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DE 102006024149 A1 **US 20060234243 A1**
US 20050105077 A1 **US 20040157343 A1**

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Other: **WPI, EPODOC**

(54) Abstract Title: **Module for preparing a biological sample, biochip-assembly and use of the module**

(57) The invention relates to a module for preparing a biological sample for an analysis-examination, with the preparation module having an interface (14) at which the preparation module (1) can be connected to a cartridge (16) with a lab-on-a-chip, in which cartridge the steps of analysis are carried out. The invention is also directed to a biochip-assembly consisting of one or more preparation modules (1) for different sample materials that can be connected to the same cartridge type.

FIG 4

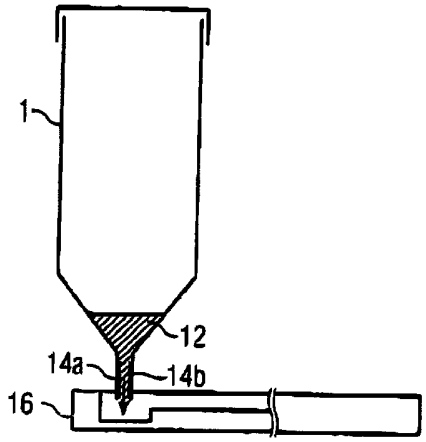

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FIG 1

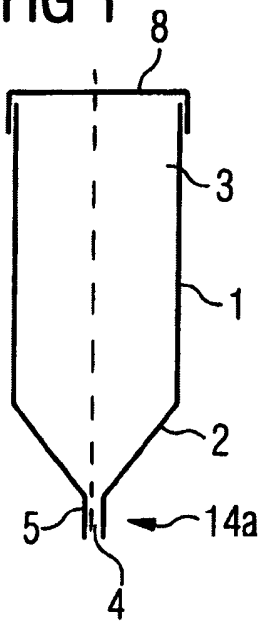


FIG 2

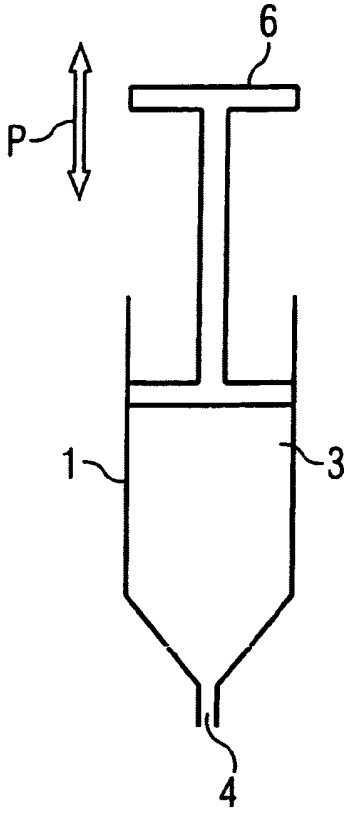


FIG 3

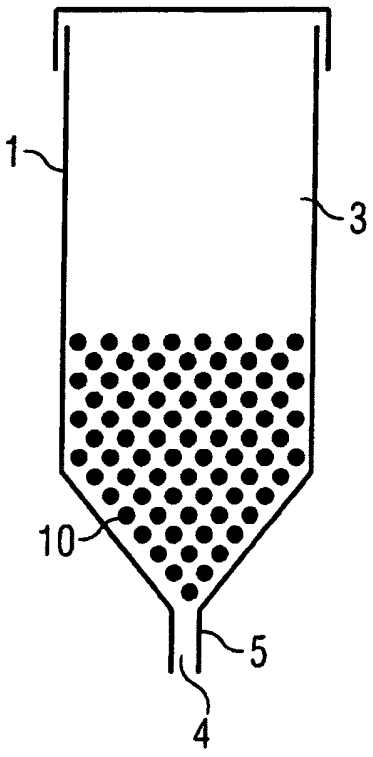


FIG 4

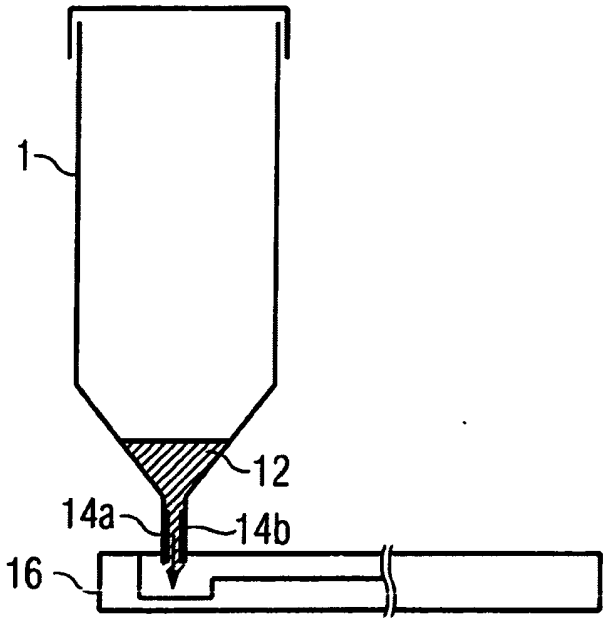


FIG 5

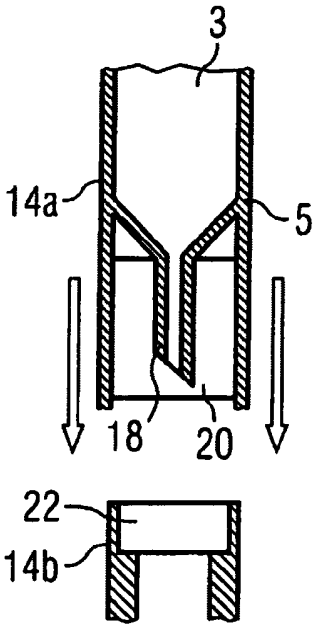


FIG 6

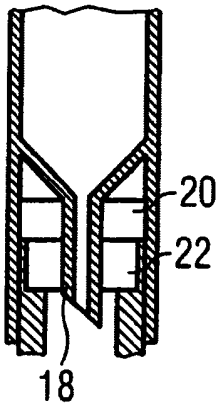


FIG 7

