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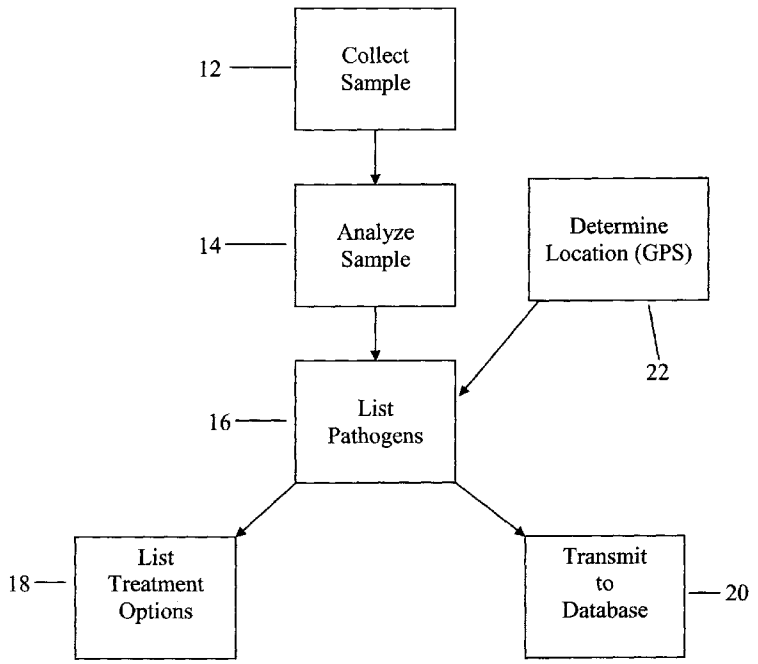
(54) Title: METHOD FOR DETECTING PATHOGENS USING MICROBEADS CONJUGATED TO BIORECOGNITION MOLECULES



(57) Abstract: A method and system are provided for the simultaneous detection and identification of multiple pathogens in a patient sample. The sample is combined with microbeads, which have been injected with quantum dots or fluorescent dye and conjugated to pathogen-specific biorecognition molecules, such as antibodies and oligonucleotides. Treatment options may be determined based on the identities of the pathogens detected in the sample.

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SYSTEM AND METHOD OF DETECTING PATHOGENS

Field of the Invention

[0001] The present invention relates to the field of detecting pathogens. In particular, it relates to a system and method for detecting, identifying, characterizing and surveilling pathogen and host markers, collecting and disseminating information concerning those pathogens and their hosts in real time to and from an instant location, providing instantaneous treatment recommendations and educational information.

Background of the Invention

[0002] Detection and characterization of an infectious disease is a complex process that ideally begins with the identification of the causative agent (pathogen). This has traditionally been accomplished by direct examination and culture of an appropriate clinical specimen. However, direct examination is limited by the number of organisms present and by the observer's ability to successfully recognize the pathogen. Similarly, *in vitro* culture of the etiologic agent depends on selection of appropriate culture media as well as on the microbe's fastidiousness. The utility of pathogen culture is further restricted by lengthy incubation periods and limited sensitivity, accuracy and specificity.

[0003] When *in vitro* culture remains a feasible option, the identification and differentiation of microorganisms has principally relied on microbial morphology and growth variables which, in some cases, are sufficient for strain characterization (i.e. isoenzyme profiles, antibiotic susceptibility profiles, and chematographic analysis of fatty acids).

[0004] If culture is difficult, or specimens are not collected at the appropriate time, the detection of infection is often made retrospectively, if at all, by demonstrating a serum antibody response in the infected host. Antigen and antibody detection methods have relied on developments in direct (DFA) and indirect (IFA) immunofluorescence analysis and enzyme immunoassay (EIA)-based techniques, but these methods can also possess limited sensitivity.

[0005] These existing methods have several drawbacks. First, the process can take several days to return results. In the case of highly communicable and/or dangerous pathogens, confirmation of pathogen type may not be received until the host has already exposed others or has passed beyond treatment. Second, the transportation of samples to laboratories for culture growth increases the risk of errors, such as misidentifying the sample, or exposure of unprotected personnel to a sample containing a highly communicable pathogen. Thirdly, the pathogen tests are limited based on the suspected pathogen list provided by the observer (i.e. doctor), meaning that additional unsuspected pathogens are not tested for but may be present.

[0006] Related to this method of diagnosis is the response to an outbreak of infectious disease. If an outbreak is suspected or detected, the existing response is the hundreds of years old method of quarantine. In cases of infectious disease outbreaks for which appropriate treatments and/or sensitive, specific, and rapid screening/diagnostic tests are lacking, quarantine remains the only means of preventing the uncontrolled spread of disease. When infection is suspected simply based on epidemiological grounds, or even based on comparable disease presentation, healthy or unexposed individuals may be quarantined along with infected individuals, elevating their likelihood of contracting the disease as a consequence of quarantine. Availability of a rapid confirmatory test for the pathogen in question would greatly reduce the time spent in quarantine, and would therefore reduce the likelihood of contacting the disease from truly infected persons.

[0007] Although quarantine remains a method of last resort for protecting public health, delays in providing a correct diagnosis, and subsequently appropriate treatment, occur on a daily basis in hospitals and physician's offices alike. The problem stems from the fact that many diseases have very similar clinical presentations in the early stages of infection, and in the absence of a thorough patient/travel history, malaria or SARS for example, can be misdiagnosed as the common flu (i.e. fever, chills), albeit with potentially fatal consequences. Had a multi-pathogen test which differentiates diseases with similar presentations been available, a tragedy may have been averted.

[0008] In contrast to reliance on morphological characteristics, pathogen genotypic and proteomic traits generally provide reliable and quantifiable information for the detection and characterization of infectious agents. Moreover, microbial DNA/RNA can be extracted directly from clinical specimens without the need for purification or isolation of the agent.

[0009] On a global scale, molecular techniques can be applied in a high throughput manner in screening and surveillance studies monitoring disease prevalence and distribution, evaluation of control measures, and identification of outbreaks.

[0010] Point-of-care diagnostic devices (PDDs) have been developed for a number of individual infectious diseases. In most cases these assays are immunochromatographic single colorimetric strip tests designed to detect a single infectious agent (either a pathogen-specific antigen or an antibody response to one) in a small volume of blood or serum.

[0011] None of these current assays has the capability to detect multiple pathogens or simultaneously detect genomic and proteomic markers of multiple pathogens. Similar limitations exist for other rapid diagnostic assays. Since almost all these tests rely on a single visual colorimetric change for their readout, the opportunities to detect multiple pathogens are severely impeded and the majority of current PDDs are restricted to the detection of a single pathogen. Consequently, evaluating patients for potential infectious agents or testing a unit of blood for common transmissible agents requires multiple consecutive point-of-care tests to be performed, complicating clinical management, slowing results and significantly escalating costs.

