, the localized release of corticosteroids appropriate for the treatment of localized inflammation is encompassed herein. Additionally, the localized release of pathogen-specific antibodies for the treatment of infection, is encompassed herein. The exact formulation and dosage can be chosen by the individual clinician in view of the patient's condition. (See e.g. Fingl et al., in The Pharmacological Basis of Therapeutics, 1975, Ch. 1 p. 1).

In one embodiment, a biological analyte indicative of unwanted cellular proliferation is detected and it is preferable to locally release therapeutic agent(s) that have an anti-proliferative effect. For example, sirolimus (rapamycin) or paclitaxel are very effective in inhibiting smooth muscle cell proliferation during neointimal hyperplasia.

In another example for responding to the presence of biological analytes indicative of unwanted proliferation, 5-FU-based chemotherapy comprises administration of 5-FU, its derivatives, alone or with other chemotherapeutics, such as leucovorin or with a DPD inhibitor such as uracil, 5-ethynyluracil, bromovinyluracil, thymine, benzyloxybenzyluracil (BBU) or 5-chloro-2,4-dihydroxypyridine, is released from the

medical device. Furthermore, it has been found that co-administration of a 5'-deoxy-cytidine derivative of the formula (I) with 5-FU or a derivative thereof significantly improves delivery of a chemotherapeutic agent selectively to tumor tissues as compared with the combination of 5-FU or a derivative thereof with a DPD inhibitor 5-ethynyluracil.

Alternatively, genotoxic agents are those that form persistent genomic lesions and are preferred for use as chemotherapeutic agents in the clinical management of unwanted cellular proliferation. The rate of cellular repair of genotoxin-induced DNA damage, as well as the rate of cell growth via the cell division cycle, affects the outcome of genotoxin therapy. A general class of genotoxic compounds that are used for treating many cancers are DNA alkylating agents and DNA intercalating agents. Psoralens are genotoxic compounds known to be useful in the photochemotherapeutic treatment of cutaneous diseases such as psoriasis, vitiligo, fungal infections and cutaneous T cell lymphoma. Harrison's Principles of Internal Medicine, Part 2 Cardinal Manifestations of Disease, Ch. 60 (12th ed. 1991). Another general class of genotoxic compounds, members of which can alkylate or intercalate into DNA, includes synthetically and naturally sourced antibiotics. Of particular interest herein are antineoplastic antibiotics, which include but are not limited to the following classes of compounds represented by: amsacrine; actinomycin A, C, D (alternatively known as dactinomycin) or F (alternatively KS4); azaserine; bleomycin; carminomycin (carubicin), daunomycin (daunorubicin), or 14-hydroxydaunomycin (adriamycin or doxorubicin); mitomycin A, B or C; mitoxantrone; plicamycin (mithramycin); and the like. Still another general class of genotoxic agents that are commonly used and that alkylate DNA, are those that include the haloethylnitrosoureas, especially the chloroethylnitrosoureas. Representative members of this broad class include carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine and streptozotocin. Haloethylnitrosourea first agents can be analogs or derivatives of any of the foregoing representative compounds.

Tumors currently manageable by platinum coordination compounds such as cisplatin or oxaliplatin include testicular, endometrial, cervical, gastric, squamous cell, adrenocortical and small cell lung carcinomas along with medulloblastomas and neuroblastomas. Other cytotoxic anti-cancer therapeutic agents include, for example,

BEP (bleomycin, etoposide, cisplatin) for testicular cancer, MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) for bladder cancer, MVP (mitomycin C, vinblastine, cisplatin) for non-small cell lung cancer treatment.

Yet another general class of genotoxic agents, members of which alkylate DNA, includes the sulfur and nitrogen mustards. These compounds damage DNA primarily by forming covalent adducts at the N7 atom of guanine. Representative members of this broad class include chlorambucil, cyclophosphamide, ifosfamide, melphalan, mechloroethamine, novembicin, trofosfamide and the like. Oligonucleotides or analogs thereof that interact covalently or noncovalently with specific sequences in the genome of selected cells can also be used as genotoxic agents, if it is desired to select one or more predefined genomic targets as the locus of a genomic lesion.

