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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 February 2008 (14.02.2008)

PCT

(10) International Publication Number
WO 2008/017829 A1

(51) International Patent Classification:
G01N 21/27 (2006.01) *G01N 33/53* (2006.01)

(21) International Application Number:
PCT/GB2007/002994

(22) International Filing Date: 7 August 2007 (07.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0165738.2 8 August 2006 (08.08.2006) GB

(71) Applicant *(for all designated States except US)*: **IVMD (UK) LIMITED,** [GB/GB]; The Green House, Beechwood Business Park North, Inverness, Scotland, IV2 3BL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CONNOLLY, Patricia** [GB/GB]; 41 Hughenden Gardens, Glasgow G12 9YH (GB). **GILMOUR, John** [GB/GB]; 1 Priory Road, Beauly, Inverness-Shire, IV4 7GD (GB). **MITCHELL, Andrew** [GB/GB]; 43 Perthshire Grove, Backshaw Village, Chorley, PR7 7AE (GB). **DJENNATI, Nasr-Eddine** [GB/GB]; 35 Sherway Drive, Timperley, Altrincham WA15 7NU (GB). **COUCHMAN, Paul** [GB/GB]; 7 Park Street, Hopeman, IV30 5SE (GB).

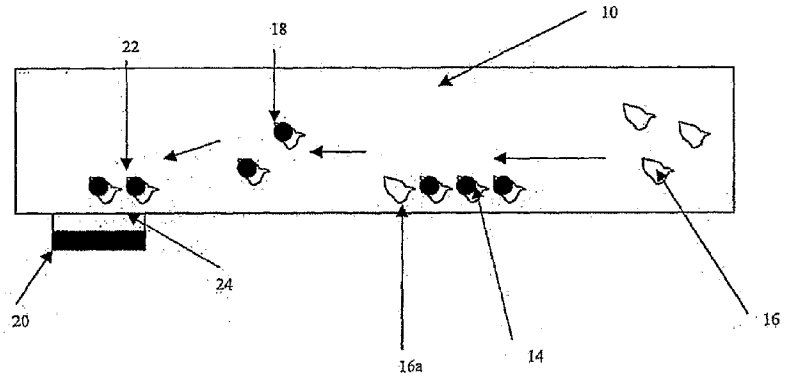
(74) Agents: **ROBEY, James, Edward** et al.; Wilson Gunn, 5th Floor, Blackfriars House, The Parsonage, Manchester M3 2JA (GB).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) **Title:** METHOD OF DETERMINING THE PRESENCE OF SUBSTANCES OF INTEREST IN FLUIDS



(57) **Abstract:** An assay apparatus for comprises an assay strip (10) having a first area with a plurality of tag particles (14) bonded thereto, the tag particles free to adhere or bind to a substance of interest in the fluid or alternatively free to be displaced by a substance of interest in the fluid. A sensing area (22) is also provided on the strip, including a collection means (20) for concentrating the tag particles in the fluid by the collection means thereby providing a visual indication of the presence or absence of a substance of interest in the fluid. The collection means may be in the shape of a word or symbol.

WO 2008/017829 A1

METHOD OF DETERMINING THE PRESENCE OF SUBSTANCES OF INTEREST IN FLUIDS

The present invention relates to a method of determining the presence of substances of interest in fluids, and including although not exclusively the presence of substances of interest in biological fluids including measurement in a living body, such as a human body. In particular, the invention relates to a method of determining the presence of substances of interest in a fluid without the requirement for complex electronics to analyse the fluid.

In many medical, biological, manufacturing and other systems there is a requirement to determine the presence and/or concentration of various substances in fluids, including, but not limited to molecules such as proteins, hormones or DNA. In the normal course of analysis immunoassay systems are employed to measure such molecules. These immunoassays rely on the presence of a tagged antibody or probe (ligand) which adheres to or binds to a molecule of interest. The presence of the tagged probe is detected and the quantity of probe detected related to the concentration of the molecule under analysis. Multiple probe systems with a capture probe or antibody and a second tagged probe or antibody to reveal the captured molecule are common. Probes have been used with tags that are radioactive, enzymatic, fluorescent, chemiluminescent and spectrophotmetric or colourimetric. End points of tagged probe measurement can therefore be revealed in a variety of systems include spectrophotometric, electrochemical, radioactive, colourimetric, amperometric or potentiometric.