[0012] Many PDDs do not meet what are considered essential requirements including: ease of performance, a requirement for minimal training, the generation of unambiguous results, high sensitivity and specificity, the generation of same day results (preferably within minutes), relative low cost, and no requirement for refrigeration or specialized additional equipment.

[0013] In summary, despite current availability of excellent diagnostic reagents (e.g. antibody and nucleic acid probes) that recognize specific targets for many microbial pathogens, the current strategies have inadequate performance characteristics. Contributing to this is the fact that these reagents are conjugated to organic dyes, gold-labelled particles or enzymes that lack sufficient sensitivity to be detected at the single molecule level. Furthermore, the current PDD platforms and detection schemes typically rely on single macroscopic colorimetric changes and are not well suited to the simultaneous detection of multiple pathogens.

[0014] More recent advances in molecular diagnostics, including real-time PCR combined with automated specimen processing, have addressed a number of the limitations of earlier "in-house" and non-standardized gene amplification assays. These assays represent a significant advance in detecting, quantifying, and characterizing many microbes and currently represent the "gold" or reference standard for infectious disease diagnostics for a number of pathogens. However, these assays are still complex, expensive, and require specialized equipment, creating a number of barriers to their potential application at point-of-care.

[0015] Finally, current genomic or proteomic detection strategies require a sample processing and technical commitment to one strategy or the other. There is no current capacity to simultaneously detect both antigenic targets for some pathogens and genetic targets for others. This limits the simultaneous detection of preferred pathogen-specific targets and presents a barrier to fully exploiting the complementary power of both strategies.

[0016] A system is needed which enables pathogen detection, identification and characterization, as well as host characterization in a much more timely manner than existing methods. Preferably, such a system would support a modular pathogen selection platform, based on the specific needs of the caring physician or clinic in the context in which the device is used (i.e. for screening or diagnosis). Further, the system would also enable simultaneous detection, identification and characterization of multiple pathogens

in a single sample whereby the pathogens are differentiated by optical pathogen-specific profiles stored in a pre-existing database.

Summary of the Invention

[0017] According to an aspect of the invention there is provided a method of performing one or more of: detecting, identifying and characterizing pathogens and characterizing pathogen hosts using markers for pathogens and hosts, comprising the steps of: a) preparing a marker-detection medium containing signatures of the identity and characteristics of pathogens and optionally of hosts; b) collecting a sample from a host; c) combining the sample with the marker-detection medium and d) analyzing the signatures to detect, identify and characterize the pathogens, and optionally, characterize the host.

[0018] Preferably, the sample collected is a blood sample, although plasma, serum, cerebral spinal fluid (CSF), bronchioalveolar lavage (BAL), nasopharyngeal (NP) swab, NP aspirate, sputum and other types of samples can also be used, and the marker detection system is a pathogen-detection medium preferably comprising microbeads conjugated to biorecognition molecules (BRMs) and the microbeads are injected with quantum dots or a similar fluorescent particle or compound. Also preferably, each of the microbeads contains a unique combination of quantum dots to provide a unique optical barcode associated with each microbead for detecting unique pathogen-specific and / or host-specific signatures.

[0019] Preferably, the analysis step comprises illuminating the microbead-pathogen sample with a laser as it flows through a microfluidic channel and collecting the resulting spectra with a spectrophotometer/CCD camera, photomultiplier tube and/or a collection of avalanche photodetectors (APDs). Each spectrum correlates with a previously assigned pathogen.

[0020] Optionally, the method may include producing a list of host characterization markers associated with said host sample as part of analysis step d).

[0021] Optionally, the method may include an additional step e) of providing a list of treatment options based on the list of pathogens generated in analysis step d).

[0022] Optionally, the method may also include step f) of correlating geographic location information data with the list of pathogen and host markers generated in analysis step d) via a GPS locator.

[0023] Preferably, the method further includes an additional step g) of transmitting, preferably wirelessly, said list of pathogen markers and said list of host identifier markers and said geographic location data to a remote database as well as transmitting treatment and educational information from the database to the filed device. It will be appreciated that the steps of the process are not necessarily conducted in the specified order.

[0024] The method further includes detection of pathogen-conjugated microbeads in a flow stream propelled by electrokinetic or hydrodynamic flow through a microfluidic channel. As the barcoded beads pass a laser beam at one end of the channel, the spectra emitted by the quantum dots within the beads, (as part of the barcode), or outside the beads (as part of a bead-pathogen complex detection mechanism, which may include fluorophores as described below) are collected by a spectrometer/CCD camera system, photomultiplier tube and/or a collection of APDs and analyzed by appropriate software.

[0025] According to another aspect of the invention a system of components is provided which is capable of executing any of the above methods.

[0026] The advantages of the present invention include a vast reduction in the amount of time necessary to identify pathogens in a patient sample, compared with most methods currently in use, as well as the ability to provide rapid on-site information concerning treatment and quarantine measures for any identified pathogens. Another advantage is the ability to collect patient and pathogen data in a global database and mine the information contained in this database to produce trends and tracking measures for various pathogens and their hosts, which information may be used for surveillance, research, therapeutic design, and other purposes.

[0027] Other and further advantages and features of the invention will be apparent to those skilled in the art from the following detailed description thereof, taken in conjunction with the accompanying drawings.

Brief Description of the Drawings

[0028] The invention will now be described in more detail, by way of example only, with reference to the accompanying drawings, in which like numbers refer to like elements, wherein:

Figure 1 is a flow chart detailing the series of steps in the inventive method disclosed herein;

Figure 2 is a block diagram for a pathogen detection device; and

Figure 3 is a block diagram of multiple devices communicating with a central database.

Detailed Description of the Preferred Embodiments

[0029] Referring now to **Figure 1**, the present inventive method is described by a series of steps set out in a flowchart.

[0030] The first step **12** is to collect a sample from a host (e.g. a human, animal or environmental sample), preferably a blood sample, although plasma samples, serum samples, CSF, BAL, NP aspirates, NP swabs, sputum and other types of physical samples can be used, as appropriate. This sample is then analyzed **14** and a list of pathogens identified in the sample is generated **16**. A GPS receiver **22** determines the location of the sample reader and thus, the sample. The list of identified pathogens and the location information are both sent **20** to a central database for storage and processing. Meanwhile, a list of treatment options is displayed at **18**, based on the identified pathogens, for the operator's consideration.