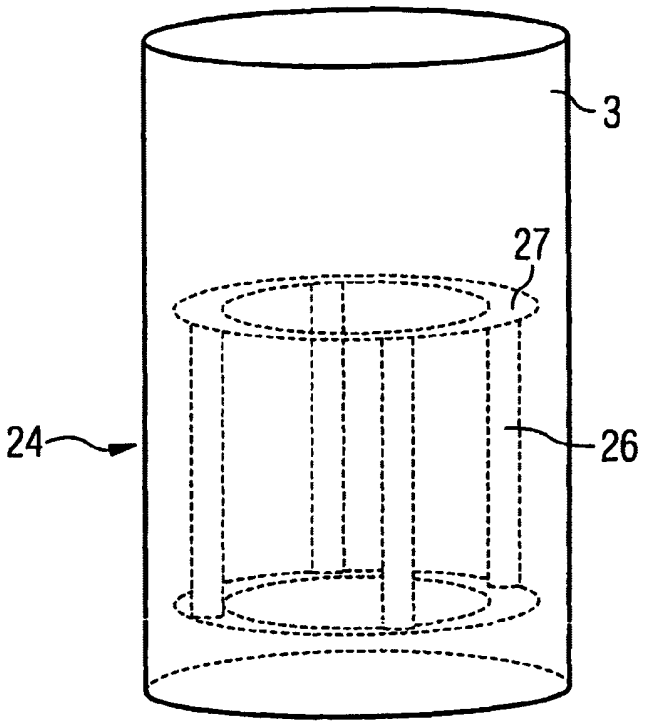


FIG 8

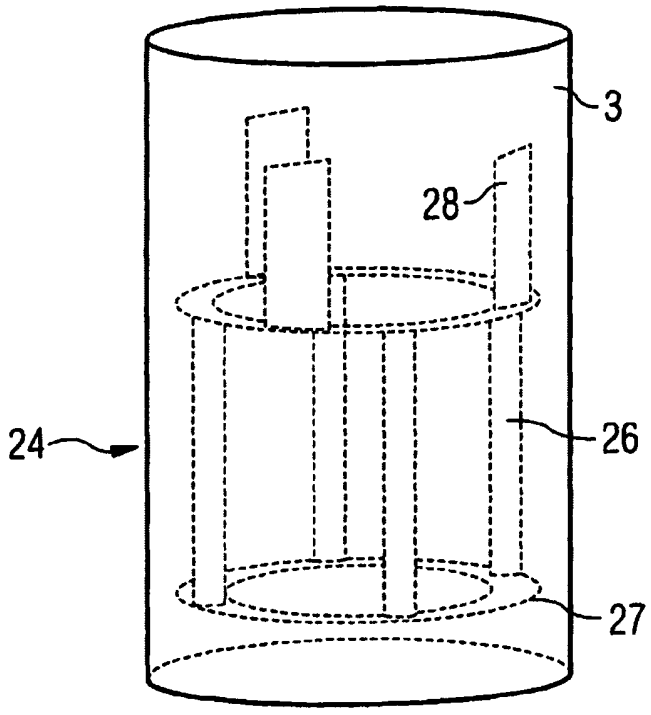
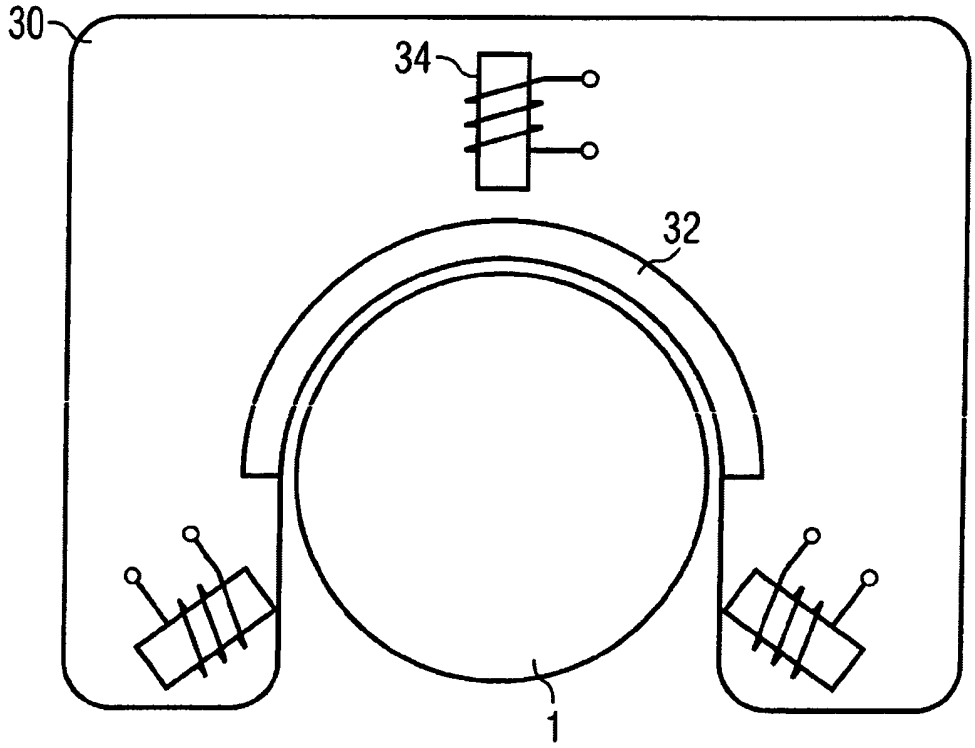


FIG 9



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MODULE FOR PREPARING A BIOLOGICAL SAMPLE, BIOCHIP-ASSEMBLY AND USE OF THE MODULE

The present invention relates to a module for preparing a biological sample for an examination in which a target substance in the sample is to be detected or quantified, with it being possible to carry out one or more preparation steps in the module. The invention is also directed at a biochip-assembly that contains one or more such preparation modules.