Another class of agents, members of which alkylate DNA, include the ethylenimines and methylmelamines. These classes include altretamine (hexamethylmelamine), triethylenephosphoramide (TEPA), triethylenethiophosphoramide (ThioTEPA) and triethylenemelamine, for example.

Additional classes of DNA alkylating agents include the alkyl sulfonates, represented by busulfan; the azinidines, represented by benzodepa; and others, represented by, e.g., mitoguazone, mitoxantrone and procarbazine. Each of these classes includes analogs and derivatives of the respective representative compounds.

Additional examples of cytotoxic therapeutic agents are antibodies complexing with a cell-specific antibody activates serum complement and/or mediate antibody-dependent cellular cytotoxicity. The antibodies which bind the cell can also be conjugated to a toxin (immunotoxins). The cytotoxic moiety of the immunotoxin may be a cytotoxic drug or an enzymatically active toxin of bacterial or plant origin, or an enzymatically active fragment of such a toxin. Enzymatically active toxins and fragments thereof used are diphtheria, nonbinding active fragments of diphtheria toxin, exotoxin (from Pseudomonas aeruginosa), ricin, abrin, modeccin, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolacca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, and enomycin. In another embodiment, the antibodies are conjugated to small molecule anticancer drugs. Conjugates of the

monoclonal antibody and such cytotoxic moieties are made using a variety of bifunctional protein coupling agents. Examples of such reagents are SPDP, IT, bifunctional derivatives of imidoesters such a dimethyl adipimidate HCl, active esters such as disuccinimidyl suberate, aldehydes such as glutaraldehyde, bis-azido compounds such as bis (p-azidobenzoyl) hexanediamine, bis-diazonium derivatives such as bis-(p-diazoniumbenzoyl)-ethylenediamine, diisocyanates such as tolylene 2,6-diisocyanate, and bis-active fluorine compounds such as 1,5-difluoro-2,4-dinitrobenzene. The lysing portion of a toxin may be joined to the Fab fragment of the antibodies. Cytotoxic radiopharmaceuticals for treating cancer may be made by conjugating radioactive isotopes to the antibodies. The term "cytotoxic moiety" as used herein is intended to include such isotopes.

In one embodiment, therapeutic agents are inhibitors of receptor tyrosine kinases such as EGFR and HER2-neu and are employed as selective inhibitors of the growth of proliferative cells such as mammalian cancer cells. For example, erbstatin, an EGF receptor tyrosine kinase inhibitor, reduces the growth of EGFR expressing human carcinoma cells. Various derivatives of styrene are also stated to possess tyrosine kinase inhibitory properties and to be of use as anti-tumour agents. Two such styrene derivatives are Class I RTK inhibitors whose effectiveness have been demonstrated by attenuating the growth of human squamous cell carcinoma injected into nude mice. Certain 4-anilinoquinazoline derivatives are useful as inhibitors of receptor tyrosine kinases. The very tight structure-activity relationships shown by these compounds suggests a clearly-defined binding mode, where the quinazoline ring binds in the adenine pocket and the anilino ring binds in an adjacent, unique lipophilic pocket. Three 4-anilinoquinazoline analogues (two reversible and one irreversible inhibitor) have been evaluated clinically as anticancer drugs. Additionally, the monoclonal antibody trastazumab (Herceptin™) for the treatment of HER2-neu overexpressing metastatic breast cancers. Scheurle, et al., Anticancer Res 20:2091-2096, 2000.