[0031] The analysis **14** is performed by a pathogen detection device **30** as shown in **Figure 2**. This device **30** is portable, preferably hand-held, and has an outlet **32** for receiving a sample and a display **36** to show the list of detected pathogens within the sample. An input device **38**, such as a keyboard, is also provided to enable scrolling and viewing of the display and input of additional information (field notes, etc.). Pathogens in a sample are identified based on matching of spectra to previously stored data corresponding to each pathogen supported by the device. The spectra database may be an internal database on the device **30** (kept in flash memory or similar storage to allow for updating) or retrieved by communicating with an external database. A GPS receiver **35** is also preferably located in the device **30**, along with a display showing the GPS co-ordinates. Ideally, all communication is conducted wirelessly for maximum range and portability. The pathogen detection device **30** is ideally capable of detecting multiple pathogen, multiple BRMs from the same pathogen as well as host markers within a single sample, and preferably markers of different types, such as protein-based markers and gene-based markers.

[0032] The method of detection used can be varied among suitable available methods, however, a preferred method is the use of biorecognition molecules (BRMs) conjugated to quantum dot-doped microbeads or nanobeads/nanoparticles. Alternatives include single quantum dots or fluorophores conjugated to BRMs. Quantum dots, also known as semiconductor nanocrystals, are electromagnetically active nanotechnology-based particles, ranging in size from 2 nanometers (nm) to 8 nm. A particularly useful property of quantum dots is that they are fluorescent, that is they emit light after brief illumination by a laser. In addition, quantum dots of different sizes will fluoresce in different colors and the fluorescing color can be modified by the particle's shape, size and composition. BRMs are biological molecules that bind only to a single other biological molecule and are pathogen specific. For example, "antibodies" are BRMs that bind to proteins and "oligonucleotide probes" are BRMs that bind to complementary gene sequences (e.g. DNA or RNA). Pathogens and hosts have both unique and shared genetic and protein markers, and each marker can be bonded to by a specific BRM.

[0033] A microbead, which is a polystyrene (or similar polymer) bead that can be 100 nanometers-10 micrometers in diameter and doped with a collection of quantum dots, is physically conjugated to a BRM. By introducing unique combinations of quantum dots of different sizes (i.e., colors) and at different concentrations into the microbeads, microbeads with thousands of distinctive combinations of quantum dot colors and intensities can be created. When a laser illuminates the microbeads, the quantum dots fluoresce to produce a distinctive combination of colors. These color combinations are an example of a barcode, in this case an optical bar code, analogous to a UPC symbol, and similar known types of imprinted barcodes. Since each BRM recognizes a distinct pathogen or host marker and each microbead has a unique barcode, each BRM-conjugated microbead provides a barcode for the specific pathogen or host marker recognized by its BRM. These BRM-conjugated microbeads, as well as BRM-conjugated quantum dots, may be lyophilized into a powder and provided in the sample analysis kit.

[0034] To differentiate between BRM-conjugated beads bound to pathogens and those that are not, an additional confirmatory detection signal in the form of anti-human IgG, and/or an anti-human IgM molecule, or a pathogen-specific antibody (i.e. anti-X antibody), or an oligonucleotide (complementary to a pathogen gene of interest) conjugated to a fluorophore, is included. The readout of a successful pathogen detection test comprises the bead barcode signal and a second signal generated by the fluorophore.

[0035] One example of pathogen detection is an antigen capture system. The antigen capture system includes a capture antibody (i.e. a BRM) which is bound to the barcoded microbead which is responsible for capturing the antigen from the sample. A second antibody (detection antibody) which recognizes the pathogen antigen/protein then binds to the complex. This detection antibody is conjugated to a fluorophore. When the sample is analyzed, if the signal for the detection antibody is not detected, the pathogen does not register as detected, either because it is not present in the sample or because of assay failure. The latter case is eliminated if the correct signals from the positive control sample, i.e. detection of the appropriate bar code of the BRM-quantum dot-containing microbead run in parallel with all clinical tests are detected.

[0036] Another example of pathogen detection is an antibody capture system. In the antibody capture system the BRM which is bound to the barcoded microbead is a pathogen-specific antigen or protein (natural, recombinant, or synthetic). The complementary antibody to the antigen, if present in the clinical sample would bind the antigen attached to the bead. This complex is recognized by the addition of a secondary (detection) anti-human antibody (Anti-Human IgM or Anti-Human IgG). This detection antibody is conjugated to a fluorophore. Again, when the sample is analyzed, if the signal for the detection antibody is not detected alongside the signal from the bead barcode the pathogen does not register as detected, either because it is not present in the sample, or due to assay failure. The latter case is eliminated if the expected signals from positive control sample, as mentioned above, register correctly.

[0037] Still another example of pathogen detection is a genomic analysis system. In the genomic analysis system the BRM which is bound to the barcoded microbead is a pathogen-specific oligonucleotide (RNA or DNA) (1-25 bases in length). Upon addition to the sample, the oligonucleotide will hybridize to its complementary sequence on the pathogen gene. A second oligonucleotide sequence complimentary to a downstream portion of the gene of interest is subsequently added and will hybridize to the gene, if present. This second sequence is conjugated to a fluorophore. Again, when the sample is analyzed, if the signal for the second sequence is not detected, the pathogen does not register as detected, either because it is not present in the sample or because of assay failure. A correctly detected positive control sample as referred to above eliminates the latter scenario.

[0038] The biological (e.g. blood) sample is added to a vial, and different pathogen markers bind the various microbeads carrying specific pathogen BRMs. The combined sample is then washed or otherwise treated to remove extraneous matter and unattached microbeads. The detection antibodies conjugated to the fluorophores are then added to produce a bead-sample-detector complex.

[0039] The bead-sample-secondary detector complex is flowed through a microfluidic channel via hydrodynamically or electrokinetically-driven flow and passed

through a laser beam located at one end of the channel. The laser beam illuminates the quantum dots in the complex and the emitted wavelengths are guided to either a spectrometer/CCD system, photomultiplier tube and/or a series of APDs. Signal deconvolution software translates the signal and the corresponding optical code is compared to pathogen-specific spectra stored in the database of pathogens or host characteristics supported by the detection device. Then, a list of detected pathogens and pathogen and host characteristics is produced. The response time from the taking of the original biological sample to the production of the pathogen list can be measured in minutes.

[0040] Ideally, the pathogen detection device **30** is a portable, hand-held device with an integrated laser and spectrophotometer, photomultiplier tube and/or series of APD units, specifically designed PDMS microfluidic channel chips, a supply of BRM conjugated barcoded beads for identification of various pathogens as well as appropriate bead-pathogen complex detection markers (quantum dot, fluorophore, small bead labeled IgG/IgM/anti-pathogen antibodies or oligonucleotides). The device **30** may store a pathogen identity database on board, or access a remote database, preferably via the Internet, preferably wirelessly, and identify the pathogen from a remote, central database. If an on-board database is used, a communications system **34** for contacting and receiving updates from a larger, central database is provided.

[0041] The pathogen detection device **30** may include a GPS tracking device which transmits specific geographic information, preferably wirelessly to the same central database.