Magnetic beads have been employed in multiple probe systems as a solid phase for the capture probe, providing a highly mobile bead system with high surface area for capture probe attachment. Secondary probes or antibodies can then be added after molecular attachment to the capture probe and in the commonest application a magnetic field is then used to draw together the beads allowing a concentrate to form where the level of the tag can be measured.

Typically, this is achieved by using suitable sensing electronics to determine the concentration of the probe and hence determining the concentration of the molecule of interest. This can be read directly by sensing increases in the magnetic field density at positions where the probe tags concentrate as described in WO2005/124345. Alternatively, other properties of the tags may be utilised to enable the measurement of the probe concentration, for example light sensing electronics may be used if the tag is fluorescent. It is also possible to provide an indirect reading of the probe concentration by introducing another solution to react with the probe tag producing an effect measurable by suitable sensing electronics (such as the production of light by chemiluminescent reactions with the tag).

In some prior art methods, a displacement assay is used in the analytical system and measurement of concentration is made by a complex oscillating coil system, and an antibody capture site for particles. This results in more complex manufacture for both the sensing system and the test element.

All of the above methods rely on at least some complex electronics either for controlling an applied magnetic field or for analysing the sample to determine the presence and concentration of the substance of interest. The requirement for such complex electronics increases the cost of such systems and thus reduces the potential market for their application. Furthermore, such electronics mean that users of the methods require a not inconsiderable amount of training before they may be utilised correctly.

It is an object of the present invention to provide an alternative method of determining the presence of substances of interest in a fluid without the use of complex electronics.

According to an aspect of the present invention there is provided a method of determining the presence or absence of one or more substances of interest in a fluid, the method comprising the steps of: passing the fluid over a surface having a quantity of tag particles bound thereto, the tag particles free to adhere or bind to a substance of interest in the fluid or alternatively free to be displaced by a substance of interest in the fluid; introducing the fluid and any tag particles in the fluid into a sensing area; and providing a tag particle collection means in the sensing area so as to concentrate the tag particles by the collection means and thereby provide a visible indication of the presence or absence of a substance of interest.

In this manner, the method of the present invention may provide a clear signal of the presence of substances of interest without the need for extensive electronics.

Moreover the method is ideally suited to a threshold assay or, alternatively, a quantitative response. Furthermore, employing this technique enables rapid analysis of a fluid, and effective analysis of very small volumes of fluid.

The invention may be implemented in a classic 'displacement array' or 'flow displacement array' and the sensing area may be downstream of the surface with the tag particles bonded thereto. The tag particles bound to the surface may be released into the fluid by becoming attached to the substance of interest or by being displaced by the substance of interest. This may occur though a specific bonding substance such as an antibody. A sample of the fluid is introduced to this surface which contains the substance of interest in an unknown quantity. Competition for the binding site on the tag particle from the substance of interest in the sample will release the tag particles into solution in proportion to the concentration of the substance of interest in the sample. The immobilised tag particles can be bound via any suitable bonding substance to substances of interest, multiple layers of different bonding substances can be used to create suitable sites for competition from substances of interest in the sample.

The sensing area may be a chamber such as a fluidics chamber. The chamber may have a volume of less than 10 uL, preferably less than 5uL. Alternatively, this method may be used in other assays with volumes greater than 10uL. In further embodiments, the sensing area may be an area of an assay strip.

The collection means may be in the shape of a word or symbol. The concentration of the tag particles on or around the collection means thus provides a visible pattern in the shape of the collection means, which may be easily and instantaneously read by the user. The shape or word may alternatively be formed by a plurality of collection means mounted adjacent to one another.

In embodiments wherein the presence of a substance of interest stimulates the release of tag particles, the collection means may be in the shape of the word YES or similar. In embodiments wherein the absence of a substance of interest stimulates the release of tag particles, the collection means may be in the shape of the word NO or similar. This provides a clear and simple indication of the presence or absence of a substance of interest within the sample which can be rapidly read by even an unskilled user.