In another embodiment, when a biological analyte indicative of a microbial pathogen is detected, it is preferable to locally release therapeutic agent(s) that have an antimicrobial effect. For example, it is preferable to release an antibiotic such as beta-Lactam Antibiotics, Aminoglycosides, Macrolides, Lincomycin, and Clindamycin

Tetracyclines, Quinolones, Sulfonamides, Trimethoprim-Sulfamethoxazole and specifically: Amoxicillan, amoxicillian, Amoxicillin, ampicillin, Augmentin, Bactrim, BIAXIN, Ceclor, CEFTIN, Cipro, Clindamycin, Decadron, Diflucan, Doxycycline, erythromyacin, erythromycin, Erythromycin, flagyl, Floxin, Keflex, levoxil, macrobid, Metronizadole(Flagyl), Minocin, Minocyclin / Minocin, nizarol, norfloxacin, Nystatin, Penicillin, Polarol, Rocefin, Sulfa, Septra, Streptomycin, Tequinn, Tetracycline, tinnidazole, Valtrex, vibramcin, Zithromax, or zithromycin.

Upon detection of biological analytes indicative of viral infection, it is preferable to release antiviral compounds including protease inhibitors such as Invirase, Norvir, Viracept, Crixivan, or Frotovase, Saquinavir or other antivirals such as amantadine, rimantadine, zanamivir, oseltamivir, ribavirin, AZT, Didanosine, Zalcitabine, Stavudine, Lamivudine, Nevirapine, Delavirdine, Idoxuridine, Vidarabine, Trifluridine, Acyclovir, Famciclovir, Penciclovir, Valacyclovir, Ganciclovir, Foscarnet, Ribavirin, Amantadine and Rimantadine, Cidofovir, Interferons.

In another embodiment, when a biological analyte indicative of a inflammation is detected, it is preferable to locally release therapeutic agent(s) that have an anti-inflammatory effect. Preferably such therapeutic agents are steroids such as prednisone/prednisolone, or non-steroidal an anti-inflammatory drugs (NSAIDs) such as Ibuprofen, Naproxen, Nabumetone, Celecoxib, Rofecoxib, or Valdecoxib. Such agents are particularly appropriate for the treatment of inflammation related diseases as Inflammatory Bowel Disease, Rheumatoid Arthritis and the like.

The invention contemplates a medical device capable of the localized delivery of one or more therapeutic agents upon detection of a disease marker. In another embodiment of this aspect of the invention, the device releases a single therapeutic agent in response to detection of several disease markers. Alternatively, the device may release different therapeutic agents appropriate for the detection of different disease markers. In another embodiment, a therapeutic agent can be released into a saline solution compartment within the device which serves as a carrier fluid. In yet another embodiment of this aspect of the invention, liposomes are filled with a therapeutic agent and the liposomes are coated with antibodies specifically binding a specific cell-type.

This method permits delivery of large amounts of drug to the appropriate cell type upon detection of a disease marker.

The device may contain one or more reservoirs comprising therapeutic agent(s). The reservoir holds therapeutic agent until it is directed by the biorecognition device upon detection of a disease marker, to release therapeutic agent in a controlled fashion, e.g., receives instruction as to release rate and quantity of drug to be released. Alternatively, a single release rate or dose may be programmed into the device. The reservoir can contain a mixture of one or more therapeutic agents. Alternatively, the device can comprise several reservoirs of one or more therapeutic agents. Preferably there are a plurality of reservoirs.

The invention envisages the medical device to have a plurality of microchips. Preferably, the microchips have the greatest currently available processing ability. Preferably, the plurality of microchips are all in communication with one another. Most preferably, the microchips are made of silicon germanium. Even more preferably, the microchips are International Business Machines (IBM)'s CMOS 9S low-k dielectric insulation high-performance chips to further provide for the highest efficiency, speed and power available in operating the medical device. The skilled artisan can readily appreciate that the device can have varying number of microchips because of the fact the devices listed below are capable of being embedded on a variable numbers of microchips.

Furthermore, each technological component of the device is optimized by the method in which it is uniquely integrated into this system. Recently, low-k dielectric insulation and silicon germanium technology has maximized microchip processing capabilities and efficiency. These chips are ideal for optical communication networks and by combining them with microarray bead technology, which conducts data by means of photo-optic signaling, the power behind both systems is optimized.