[0042] Once the pathogen list is produced, the pathogen detection device **30** may additionally provide further information of value to the diagnosing doctor. Ideally, a treatment protocol is provided (step **18**), including any special measures necessary to avoid communication of the pathogen. Other information, such as pathophysiology, disease history and bibliographic references can be provided, enabling the pathogen detection device **30** also to be used as an educational tool in the appropriate scenarios.

[0043] An outbreak scenario for use of the device in a standard pathogen detection setting follows. An airport is a point of entry representing a major pathogen travel vector, as well as presenting problems with implementing traditional detection and quarantine methods. By equipping medical staff with a number of pathogen detection devices as described herein, and a supply of microbead sample vials able to detect pathogens typically transmitted by travelers, incoming passengers can be processed on-site by taking a blood sample and injecting it into a sample vial. The analysis is performed by the pathogen detection device within minutes and the sampled passenger can be quickly released or redirected for treatment and observation, as necessary. While a single device is limited in processing capability, the ability to provide multiples of identical devices can enable processing of passengers in a matter of hours, not days. Faster processing allows appropriate treatment and quarantine measures to be taken earlier, and be more effective, reducing the probability of the pathogen spreading unchecked.

[0044] As an example, a pathogen detection device may contain BRM-conjugated barcoded microbeads for detection of three different pathogens, say, HIV, Hepatitis B and Hepatitis C. The microbeads associated with each pathogen have a separately identifiable barcode, for example, HIV may have red beads (e.g. detecting the antibody gp41 as indicator of HIV infection), Hepatitis B yellow beads (e.g. detecting the antibody NSP_4 as indicator of Hepatitis B infection), and Hepatitis C red-yellow beads (e.g. detecting the antibody anti-NSP_4 as indicator of Hepatitis C infection), and preferably all using orange probes-pathogen complex detection markers or any color-probe that is spectrally different than the color of the barcodes. Thus, the detection system can readily identify any detected pathogen merely by the wavelength (which identifies color) or intensity of the bead spectra.

[0045] From this model, the system can readily be expanded, for example, to five pathogens, adding, for example, pathogen detection microbeads for malaria and dengue virus. From there, extrapolation to more pathogens (10, 20, 100) is mostly limited by the ability to create a sufficient number of barcodes, which is based primarily on the doping

of the microbeads and limits of the detection mechanism. As the number increases, barcodes may be based on intensity levels, as well as wavelength.

[0046] Detecting and providing a treatment protocol for a pathogen represents merely the first step in a potentially much larger process for tracking and controlling the spread of pathogens as shown in **Figure 3**. Tailoring the device to be modular and be able to detect either an array of pathogens (i.e. BRMs for multiple pathogens) with similar clinical presentations, act as a screening tool (e.g. for identifying individuals vaccinated for selected diseases) or allowing physicians or clinics to select the pathogens of interest in their particular communities, allows for unprecedented diagnostic flexibility at the bedside. Incorporation of multiple BRMs for the same pathogen enhances detection accuracy and overcomes the limitations associated with use of single BRMs for pathogen detection (i.e. mutations and strain differences which may result in false negative or false positive results). The test results data along with the geographic location data (but no other information about the patient e.g. name, address and other privacy-protected data) provided by the GPS unit, are transmitted to a central database **40**. The information is preferably sent wirelessly, and immediately upon generation of the pathogen list (step **20**). The central database **40** is in contact with a substantial number of pathogen detection devices **30** at any given time.

[0047] The central database **40** can be local, national or global, or a combination of different databases of these types. Ideally, one top-level central database **40** is provided which receives information constantly from all devices **30** worldwide. Over time, the database becomes a repository of information on every pathogen supported by the detection platform lending itself to mining for, among others, frequency and global patterns of detection of pathogens, long-term pathogen trends (i.e. colonization of new territories), and correlations between pathogens and host markers which may indicate enhanced susceptibility or resistance to the disease.

What is claimed is:

1. A method of performing one or more of: detecting pathogens, identifying pathogens, characterizing pathogens or characterizing pathogen hosts, comprising the steps of:

preparing a pathogen-detection medium for detection of pathogen and host markers;

collecting a sample from a host;

combining said sample with said pathogen-detection medium containing pathogen-specific detectors; and

analyzing said combined sample to produce a list of pathogens contained within the host, and a list of pathogen and host characteristics.

2. The method of claim 1, further including collecting location information for one or more of: said pathogen and said host.

3. The method of claim 2, wherein said location information is collected via a GPS-enabled device.

4. The method of claim 1, wherein said sample collected in said collecting step is one of: a blood sample, a plasma sample, CSF, a serum sample, BAL, NP swabs, NP aspirates, or sputum.

5. The method of any of claims 1-4, wherein said pathogen-detection medium comprises microbeads conjugated to pathogen-specific biorecognition molecules (BRMs) and said microbeads contain one of: quantum dots, fluorescent dyes, or a combination thereof.

6. The method of claim 5, wherein each of said microbeads contains a unique combination of quantum dots, based on color and intensity of said quantum dots, to

provide a unique optical barcode associated with said each microbead-pathogen detection combination.

7. The method of claim 6, wherein each barcoded microbead conjugated to its appropriate pathogen is further conjugated to a detection molecule and the resulting combination complex is detected by a second signal from said detection molecule to generate a pathogen-detection optical signature.

8. The method of claim 7, wherein said second signal in said detection molecule is produced by a fluorophore.

9. The method of any of claims 7-8, wherein said detection molecule is conjugated to one of: an anti-human IgG molecule, an anti-human IgM molecule, an anti-pathogen detection antibody, or an oligonucleotide sequence.

10. The method of any of the preceding claims, wherein said analyzing step comprises illuminating said bead-pathogen-detection signal complex with a laser, measuring a resulting spectrum and identifying the pathogen from a database.

11. The method of claim 10, wherein said measuring step is performed by: a combined spectrophotometer/CCD camera, a photomultiplier tube, a collection of Avalanche Photodetectors, or a combination thereof.

12. The method of any of claims 9-11, wherein said analyzing step comprises flowing the sample complex through a microfluidic channel under the influence of flow forces, through a laser beam and capturing a resulting spectrum.

13. The method of claim 12 wherein said microfluidic channel comprises a PDMS cast channel which is plasma treated, and bound to a glass slide.

14. The method of claim 12 or claim 13, wherein said flow forces are either electrokinetic or hydrodynamic forces.

15. The method of any of claims 9-14, wherein said identification of the pathogen is achieved via matching of the resulting sample spectrum to a collection of pathogen-specific spectra from a database.

16. The method of claim 15, wherein said database is located on-board the GPS-enabled device.

17. The method of claim 15, wherein said database is remote and accessed wirelessly.

18. The method of any of the preceding claims, further including producing a list of host characteristic markers associated with the sample from the host as part of said analyzing step.