In numerous examinations, in particular in diagnostic tests, certain target substances are to be detected in a biological sample, in particular a tissue sample or body fluid. The target substances are, for example, certain cells such as viral or bacterial pathogens or specific proteins or nucleic acids of a cell type, tissue type or organism.

For clinical routines, systems are desirable in which all the steps of preparation and analysis are integrated on a so-called "cartridge". Novel biochips, with which in particular microbiological tests can be carried out, are what is meant by the term "cartridge". Cartridges as a rule have a microfluidics system consisting of cavities and channels that are required, for example, for the break-up of the sample, the clean-up of the target molecules, possible amplification and detection (on a microarray). Such biochips can be miniaturized to cheque-card format and are also referred to as a "lab-on-a-chip". The terms "biochip" and "cartridge" are used side by side in the following and in each case denote such a "lab-on-a-chip".

It would be desirable to be able to use such a cartridge for diverse sample materials. However, this is not yet possible at the present time since different procedures for break-up of the sample are required for different sample materials (in the case of human samples, for example, blood, sputum, biopsies etc.). Depending on the question set in the examination, likewise diverse sample-preparation steps are required:

In order to be able to detect certain intracellular or membrane-bound proteins or nucleic acids in the blood or plasma, in the first place a cell break-up (lysis) is required in order to release and dissolve the target molecules that are sought. For this, generally only small quantities of blood are required if, for example, human genes or ubiquitous proteins are to be detected. A more elaborate type of sample-preparation is necessary, on the other hand, if the sample material is more compact, for example in the case of tissue samples from biopsies, if the cells are robust with respect to chemical agents (for example mycobacterium tuberculosis), or if they are only present in a small concentration in the sample (for example HIV viruses or staphylococcus aureus pathogens in urine). In the case of such samples more aggressive chemical lysis-reagents, higher temperatures, freeze/thaw cycles and in part mechanical methods have to be used in order to break up the cells efficiently and dissolve the target molecules. When detecting small concentrations of viral and bacterial pathogens, large quantities of body fluid (> 1 ml) are to be worked up in order to obtain sufficient material for the subsequent steps of

analysis. Optionally, the pathogens are to be concentrated in the tissue sample. Ultra-centrifugation or binding to matrixes or resins (chromatographic methods) are used for this, for example.

Such elaborate sample-preparation steps can only be carried out manually or semi-manually at the present time, something which is not, however, desirable in the clinical routine for reasons of cost and reasons of reproducibility and risk of infection. Alternatively, different cartridges would have to be developed for diverse sample materials or else an extremely complex and large "universal cartridge" integrating all the possible methods would have to be made available.

In order to circumvent the problems of concentrating viral and bacterial pathogens, it would also be possible to process larger quantities of sample material, something which would, however, in turn result in the dimensions of the cartridge growing and in it no longer being possible to realize the assay in the size of a cheque card (as, for example, in the case of the EDD system of directif).

The problem presents itself in a particularly unfavourable way if the same test is to be applied in a standard way to different sample materials. For example, a human-genetic test can be effected both with blood samples and with smear material. However, the latter requires a different sample input and another sample-preparation. In the case of the fully integrated system known today, diverse cartridges would

have to be produced for this for the same test. This state of affairs entails disadvantages in the costs of production and the outlay for the corresponding authorized methods.

It is therefore desirable to develop a system which renders possible sample-preparation for different types of sample materials for the above-described lab-on-a-chip-systems.

The invention is defined in the independent claim, to which reference should now be made. Advantageous embodiments are set out in the sub claims.

Embodiments of the invention provide a module for preparing a biological sample according to claim 1 that has a hollow space and an interface at which the preparation module can be connected to a cartridge with a miniaturized laboratory, in which cartridge the steps of analysis that are necessary to detect or to quantify the target substance can be carried out.