One feature of this aspect of the invention relates to a microarray scanning device. The scanning device is able to discern between the physical characteristics of an interaction between 1) a disease marker biological analyte and a bioactive agent on the microarray and 2) a normal biological analyte with a bioactive agent on the microarray. "Physical parameter data" as referred to herein include information relating to interaction between biological analytes with bioactive agents on the microarray gathered by the

microarray scanning device. Physical parameter data are transmitted to the biometric recognition device for analysis. The scanning device measures the physical, e.g., bio-electric, bio-magnetic, or biochemical, characteristics of interactions between biological analytes and the bioactive agent of the microarray by collecting data on one or more physical parameters relating to the interaction. Such parameters can include but are not limited to: fluorescence, binding strength, binding specificity, charge, etc.

In one embodiment of this feature, the arrays are designed such that fiber optical elements are capable of emitting and receiveing light at a particular wavelength to enable physical parameter data acquisition relating to binding between the bioactive agent and biological analyte. Once the light has been absorbed by a dye on the bioactive agent, some light of varying wavelength and intensity returns, and is conveyed through either the same fiber or collection fiber(s) to the microarray scanning device for quantification. The interactions between the light conveyed by the optical fiber and the properties of a light absorbing dye provide an optical basis for both qualitative and quantitative determinations of changes in physical characteristics evidenced by the interaction between biological analytes and bioactive agents. See U.S. Patent No. 6,482,593 and 6,544,732, which are incorporated by reference in their entirety. The biometric recognition device receives optical and fluorescence reception signals, i.e. physical parameter data, which are forwarded to the therapeutic agent release device which dispenses specified therapeutic agents. A suitable microarray scanning device is available commercially from several sources such as Illumina, Inc. San Diego, CA.

Another feature of this aspect of the invention relates to a biometric recognition device which through analysis of the physical parameter data collected by the microarray scanning device, determines the absence or presence of a disease marker analyte. When a disease marker biological analyte interacts with a bioactive agent on the microarray, the microarray scanning device conveys data on the physical parameters of the interaction to the biorecognition device which in turn, matches that data with a known disease marker analyte interaction profile to determine the presence of a disease marker. Disease marker biological analytes interact with a bioactive agent on a microarray in stereotyped and predicable fashion and the interaction is evidenced by reproducible and predictable physical parameter data. Known data are referred to herein as an "analyte interaction

profile." Such profiles will have been established in vitro and the biometric recognition device may have access to both analyte interaction profiles of disease markers and normal analytes. The biometric recognition device receives raw physical parameter data from the microarray scanning device and compares that information with stored analyte interaction profiles. The biometric recognition device may have access to both analyte interaction profiles of disease markers and normal analytes.

Another feature of this aspect of the invention relates to a therapeutic agent releasing device capable of controlling release of therapeutic agent from the reservoir. When the biometric recognition device determines the presence of a disease marker, the therapeutic agent releasing device is signaled to release therapeutic agent from a reservoir in a controlled fashion, i.e., it receives instruction as to release rate and/or quantity of drug to be released. In one embodiment, the therapeutic agent releasing device is a microchip located below microchips containing the device listed above and includes reservoirs for the controlled release of therapeutic agents. The substrate of the microchip contains the etched, molded, or machined reservoirs and serves as the support for the microchip. Any material that can serve as a support, is suitable for etching, molding, or machining, and is impermeable to the molecules to be delivered and to the surrounding fluids, for example, water, organic solvents, blood, electrolytes or other solutions, may be used as a substrate. Examples of substrate materials include ceramics, semiconductors, and degradable and non-degradable polymers. It is preferred that the substrate itself is non-toxic, sterile, and biocompatible. Nevertheless, toxic or otherwise non-biocompatible materials may be encapsulated in a biocompatible material, such as poly(ethylene glycol) or tetrafluoroethylene-like materials, before use. See U.S. Patent No. 6,491,666 which is incorporated by reference in its entirety. A suitable therapeutic agent releasing device is available from MicroChips (Cambridge, MA). Preferably, the therapeutic agent releasing device has a plurality of reservoirs. In another embodiment of this aspect of the invention, the therapeutic agent releasing device signals the other devices or an external database as to the status of appropriate therapeutic agent release. In yet another embodiment, therapeutic agent release is in small doses serving as preliminary treatment while the therapeutic agent passes through additional microchips with independent

wireless signaling systems which serve as checkpoints to ensure correct dosage prior to delivery.