In alternative arrangements, a plurality of separate collection means may be provided, such that a rough quantisation of the amount of tag particles can be obtained by counting the number of collection means over which particles have gathered. In some embodiments, the sensing area may be adapted to aid the gradual collection of tag particles by the provision of a series of collection means along a direction of fluid flow to collect the tag particles in quantised amounts. In such embodiments with a plurality of collection means, the individual collection means may be in the shape of integers. This allows a rough count to be made of the number of particles if say five collection means in the shape of integers 1 to 5 are provided in series but tag particles are visible only over collection means 1 to 3.

In an alternative embodiment, the collection means in the sensing area may be provided over a photovoltaic cell. If tag particles gather over the photovoltaic cell, they will reduce the amount of light incident on the photovoltaic cell and thus reduce the signal level output by the photovoltaic cell. At a predetermined drop in signal level, an indication means connected to the photovoltaic cell may be operable to indicate the presence or absence of a substance of interest in the fluid. The indication means may comprise one or more LEDs. Additionally or alternatively, the indication means may comprise an LCD screen, which may be operable to display text such as YES indicating the presence of a substance of interest and NO indicating the absence of a substance of interest.

In alternative arrangements, an array of photovoltaic cells may be provided, such that a rough quantisation of the amount of tag particles over the photovoltaic cells may be determined. In some embodiments, the sensing area may be adapted to aid the gradual collection of tag particles by the provision of a series of collection means along a direction of fluid flow to collect the tag particles in quantised amounts. A separate photovoltaic cell or photovoltaic cell array may be provided under each collection means.

In embodiments with a plurality of LEDs the number of LEDs lit at any one time may be indicative of the amount of substance present. In embodiments with a plurality of LEDs or an LCD screen may be indicated by an alphanumeric figure indicated on the LCD screen.

In alternative embodiments, one or more additional electronic sensing devices may be provided in addition to or in place of the photovoltaic cell. Such devices may be operable to sense other properties of the tag particles.

The collection means may comprise capture molecules bonded to a surface in the sensing area, the capture molecules adapted to bond with and thereby collect tag particles in the fluid. Typically, suitable capture molecules may include antibodies, probes (ligands) or similar. The collection means may additionally or alternatively comprise suitable traps or wells in a surface over which the fluid sample flows.

In some embodiments, the tag particles may be magnetic tag particles. In such embodiments the collection means may comprise one or more magnets mounted in or adjacent to the sensing area. If one magnet is provided, the magnet is preferably mounted on a surface adjacent to the sensing area and is most preferably comprised of permanent magnetic material printed on to said surface. In some embodiments, a plurality of magnets may be provided so as to collect tag particles on a surface which is not a surface adjacent to that on which the magnets are mounted. In embodiments wherein the collection means has a distinctive shape, the or each magnet may have a distinctive shape in order to provide a collection means having a distinctive shape.

In a further alternative embodiment, the magnet may be aided in the trapping of the magnetic particles by the addition of a capture molecule at certain parts of the assay strip. Said capture molecules can be so placed to aid the kinetics of the assay. Said capture molecules may in photovoltaic cell embodiments increase the electronic

signal from the cell. In purely magnetic embodiments, there is of course, no requirement for a secondary antibody capture site to "collect" the particles together for sensing. This makes the disposable element simpler and cheaper. Additionally, there is no requirement for complex alignment systems between sensor and the sensing area to give accuracy and consistency. The magnet automatically concentrates all freed particles in the sensing area.

In such magnetic embodiments, the photovoltaic cell may be supplemented by or replaced by one or more other sensing devices including but not limited to a Hall effect sensor, a capacitive measurement circuit or a magnetoresistor. Each device may be configured so as to operate an indicator means. Such indicator means may be LED or LCD indicator means as described above.

The fluid may be a liquid or gas, and may be a biological fluid such as a body fluid.

Substances of interest may include naturally occurring substances, substances that are the result of a chemical or biological reaction, such as drug by-products, and substances introduced into a fluid sample. The substance may be a compound, especially a molecule and could be, for example a protein, hormone or DNA section.

The or each tag particle may become attached to a substance of interest by means of a further substance, which shall be referred to as a bonding substance. The or each tag particle may be coated with the bonding substance. The bonding substance may be a protein, and in some embodiments it is an antibody or probe (ligand).