This has one advantage that for diverse sample materials it is possible to use different preparation modules which may involve different functions and reagents that are matched to a certain tissue type. All the preparation modules can be connected to one and the same cartridge type which then takes over the analysis of the prepared sample. Thus one and the same cartridge can be used for diverse types of sample material (smears, lavage fluid, blood). It is also possible to use a universal cartridge that is suitable for diverse applications.

The preparation of the sample may include, for example, the steps of concentration, extraction and/or multiplication of cells, in particular of viruses or bacteria, the steps of concentration, extraction and/or amplification of molecules, homogenization or liquefaction of the sample, cell-lysis or combinations of these steps.

Particularly preferably, the preparation module is a vessel with, for example, a cylindrical hollow space. The latter preferably has a tapering end, in particular a funnel-shaped end, located at whose tip as an interface to the cartridge there is an opening. As a result, after the preparation of the sample the preparation module can be set down with the tip onto the cartridge so that the sample is transferred into the latter by gravitational force. Alternatively, a different transfer of the prepared sample exchanging a volume of fluid between the module and the cartridge is also possible, for example by means of the plunger that is described below.

In accordance with a preferred embodiment, a displaceable plunger is furthermore arranged in the hollow space so that in particular liquid samples can be introduced by drawing back the plunger in a manner similar to that of a doctor's syringe. In this connection, the sample can reach the preparation module through the opening that is to be later connected to the cartridge. The sample can also be input into the cartridge by means of the plunger, later after the preparation. In order to input samples in a solid

form, for example biopsies, the preparation module can be provided with a closable cover.

In the case of a preferred embodiment, the extraction and/or the transfer of the sample into the cartridge can take place with the aid of spherules or "beads" which on their surface are provided with binding partners (for example, monoclonal antibodies or oligonucleotides) of the target substance. The target substance can therefore be deposited on the spherules and transferred with the latter into the cartridge. A liquid exchange between the preparation module and cartridge is not necessary in this case. Furthermore, a concentration of the target substance takes place. The spherules can either be added to the sample before being filled into the preparation module or already be held in the hollow space in the form of a dry reagent or in solution or suspension. In the case of large liquid samples, the cells that are sought (for example bacteria) are bound by the spherules after an incubation period and concentrated in further steps.

Particularly preferably, the spherules are so-called magnetic beads (or magnet beads). Such magnetic beads preferably have a shape that is at least approximately spherical or elliptical and a diameter of approximately 30-350nm, in particular 50-310 nm and particularly preferably approximately 110-220nm. They can be produced, for example, in accordance with the method that is described in the article by Albrecht M. et al. "Magnetic multilayers on nanospheres", Nature Materials, 2005, pages 1-4, that is, they can have a

core of polystyrene and a magnetic or magnetizable coating, in particular of CoPb.

The use of magnetic beads in the case of the present invention has the advantage that the beads together with the bound target substance can be transferred from the preparation module into the cartridge by means of a magnetic field. In the case of the steps of analysis that follow, the target substance can be released from the magnetic beads, for example by denaturation, or be analyzed together with the magnetic beads.

As already mentioned above, the geometry of the preparation module and of the interface to the cartridge is also preferably selected in the case of this embodiment so that the cross section of the hollow space continuously tapers in the direction of the cartridge. As a result of this funnel shape a situation is avoided where magnetic beads are moved as a result of magnetic fields and/or the gravitational force into regions of the hollow space from which they are unable to reach the cartridge.

The magnetic field for driving the magnetic beads is generated, for example, by means of a permanent magnet or an electromagnet, which is preferably arranged outside the preparation module and the cartridge.

The interface between the module and the cartridge can contain, for example, a firm plug-, bayonet- or screw-connection or a flexible hose-connection.

By means of the interface preferably a fluidic connection between the module and the cartridge is established that can already exist before or during the preparation phase and can also continue to exist during the subsequent analysis phase.