19. The method of any of the preceding claims, further including an additional step of providing a list of treatment options based on the list of pathogens generated in the analysis step.

20. The method of any of the preceding claims, further including an additional step of transmitting said list of pathogens and pathogen characteristics and said list of host characteristics to a remote database.

21. The method of any of the preceding claims, wherein the pathogen-detection medium includes detectors for at least three specific, predetermined pathogens.

22. The method of any of the preceding claims, wherein the pathogen-detection medium includes detectors for HIV, Hepatitis B and Hepatitis C.

23. The method of any of the preceding claims, wherein the pathogen-detection medium includes detectors for HIV, Hepatitis B, Hepatitis C, malaria and Dengue virus.

24. A system for one or more of: detecting pathogens, identifying pathogens, characterizing pathogens or characterizing pathogen hosts, comprising:

a) a sample medium containing pathogen-specific biorecognition molecules (BRMs) to be combined with a host sample; and

b) a pathogen detection device for analyzing said sample medium and generating a list of pathogens and pathogen and host characteristics detected within said sample medium.

25. The system of claim 24, further including a database containing information on different pathogens and a connection on said pathogen detection device to enable communication with said database.

26. The system of any of claims 24-25, wherein said connection to said database is provided by a wireless communications network.

27. The system of any of claims 24-26, wherein said sample medium comprises microbeads conjugated to pathogen-specific biorecognition molecules (BRMs) and said microbeads contain quantum dots and said host sample is one of: a blood sample, a plasma sample, CSF, a serum sample, a BAL, a NP swab, an NP aspirate, or a sputum sample.

28. The system of claim 27, wherein each of said microbeads contains a unique combination of quantum dots to provide a unique optical barcode associated with each pathogen.

29. The system of claim 27, wherein each barcoded microbead conjugated to its appropriate pathogen is further conjugated to a second signal generating complex to generate a pathogen-detection optical signature.

30. The system of claim 29, wherein said second signal generating complex is a fluorophore.

31. The system of claim 30, wherein said fluorophore is conjugated to one of: an anti-human IgG molecule, or an anti-human IgM molecule, or an anti-pathogen detection antibody, or an oligonucleotide sequence.

32. The system of any of claims 24-31, wherein said pathogen detection device comprises a laser for illuminating said sample and one of: a spectrometer/CCD camera

combination , a photomultiplier tube, a collection of Avalanche Photodetectors (APDs) or a combination thereof for detecting a resulting spectrum.

33. The system of any of claims 24-32, wherein said pathogen detection device further includes a list of treatment options based on the list of pathogens generated.

34. The system of any of claims 24-33, wherein said pathogen detection device further includes means to generate a list of host characterization markers associated with said host sample.

35. The system of any of claims 25-34, wherein said list of host characteristics and said list of pathogens and pathogen characteristics is transmitted to said database.

36. The system of claim 35, wherein transmission to said database occurs automatically upon generation of said lists.

37. The system of any of claims 24-36, wherein said analyzing step comprises illuminating said bead-pathogen-detection signal complex with a laser and measuring a resulting spectrum and identifying the pathogen from a database.

38. The system of claim 37, wherein the analyzing of said sample involves driving the sample through a microfluidic channel and through a laser beam by flow forces and capturing a resulting spectrum.

39. The system of claim 38, wherein said microfluidic channel comprises a PDMS cast channel which is plasma treated, and bound to a glass slide.

40. The system of any of claims 38-39, wherein said flow forces are either electrokinetic or hydrodynamic forces.

41. The system of any of claims 37-40, wherein said resulting spectrum is directed via a filter to one of: a spectrometer, a series of avalanche photodetectors (APD)s, a photomultiplier tube,or a combination thereof.

42. The system of any of claims 37-41, wherein said identification of the pathogen is achieved via matching of the resulting sample spectrum to a collection of pathogen-specific spectra from said database.

43. The system of any of claims 25-42 wherein said database is on-board the device.

44. The system of any of claims 25-42, wherein said database is remotely located and accessed wirelessly.

45. The system of any of claims 24-44, the device further including a GPS locator device to provide location data associated with said sample.

46. The system of any of claims 27-45, wherein said BRM-conjugated microbeads and BRM-conjugated fluorophores are provided as a lyophilized powder.

47. The system of any of claims 24-46, wherein said BRMs are one or more of: native, recombinant or synthetic pathogen and host specific antibodies or antigens or oligonucleotides complementary to pathogen or host genes of interest.

48. The system of any of claims 24-47, wherein pathogen-specific biorecognition molecules includes BRMs for at least three specific, predetermined pathogens.

49. The system of any of claims 24-48, wherein the pathogen-specific biorecognition molecules includes BRMs for HIV, Hepatitis B and Hepatitis C.

50. The system of any of claims 24-49, wherein the pathogen-specific biorecognition molecules includes BRMs for HIV, Hepatitis B, Hepatitis C, malaria and Dengue virus.

AMENDED CLAIMS
received by the International Bureau on 25 July 2007 (25.07.2007)

1. A method of performing one or more of: detecting one or more pathogens, identifying one or more pathogens, characterizing one or more pathogens or characterizing a pathogen host, comprising the steps of:

providing a detection medium containing pathogen-specific identification complexes and host marker identification complexes for detection of pathogens and host markers;

collecting a clinical sample from a host;

combining said clinical sample with said detection medium and a detection molecule to generate a detection complex

analyzing said detection complex with a detection element in a diagnostic device by detecting spectral signals from detection molecules and pathogen / host marker identification complexes to produce a list of pathogens contained within the host, and a list of pathogen characteristics and host characteristics.

2. The method of claim 1, further including collecting geographic location information from said detection device for one or more of: said pathogens and said host.

3. The method of claim 2, wherein said location information is collected via a GPS-enabled (Global Positioning System) element within the diagnostic device.

4. The method of claim 1, wherein said clinical sample collected in said collecting step is one of: a blood sample, a plasma sample, CSF (Cerebrospinal Fluid), a serum sample, BAL (Bronchoalveolar lavage), NP (nasopharyngeal) swabs, NP aspirates, or sputum.

5. The method of any of claims 1-4, wherein said identification complexes in said detection medium comprise microbeads conjugated to pathogen-specific or host-specific biorecognition molecules (BRMs) and said microbeads contain one of: quantum dots, fluorescent dyes, or a combination thereof to provide a first signal to the detection element.

6. The method of claim 5, wherein each of said microbeads contains a unique combination of quantum dots, based on color and/or intensity of said quantum dots, to provide a unique optical barcode as said first signal associated with said each pathogen or host marker identification complex.

7. The method of claim 6, wherein said detection complex identifies a pathogen or host characteristic by the combination of said first signal and a second signal emitted by said detection molecule to generate a specific detection optical signature.