The or each tag particle may be coated with a material to facilitate adherence of a bonding substance to the tag particle. A suitable coating material is polystyrene.

By appropriate selection of the bonding substance it is possible to arrange for tag particles to attach to a variety of substances of interest or to be displaced by a variety of substances of interest. The or each tag particle may be arranged so that it can only become attached to or displaced by a single unit of a substance of interest, for example a single molecule. As such each tag particle may be provided with a single antibody or capture probe.

In the embodiments using non-magnetic collection means, the tag particles may be formed from gold, latex or other light absorbing substance. Particles of size in the range 5 nanometers to 100 micrometers may be used or in some embodiments particles of size in the range 5 nanometers to 50 micrometers may be used.

In the embodiments utilising magnetic tag particles, by "magnetic" tag particles is to be understood particles of non-zero magnetic susceptibility. The or each magnetic particle may be ferromagnetic, diamagnetic, paramagnetic or superparamagnetic. A homogeneous or heterogeneous mixture of such particles may be employed. In one embodiment the or each particle is formed from iron oxide. Particles of size in the range 5 nanometers to 100 micrometers may be used or in some embodiments particles of size in the range 5 nanometers to 50 micrometers may be used.

According to a second aspect of the present invention there is provided an assay apparatus for determining the presence or absence of one or more substances of interest in a fluid comprising: an assay strip having a first area with a plurality of tag particles bonded thereto, the tag particles free to adhere or bind to a substance of interest in the fluid or alternatively free to be displaced by a substance of interest in the fluid; and a sensing area, said sensing area having a collection means for concentrating the tag particles in the fluid by the collection means thereby providing a visual indication of the presence or absence of a substance of interest in the fluid.

The assay apparatus according to the second aspect of the present invention may contain any or all of the features described in respect of the method of the first aspect of the present invention, as desired or as appropriate. The assay strip is preferably at least partially transparent.

In order that the invention may be more clearly understood embodiments thereof will now be described by way of example with reference to the accompanying drawings of which:

Figure 1 is a schematic view of apparatus for implementing a magnetic embodiment of the present invention; and

Figure 2 is a schematic view of apparatus for implementing a non-magnetic embodiment of the present invention.

One embodiment of the present invention is illustrated by the assay depicted in Figure 1, the assay operable to test a sample for the presence of a substance of interest. For the ease of explanation, the following description will detail an example wherein the present invention is applied to the determination of the presence of hCG 16 (full name of hCG) in a urine sample. A level of hCG above a particular threshold may provide an indication of pregnancy in the sample donor.

The assay apparatus comprises an assay strip 10 formed of substantially transparent material. The liquid sample is introduced to the assay strip 10 and flows over an area 12 containing pre-deposited hCG 16 or hCG analogue 16a. The pre-deposited hCG 16 or hCG analogue 16a is labelled with tag particles 14 which in this example are magnetic particles 14 that contain a specific probe for the hCG molecule. During the flow, by kinetics or preferential binding, the magnetic particles 14 to become bound to free hCG 16 in the sample to produce magnetic hCG complexes 18 which are released into the solution.

A sensing area 22 is provided at one end of the strip 10, the sensing area 22 being provided with collection means for collecting tag particles 14 that are released into the sample. Adjacent to the sensing area 22 is provided a magnet 20 placed beneath the assay strip 10, which in this example provides the collection means. The magnet 20 draws the complexes 18 through the solution towards the magnet 20. A photovoltaic cell 24 is been placed between the magnet 20 and the assay strip 10. It should of course be appreciated that the magnet 20 may be placed in any other suitable orientation relative to the strip 10 and the photovoltaic cell 24 or that the

magnet 20 may be replaced by an array of magnets (not shown) also operable to concentrate magnetic tag particles 14 over the photovoltaic cell 24.

Before the sample is introduced to the assay strip 10, the photovoltaic cell 24 produces an output voltage proportional to the amount of incident ambient light. As free complexes 18 gather above the photovoltaic cell 24 drawn by the magnetic field of magnet 20, they provide a block to incident light reaching the photovoltaic cell 24 and thus the voltage output of the photovoltaic cell falls. At a threshold level of voltage drop, an indicator means (not shown) is activated, which provides a user with an indication of whether the sample tests positive for a threshold level of hCG 16.