Another feature of this aspect of the invention relates to an interface device capable of facilitation communications between the microarray scanning device, the biorecognition device, and the therapeutic agent releasing device. Preferably, the interface device receives information regarding the presence of a disease marker from the biorecognition device and signals therapeutic agent releasing device to release a therapeutic agent or mixture of agents from one or more reservoirs. In one embodiment, the interface device has a wireless transmitter and receiver. In particular see U.S. Patent No. 5,832,296 or 6,542,717 which are hereby incorporated by reference in their entirety. In another embodiment the invention contemplates the use of a Personal Area Network (PAN) electrostatic communication to transmit signals between microchips and utilizes atherapeutic agent releasing device associated with reservoirs for therapeutic agent release in order to deliver drugs into the body upon receiving respective signals from the analysis in the biorecognition device. Preferably, two bordering PAN transmitters are located underneath the microarray – one bordering the microarray scanning device and the other bordering the therapeutic agent releasing device controlling the reservoir below. PAN transmitters signal for release of therapeutic agent as specified by array results. Appropriate hardware may be obtained from Interval Research Corp., Palo Alto, CA and PAN transmitters from International Business Machines Corp., Armonk, NY.

In another embodiment of this aspect of the invention, the plurality of microchips transmit their information to an external sources such as a hand held monitoring device or computers at network headquarters operated by wireless data communications systems.

Another aspect of the invention relates to an energy source to power the medical device. In one embodiment of this aspect of the invention, the device is powered by a battery. In another embodiment, the power source is provided by a Personal Area Network.

Applications of this invention range from military to commercial use. For instance, the device could be used by civilians in nations afflicted by viruses such as SARS where real-time diagnosis acquires a substantial importance. With the rise of bioterrorism methods of detecting pathogens are of increasing value to defense

departments worldwide. Likewise, the invention could be used to detect bacterial infections or other gut-related diseases and to deliver an immediate real time diagnosis of protein activity as it travels through the intestinal system seeing as the gut is one of the largest centers for the growth of infectious diseases. Likewise, applications of protein microarray technology which are currently limited by problems such as isolating high affinity and specificity protein ligands or BSA obscuring peptides of interest on aldehyde slides could be maximized by using selective protein arrays in vivo and dispensing antibodies or drugs corresponding to targeted protein classes. Indeed, there could be commercial, medical, research / educational, and military and community service / humanitarian applications of this device.

In this disclosure there is described only the preferred embodiments of the invention and but a few examples of its versatility. It is to be understood that the invention is capable of use in various other combinations and environments and is capable of changes or modifications within the scope of the inventive concept as expressed herein. Thus, for example, those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific substances and procedures described herein. Such equivalents are considered to be within the scope of this invention, and are covered by the following claims.

What is claimed is:

1. A coated medical device comprising:

   a) a microarray comprising a bioactive agent capable of interacting with a disease marker biological analyte;

   b) at least one reservoir comprising at least one therapeutic agent and capable of releasing said at least one therapeutic agent from said medical device;

   c) a plurality of microchips comprising;

      i) a microarray scanning device capable of obtaining physical parameter data of an interaction between the disease marker biological analyte with said bioactive agent;

      ii) a biometric recognition device capable of comparing said physical parameter data with an analyte interaction profile;

      iii) a therapeutic agent releasing device capable of controlling release of said therapeutic agent from said reservoir; and

      iv) an interface device capable of facilitating communications between said microarray scanning device, said biometric recognition device and said therapeutic agent releasing device;

   d) an energy source to power the medical device.