8. The method of claim 7, wherein said second signal from said detection molecule is produced by a fluorophore.

9. The method of claim 7 or claim 8, wherein said detection molecule comprises a fluorophore conjugated to one of: an anti-human IgG molecule, an anti-human IgM molecule, an anti-pathogen / host marker detection antibody, or an oligonucleotide sequence.

10. The method of any of claims 7-9, wherein said analysis step comprises illuminating said detection complex with a laser, measuring a resulting spectrum and identifying the pathogens.

11. The method of claim 10, wherein said measuring step is performed by: a combined spectrophotometer/CCD (Charge-coupled Device) camera, a photomultiplier tube, a collection of Avalanche Photodetectors, or a combination thereof.

12. The method of any of claims 7-11, wherein said analysis step comprises flowing the detection complex through a microfluidic channel under the influence of flow forces, through a laser beam and capturing a resulting spectrum.

13. The method of claim 12 wherein said microfluidic channel comprises a PDMS (polydimethylsiloxane) cast channel which is plasma treated, and bound to a glass slide.

14. The method of claim 12 or claim 13, wherein said flow forces are either electrokinetic or hydrodynamic forces.

15. The method of any of claims 10-14, wherein said identification of the pathogens is achieved via matching of a detection optical signature of a sample to a collection of pathogen-specific / host maker specific spectra from a database.

16. The method of claim 15, wherein said database is located on-board the diagnostic device.

17. The method of claim 15, wherein said database is remote and accessed wirelessly.

18. The method of any of claims 1-17, further including producing a list of host characteristics associated with the clinical sample from the host as part of said analysis step.

19. The method of any of claims 1-17, further including an additional step of providing a list of treatment options based on the list of pathogens generated in the analysis step.

20. The method of any of claims 1-17, further including an additional step of transmitting said list of pathogens and pathogen characteristics and said list of host characteristics to a remote database.

21. The method of any of claims 1-17, wherein the detection medium includes identification complexes for at least three specific pathogens.

22. The method of any of claims 1-17, wherein the detection medium includes identification complexes for HIV, Hepatitis B and Hepatitis C.

23. The method of any of claims 1-17, wherein the detection medium includes identification complexes for HIV, Hepatitis B, Hepatitis C, malaria and Dengue virus.

24. A system for one or more of: detecting pathogens, identifying pathogens, characterizing pathogens or characterizing pathogen hosts, comprising:

a) a detection medium containing pathogen-specific identification complexes and host marker identification complexes operative to be combined with a clinical sample and a detection molecule to form a detection complex; and

b) a diagnostic device, including a detection element for detecting and analyzing signals from said detection complex and operative to generate a list of pathogens and pathogen characteristics and host characteristics detected within said clinical sample.

25. The system of claim 24, further including a database containing information on different pathogens and pathogen / host characteristics and a connection on said diagnostic device to enable communication with said database.

26. The system of claim 25, wherein said connection to said database is provided by a wireless communications network.

27. The system of any of claims 24-26, wherein said detection medium comprises microbeads conjugated to pathogen-specific or host marker biorecognition molecules (BRMs) to form an identification complex and said microbeads contain quantum dots to provide a first signal and said clinical sample is one of: a blood sample, a plasma sample, CSF (Cerebrospinal Fluid), a serum sample, a BAL (Bronchoalveolar lavage), a NP (nasopharyngeal) swab, a NP aspirate, or a sputum sample.

28. The system of claim 27, wherein each of said microbeads contains a unique combination of quantum dots to provide a unique optical barcode representing said first signal associated with each pathogen / host marker identification complex.

29. The system of claim 27 or claim 28, wherein said detection molecule comprises a signal generating molecule operative to generate a second signal and together with said first signal define a specific detection optical signature for said detection complex.

30. The system of claim 29, wherein said signal generating detection molecule is a fluorophore.

31. The system of claim 30, wherein said fluorophore is conjugated to one of: an anti-human IgG molecule, or an anti-human IgM molecule, or an anti-pathogen / host marker detection antibody, or an oligonucleotide sequence.

32. The system of any of claims 24-31, wherein said detection element comprises a laser for illuminating said clinical sample and one of: a spectrometer/CCD (Charge-coupled Device)

camera combination , a photomultiplier tube, a collection of Avalanche Photodetectors (APDs) or a combination thereof for detecting a resulting spectrum.

33. The system of any of claims 24-32, wherein said diagnostic device further includes a viewable database containing a list of treatment options based on the list of pathogens generated.

34. The system of any of claims 24-33, wherein said diagnostic device is further operative to generate a list of host characteristics associated with said clinical sample.

35. The system of any of claims 25-34, further including a transmitter to transmit said list of host characteristics and said list of pathogens and pathogen characteristics to said database.

36. The system of claim 35, wherein said transmitter is operative to automatically initiate transmission to said database upon generation of said lists.

37. The system of any of claims 29-36, further including a laser operative to illuminate said detection complex and produce a detection optical signature which is captured and measured by the detection element to identify the pathogens.

38. The system of claim 37, further including a microfluidic platform operative to analyze said detection complex by driving the detection complex using flow forces through a microfluidic channel past a point illuminated by said laser.

39. The system of claim 38, wherein said microfluidic channel comprises a PDMS (polydimethylsiloxane) cast channel which is plasma treated, and bound to a glass slide.

40. The system of claim 38 or claim 39, wherein said flow forces are either electrokinetic or hydrodynamic forces.

41. The system of any of claims 37-40, wherein said detection element includes a filter operative to direct said spectrum to one of: a spectrometer, a series of avalanche photodetectors (APDs), a photomultiplier tube, or a combination thereof.

42. The system of any of claims 37-41, further including an analysis device operative to identify the pathogens via matching of the resulting detection optical signature to a collection of previously assigned pathogen or host marker spectra from said database.

43. The system of any of claims 25-42 wherein said database is on-board the diagnostic device.

44. The system of any of claims 25-42, wherein said database is remotely located and accessed wirelessly.

45. The system of any of claims 24-44, the diagnostic device further including a GPS (Global Positioning System) locator element to provide geographic location data associated with said clinical sample.

46. The system of any of claims 27-45, wherein said identification complex is provided as a lyophilized powder.

47. The system of any of claims 24-46, wherein said BRMs are one or more of: native, recombinant or synthetic pathogen and host specific antibodies or antigens or oligonucleotides complementary to pathogen or host genes of interest.

48. The system of any of claims 24-47, wherein the detection medium includes identification complexes for at least three specific, predetermined pathogens.

49. The system of any of claims 24-48, wherein the detection medium includes identification complexes for HIV, Hepatitis B and Hepatitis C.

50. The system of any of claims 24-49, wherein detection medium includes identification complexes for HIV, Hepatitis B, Hepatitis C, malaria and Dengue virus.