Typically, the indicator means may comprise an LCD screen operable to display the messages 'Pregnant' or 'Not Pregnant' dependent upon the level of voltage drop compared to the threshold. Alternatively, the indicator means may comprise on ore more LEDs which may be lit or not lit to indicate dependent upon the level of voltage drop compared to the threshold.

The threshold may be a preset value. In some embodiments, the threshold voltage drop may be monitored by comparison with the output of a further photovoltaic cell (not shown) in proximity to the photovoltaic cell 20. The further cell is positioned such that the magnetic complexes 18 do not gather over it and cause its output signal to drop.

Those skilled in the art of electronics will realise that there a number of simple circuits operable to provide the above required functionality. It should also be

realised that the additional photovoltaic cell may be used to generate power from ambient light to operate such circuitry and the indicator means. Alternatively, a battery, electrochemical energy from metals in contact with the sample itself or any other local power source such as electromechanical energy, piezo electric energy may additionally be used to power the indictor means. Additionally, another photovoltaic cell may be provided as a safety feature, the additional photovoltaic cell operable to provide a check that ambient or supplied light is reaching the photovoltaic cells.

In an alternative implementation, the magnetic particles 14 and hCG probe could have been separately introduced to the urine sample before the sample flowed over the bound hCG 16 or hCG analogue 16a. In this mode the free particles 14, which have not bound to the hCG 16 in the sample, will then bind to the surface deposited hCG 16 or surface deposited hCG analogue 16a and be removed from flow in the strip 10. In such circumstances, the amount of complexes 18 drawn to the magnet 20 are in proportion to the amount of hCG 16 in the donor's sample.

Turning now to figure 2, an alternative embodiment of the invention is shown wherein the tag particles 14 are not necessarily magnetic tag particles. Accordingly, no magnet is provided and the collection means are comprised of tag capture molecules 16b. These tag capture molecules 16b may (in the present example) be hCG 16 or hCG analogues 16a, if desired. The tag capture molecules 16b cause the tags (at least) of complexes 18 to be collected over the photovoltaic cell 24. The captured tags 14 thus cause a dip in the output voltage of the photovoltaic cell 24

which can be utilised as described above to provide an indication of the presence or absence of hCG in the fluid sample.

It is of course to be understood that the invention is not to be restricted o the details of the above embodiments which have been described by way of example only.

CLAIMS

1. A method of determining the presence or absence of one or more substances of interest in a fluid, the method comprising the steps of: passing the fluid over a surface having a quantity of tag particles bound thereto, the tag particles free to adhere or bind to a substance of interest in the fluid or alternatively free to be displaced by a substance of interest in the fluid; introducing the fluid and any tag particles in the fluid into a sensing area; and providing a tag particle collection means in the sensing area so as to concentrate the tag particles by the collection means and thereby provide a visible indication of the presence or absence of a substance of interest.

2. A method as claimed in claim 1 wherein the sensing area is a chamber.

3. A method as claimed in claim 2 wherein the chamber has a volume of less than 10μL.

4. A method as claimed in claim 1 wherein the sensing area is an area of an assay strip.

5. A method as claimed in any preceding claim wherein the collection means is in the shape of a word or symbol.

6. A method as claimed in claim 5 wherein the collection means is in the shape of the word YES or NO.

7. A method as claimed in any preceding claim wherein a plurality of separate collection means are provided.

8. A method as claimed in any preceding claim wherein the sensing area is adapted to aid the gradual collection of tag particles by the provision of a series of collection means along a direction of fluid flow..

9. A method as claimed in any preceding claim wherein the sensing area is provided over a photovoltaic cell or an array of photovoltaic cells.

10. A method as claimed in any preceding claim wherein one or more electronic sensing devices are provided.

11. A method as claimed in any preceding claim wherein the collection means comprises capture molecules bonded to a surface in the sensing area, the capture molecules adapted to bond with and thereby collect tag particles in the fluid.

12. A method as claimed in any preceding claim wherein the tag particles are magnetic tag particles and the collection means comprises one or more magnets mounted in or adjacent to the sensing area.