2. The medical device of claim 1, wherein the polymer is biocompatible.

3. The medical device of claim 1, wherein the polymer has channels.

4. The medical device of claim 1, wherein the polymer is porous.

5. The medical device of claim 1, wherein the microarray comprises microbeads.

6. The medical device of claim 1, wherein the bioactive agent is a nucleic acid.

7. The medical device of claim 1, wherein the bioactive agent is a polypeptide.

8. The medical device of claim 7, wherein the bioactive agent is an immunoglobulin.

9. The medical device of claim 1, wherein the bioactive agent is fluorescently labeled.

10. The medical device of claim 1, wherein the bioactive agent is a fluorescently labeled with a nanocrystal.

11. The medical device of claim 1, wherein the disease marker biological analyte is a nucleic acid.

12. The medical device of claim 1, wherein the disease marker biological analyte is a polypeptide.

13. The medical device of claim 12, wherein the disease marker biological analyte is an immunoglobulin.

14. The medical device of claim 1, wherein the plurality of microchips comprise silicon germanium.

15. The medical device of claim 1, wherein the microarray scanning device comprises fiber optic elements.

16. The medical device of claim 1, wherein the analyte interaction profile is stored in the biometric recognition device.

17. The medical device of claim 1, wherein the analyte interaction profile is stored externally from the medical device.

18. The medical device of claim 1 having a plurality of reservoirs.

19. The medical device of claim 1, wherein the interface device comprises a personal area network.

20. The medical device of claim 1, wherein energy source is a battery.

21. The medical device of claim 1, wherein energy source is provided by a personal area network.

22. A method of detecting and treating a disease in a patient comprising:

A) administering to said patient a coated medical device comprising;

a) a microarray comprising a bioactive agent capable of interacting with a disease marker biological analyte;

b) at least one reservoir comprising at least one therapeutic agent and capable of releasing said at least one therapeutic agent from said medical device;

c) a plurality of microchips comprising;

i) a microarray scanning device capable of obtaining physical parameter data of an interaction between the disease marker biological analyte with said bioactive agent;

ii) a biometric recognition device capable of comparing said physical parameter data with an analyte interaction profile;

iii) a therapeutic agent releasing device capable of controlling release of said therapeutic agent from said reservoir; and

iv) an interface device capable of facilitating communications between said microarray scanning device, said biometric recognition device and said therapeutic agent releasing device;

d) an energy source to power the medical device; and

B) removing said medical device from said patient or allowing said medical device to pass through said patient.