51. The system of any of claims 31-45, wherein said detection molecule is provided as a lyophilized powder.

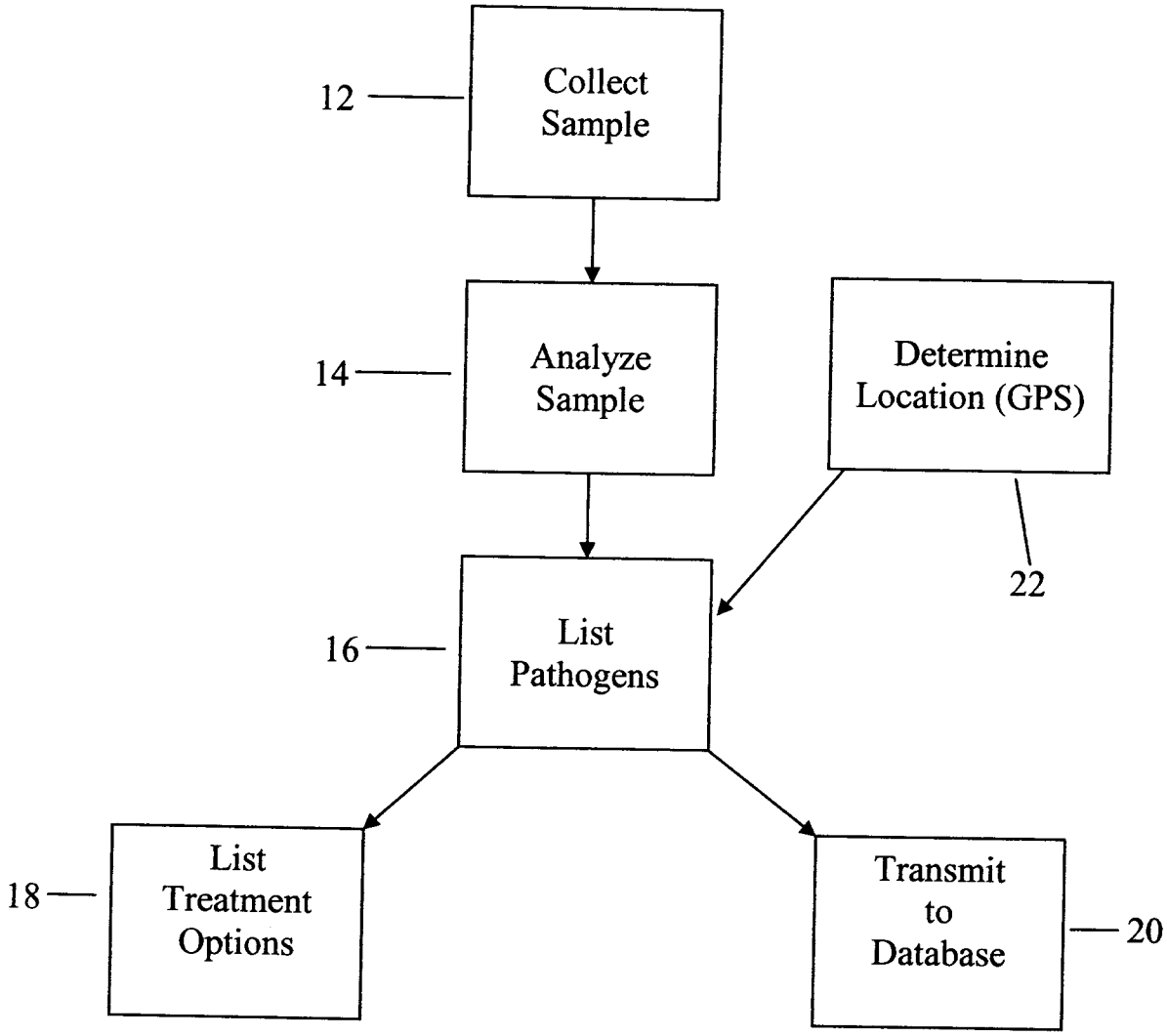
12
Collect Sample
14
Analyze Sample
Determine Location (GPS)
22
16
List Pathogens
18
List Treatment Options
Transmit to Database
20