13. A method as claimed in any preceding claim wherein the fluid is a biological fluid.

14. An assay apparatus for determining the presence or absence of one or more substances of interest in a fluid comprising: an assay strip having a first area with a

plurality of tag particles bonded thereto, the tag particles free to adhere or bind to a substance of interest in the fluid or alternatively free to be displaced by a substance of interest in the fluid; and a sensing area, said sensing area having a collection means for concentrating the tag particles in the fluid by the collection means thereby providing a visual indication of the presence or absence of a substance of interest in the fluid.

15. An assay apparatus as claimed in claim 14 wherein the sensing area is provided in a chamber.

16. An assay apparatus as claimed in claim 15 wherein the chamber has a volume of less than 10 uL.

17. An assay apparatus as claimed in any of claims 14 to 16 wherein the collection means is in the shape of a word or symbol.

18. An assay apparatus as claimed in claim 17 wherein the collection means is in the shape of the word YES or NO.

19. An assay apparatus as claimed in any of claims 14 to 18 wherein a plurality of separate collection means are provided.

20. An assay apparatus as claimed in any of claims 14 to 19 wherein the sensing area comprises a series of collection means along a direction of intended fluid flow.

21. An assay apparatus as claimed in any of claims 14 to 20 wherein the sensing area is provided over a photovoltaic cell.

22. An assay apparatus as claimed in any of claims 14 to 20 wherein the sensing area is provided over an array of photovoltaic cells.

23. An assay apparatus as claimed in either claim 21 or 22 comprising an indication means connected to the or each photovoltaic cell, arranged to indicate the presence or absence of a substance of interest in the fluid.

24. An assay apparatus as claimed in claim 23 wherein the indication means comprises one or more lamps.

25. An assay apparatus as claimed in claim 23 wherein the indication means comprises a display screen.

26. An assay apparatus as claimed in any of claims 14 to 25 comprising one or more electronic sensing devices to sense tag particles.

27. An assay apparatus as claimed in any of claims 13 to 26 wherein the collection means comprises capture molecules bonded to a surface in the sensing area, the capture molecules adapted to bond with and thereby collect tag particles in the fluid.

28. An assay apparatus as claimed in any of claims 14 to 27 wherein the tag particles are magnetic tag particles and the collection means comprises one or more magnets mounted in or adjacent to the sensing area.

29. An assay apparatus as claimed in claim 28 wherein a magnet is mounted on a surface adjacent to the sensing area.

30. An assay apparatus as claimed in claim 29 wherein the magnet is formed from magnet material printed on the surface.

31. An assay apparatus as claimed in any of claims 14 to 30 wherein one or more tag particle is coated with a bonding substance.

32. An assay apparatus as claimed in any of claims 14 to 31 wherein the tag particles are formed from gold or latex.

33. An assay apparatus as claimed in any of claims 14 to 32 wherein the tag particles are of size in the range 5 nanometers to 100 micrometers.

34. An assay apparatus as claimed in any of claims 14 to 32 wherein the tag particles are of size in the range 5 nanometers to 50 micrometers.