23. The method of claim 22, wherein the polymer is biocompatible enabling it to pass through the intestinal track.

24. The method of claim 22, wherein the polymer has channels.

25. The method of claim 22, wherein the polymer is porous.

26. The method of claim 22, wherein the microarray comprises microbeads.

27. The method of claim 22, wherein the bioactive agent is a nucleic acid.

28. The method of claim 22, wherein the bioactive agent is a polypeptide.

29. The method of claim 28, wherein the bioactive agent is an immunoglobulin.

30. The method of claim 22, wherein the bioactive agent is fluorescently labeled.

31. The method of claim 22, wherein the bioactive agent is a fluorescently labeled with a nanocrystal.

32. The method of claim 22, wherein the disease marker biological analyte is a nucleic acid.

33. The method of claim 22, wherein the disease marker biological analyte is a polypeptide.

34. The method of claim 33, wherein the disease marker biological analyte is an immunoglobulin.

35. The method of claim 22, wherein the plurality of microchips comprise silicon germanium.

36. The method of claim 22, wherein the microarray scanning device comprises fiber optic elements.

37. The method of claim 22, wherein the analyte interaction profile is stored in the biometric recognition device.

38. The method of claim 22, wherein the analyte interaction profile is stored externally from the medical device.

39. The method of claim 22, having a plurality of reservoirs.

40. The method of claim 22, wherein the interface device comprises a personal area network.

41. The method of claim 22, wherein energy source is a battery.

42. The method of claim 22, wherein energy source is provided by a personal area network.

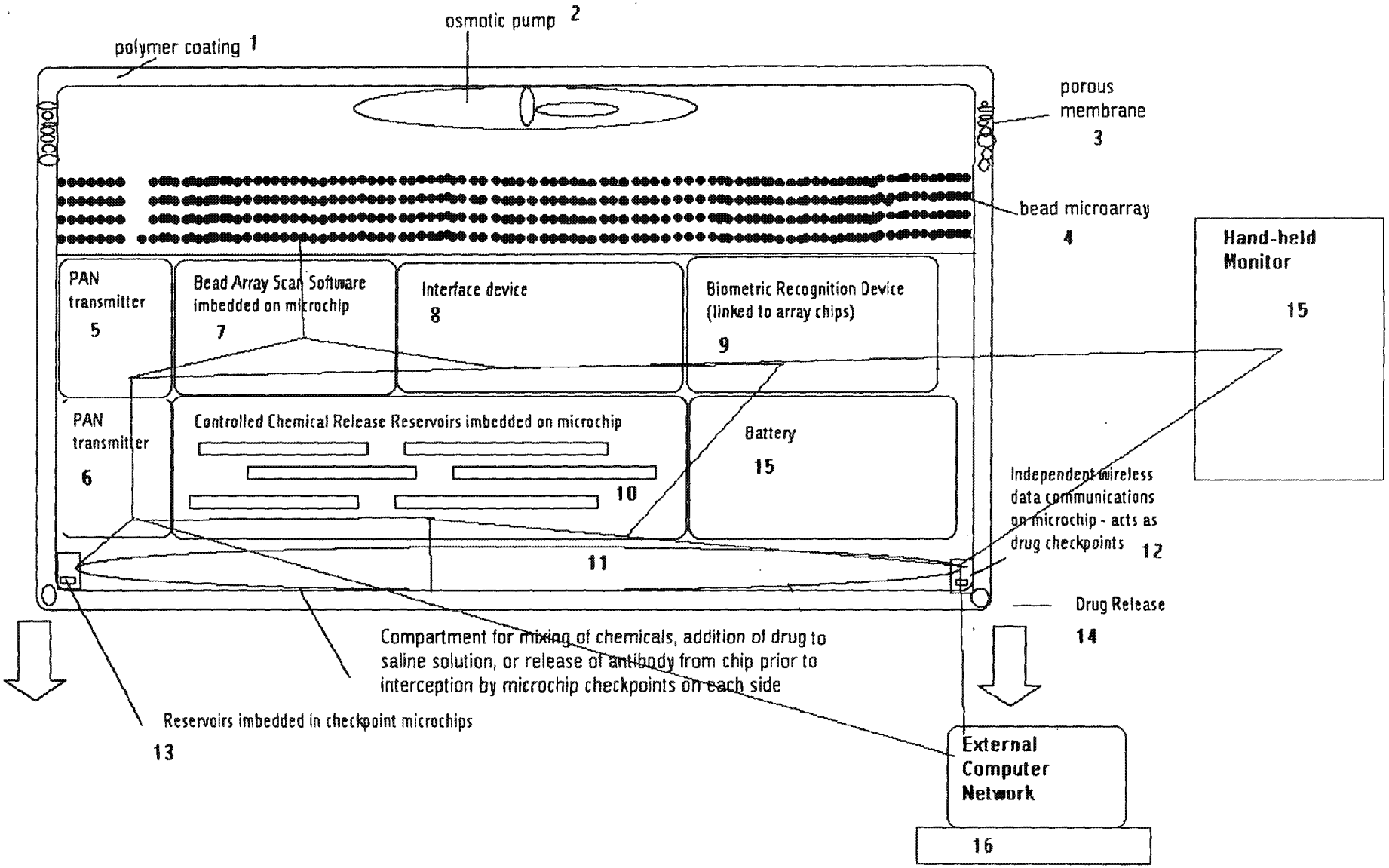
43. The method of claim 22, wherein the communications are monitored by an external computer.

44. The method of claim 43, wherein the external computer directs release of the therapeutic agent.

45. The medical device of claim 1, further comprising an osmotic pump.

46. The medical device of claim, further comprising pressurized microfluidic channels.

47. The medical device of claim 1,further comprising Personal Area Network transmitters directing the flow of bodily fluid.



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