FIGURE 1

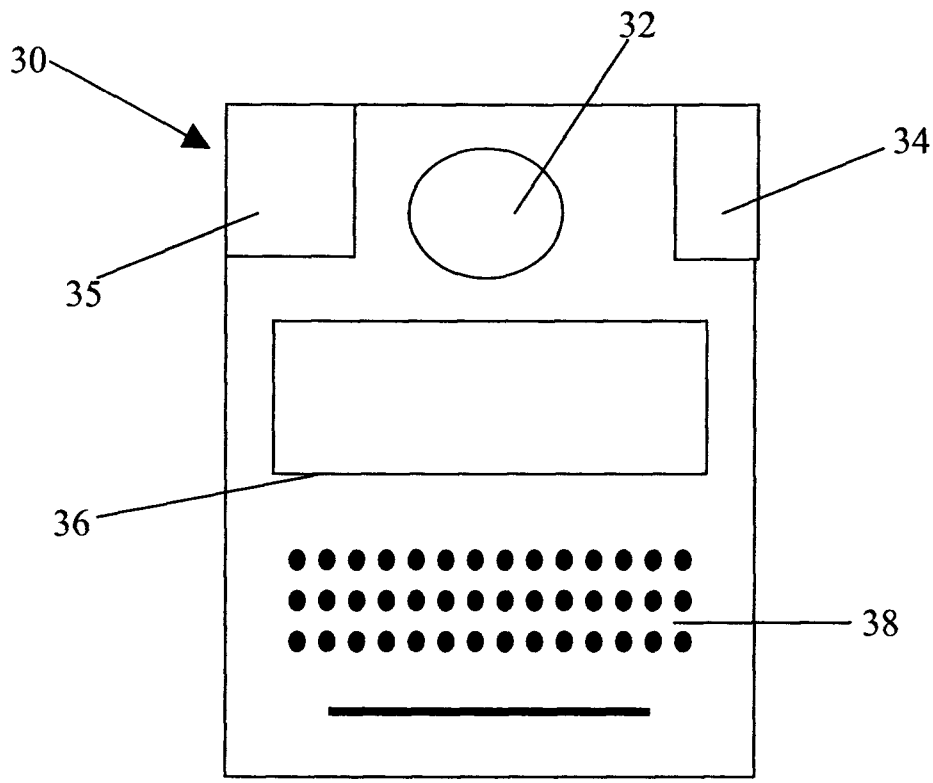

FIGURE 2

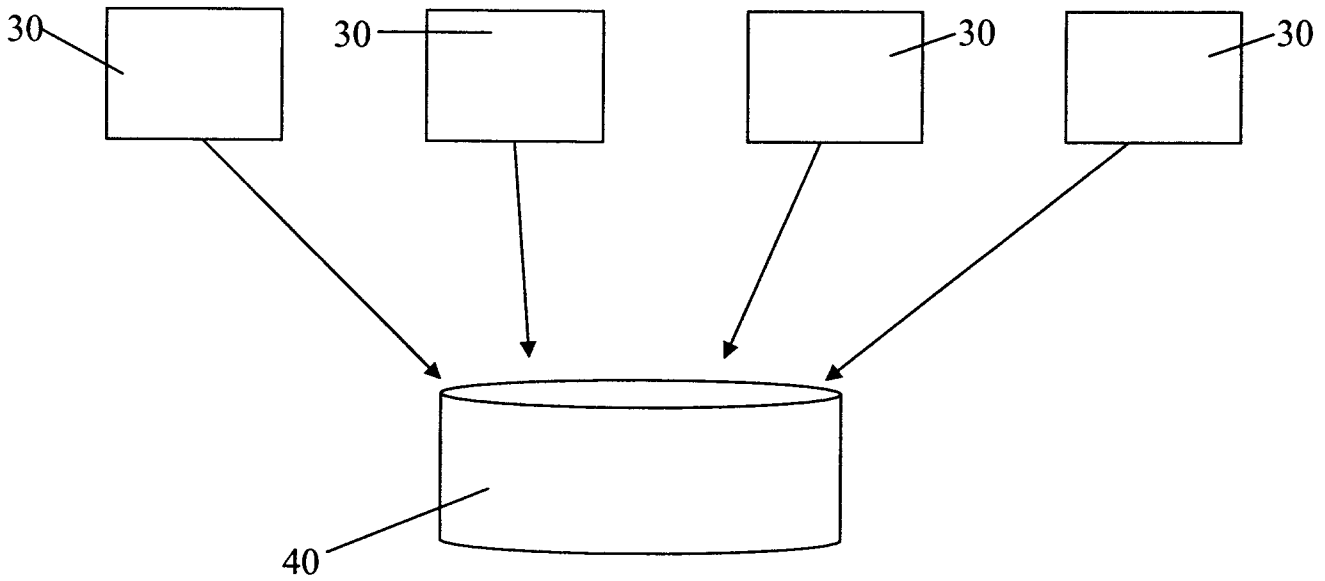

FIGURE 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000211

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C12Q 1/04*** (2006.01) , ***C12M 1/34*** (2006.01) , ***C12Q 1/68*** (2006.01) , ***C12Q 1/70*** (2006.01) , ***G01N 33/53*** (2006.01) , ***G01N 33/569*** (2006.01) , ***G01N 33/58*** (2006.01) , ***G01N 21/25*** (2006.01) , ***G01N 21/27*** (2006.01)
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)
IPC: ***C12Q 1/04*** (2006.01) , ***C12M 1/34*** (2006.01) , ***C12Q 1/68*** (2006.01) , ***C12Q 1/70*** (2006.01) , ***G01N 33/53*** (2006.01) , ***G01N 33/569*** (2006.01) , ***G01N 33/58*** (2006.01) , ***G01N 21/25*** (2006.01) , ***G01N 21/27*** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Delphion, PubMed, Scopus, CAPlus, Medline and BIOSIS; Keywords: pathogen, virus, microorganism, bacteria, biorecognition, quantum dot, semiconductor nanocrystal, microbead, microfluidic, PDMS, plasma, detect, diagnose, database, and point-of-care.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US2005/0043894 A1 (FERNANDEZ, D. S.) 24 February 2005 (24-02-2005) see especially paragraphs [0005], [0026]-[0028], [0033]-[0036], [0043], [0052], [0078], [0100], [102], [0114], [0120], [0131]-[0139], [0149]-[0155] and [0185] and figure 6.	1-5, 10-12, 14-21, 24-26, 32-38 and 40-48 ---------- 13 and 39
X --- Y	WO 03/003015 A2 (ADVANCED RESEARCH AND TECHNOLOGY INSTITUTE, INC.) 9 January 2003 (09-01-2003) see especially paragraphs [0012], [0051], [0057]-[0060], [0069], [0072], [0078]-[0083], [0087]-[0089] and claims 35-56.	1, 4-12, 14, 15, 18, 21-24, 27-32, 34, 37, 38, 40-42 and 46-50 ---------- 13 and 39
X	US 2003/0170613 A1 (STRAUS, D.) 11 September 2003 (11-09-2003) see especially paragraphs [0033]-[0035], [0044]-[0047], [0068], [0078], [0094], [0100], [0260]-[0266], [0272], [0285]-[0287], [0294], [0309], [0323], [0331] and [0391] and example 39.	1, 4, 5, 10, 11, 15, 18-25, 32-37, 41-43 and 46-50

[X] Further documents are listed in the continuation of Box C. [X] 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 another citation or other special reason (as specified)

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 April 2007 (11-04-2007)	25 May 2007 (25-05-2007)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Sandra Hurley 819- 934-7934

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000211

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GRUMANN, M. ET AL.: "Parallelization of chip-based fluorescence immuno-assays with quantum-dot labelled beads" DIGEST OF TECHNICAL PAPERS-INTERNATIONAL CONFERENCE ON SOLID STATE SENSORS, ACTUATORS AND MICROSYSTEMS, TRANSDUCERS '05, June, 2005 vol. 2, article number 3A1.4, pages 1114-1117, ISBN:0780389948 see the whole document	1, 4, 5, 21, 24, 27, and 46-48
X --- Y	ZAYTSEVA, N. V. ET AL.: "Development of a microfluidic biosensor module for pathogen detection" LAB CHIP, August, 2005; available online 6 July 2005 (06-07-2005) vol. 5, no. 8, pages 805-811, ISSN:1473-0197 see the whole document	1, 21, 24, 47 and 48 ---------- -- 13 and 39
P,Y	YUN, K.-S. ET AL.: "A microfluidic chip for measurement of biomolecules using a microbead-based quantum dot fluorescence assay" MEASUREMENT SCIENCE AND TECHNOLOGY, 1 December 2006 (01-12-2006); available online 26 October 2006 (26-10-2006) vol. 17, no. 12, article number S10, pages 3178-3183, ISSN:0957-0233 see the whole document	13 and 39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/000211

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. [X] Claim Nos. : 1-23

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 1-23 are directed to diagnostic methods, which the International Search Authority is not required to search under Rule 39.1 (iv) of the PCT. Regardless, this Authority has established an international search report as if said methods are carried out *in vitro*.

2. [ ] Claim Nos. :

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 :

3. [ ] Claim Nos. :

because they are dependant 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 additional 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 additional fees, this Authority did not invite payment of additional fees.

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 claim 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 claim 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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2007/000211

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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		WO03073817 A3	02-12-2004