35. An assay apparatus as claimed in any of clams 14 to 34 wherein the assay strip is at least partially transparent.

Figure 1

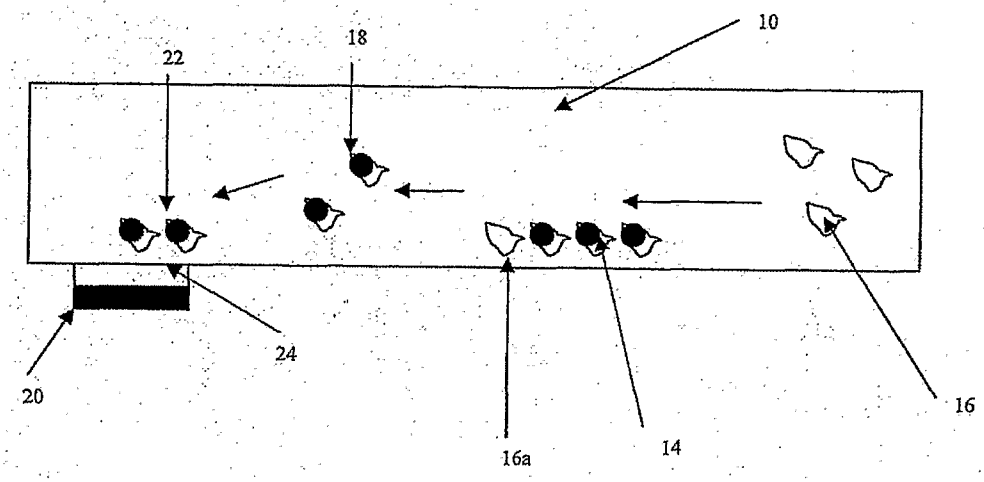
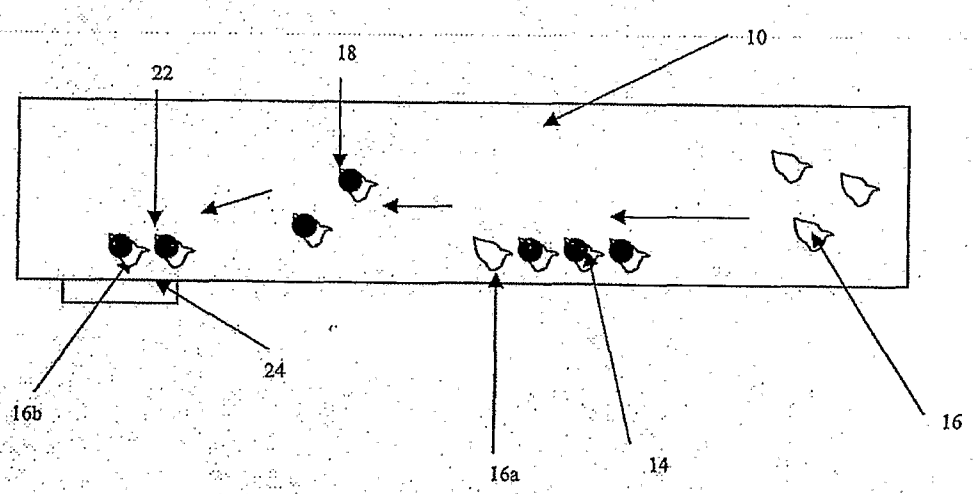


Figure 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/002994

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N21/27 G01N33/53

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)
G01N

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 136 549 A (FEISTEL CHRISTOPHER C [US]) 24 October 2000 (2000-10-24) column 4, line 21 - column 5, line 37 column 8, line 43 - column 9, line 49 column 11, line 1 - column 13, last line figures 3B-5B	1-35
Y	EP 0 421 294 A (ABBOTT LAB [US]) 10 April 1991 (1991-04-10) column 2, line 46 - column 5, line 50 column 10, line 42 - column 11, line 24 claims 1,9,15	1-35
Y	WO 2005/124345 A (HALL EFFECT TECHNOLOGIES LTD [GB]; CONNOLLY PATRICIA [GB]; FULLER JOHN) 29 December 2005 (2005-12-29) column 15, line 20 - column 17, line 2	1-35

-/--

[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 document 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
30 October 2007	16/11/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Consalvo, Daniela

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/002994

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 668 868 A (NOLLER HANS T [US]) 26 May 1987 (1987-05-26) claim 1 -----	1-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2007/002994

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6136549 A	24-10-2000	AU 1073401 A	30-04-2001
		WO 0129559 A1	26-04-2001
		US 6713271 B1	30-03-2004
EP 0421294 A	10-04-1991	AT 128235 T	15-10-1995
		AU 637830 B2	10-06-1993
		AU 6385590 A	11-04-1991
		CA 2026843 A1	06-04-1991
		DE 69022521 D1	26-10-1995
		DE 69022521 T2	25-04-1996
		DE 421294 T1	14-08-1991
		ES 2027215 T1	01-06-1992
		GR 91300086 T1	10-12-1991
		JP 2999238 B2	17-01-2000
		JP 3176659 A	31-07-1991
		US 5075078 A	24-12-1991
WO 2005124345 A	29-12-2005	EP 1766399 A2	28-03-2007
		US 2007224604 A1	27-09-2007
US 4668868 A	26-05-1987	NONE	