Particularly preferably the preparation module is a disposable article which can be produced, for example, from suitable plastics material or glass.

Particularly preferably the interface of the preparation module for the purposes of protection against contamination is provided with a membrane or partition wall that closes off the module in a liquid-tight manner as long as it is not connected to the cartridge. Similarly, the input opening of the cartridge can also or alternatively be provided with a further flexible membrane or partition wall. In accordance with a particularly preferred embodiment, provided in the preparation module or in the cartridge on the inside of the membrane or partition wall there is a spike that pierces the membrane or partition wall when the module is connected to the cartridge and as a result establishes a fluid connection between the module and the cartridge.

The reagents that are required for the preparation, such as, for example, lysis buffers, magnetic beads with nucleic acids and/or antibodies arranged on the surface, nutrients or solution buffers, are preferably held in the preparation module in a manner such that they are ready for use in a liquid or dry state so that

after the sample has been input they automatically mix with the latter.

In the case of solid tissue samples (biopsies), mucous cell suspensions (smears) or viscous samples (sputum), additional mechanical elements or chemical agents are preferably provided in the preparation module that give rise to homogenization or liquefaction of the sample. Various technologies can be used for this:

Contained in the hollow space of the preparation module there is preferably a stirring body which can be driven, for example, in the manner of an electric motor by means of magnetic fields that are applied from the outside. The stirring body can contain, for example, a permanent magnet, or alternatively be formed as a cage rotor of a three-phase asynchronous motor.

In order to homogenize the sample, the stirring body can further be equipped with blades that chop up a sample in the solid state.

In order to carry out incubation, furthermore the preparation module can have a heating element or be capable of being heated from the outside.

The invention is directed, furthermore, to a biochip-assembly (or kit of parts) which contains a preparation module, which has been described above, and also a cartridge with a miniaturized laboratory ("lab-on-a-chip") in which the steps of analysis that are necessary to detect or to quantify the target substance

can be carried out and which has an interface for connection of the preparation module.

Particularly preferably the biochip-assembly contains a plurality of preparation modules that are adapted in terms of their dimensioning and/or other features, in each case, to diverse sample materials.

Likewise, it is also possible to provide a plurality of diverse cartridges that are suitable for carrying out different detection or quantification examinations. The most diverse examinations can be carried out with different sample materials with this construction-kit principle.

Alternatively or in addition, it is also possible to provide a universal cartridge in the biochip-assembly that is suitable for many diverse applications (human-genomic, bacteriological, viral) and, as a result of the diverse preparation modules, different sample materials.

Finally, the invention is also directed to the use of the above-described preparation module for preparing a biological sample for an examination in a cartridge with a miniaturized laboratory ("lab-on-a-chip"), in which cartridge the steps of analysis that are necessary to detect or to quantify a target substance can be carried out.

The invention will now be described in greater detail with the aid of exemplary embodiments with reference to the attached drawings, in which:

Figure 1 shows a diagrammatic longitudinal section through a preparation module in accordance with a first embodiment of the invention;

Figure 2 shows a diagrammatic longitudinal section through a preparation module in accordance with a second embodiment of the invention;

Figure 3 shows the preparation module of Figure 1, filled with magnetic beads;

Figure 4 shows the preparation module of Figure 1, to which a cartridge is connected;

Figure 5 shows a longitudinal section through an interface between the preparation module and the cartridge before connection;

Figure 6 shows a longitudinal section through an interface between the preparation module and the cartridge after connection;

Figure 7 shows a perspective representation of a stirring body in accordance with a first embodiment;

Figure 8 shows a perspective representation of a stirring body in accordance with a second embodiment;

Figure 9 shows a cross section through a preparation module and a sample-preparation unit that belongs to it.

Figure 1 shows a longitudinal section through a preparation module 1 which contains an elongated hollow space 3. In the example shown, the latter is substantially cylindrical with a longitudinal axis which is shown with broken lines. Alternatively, it can also be shaped in a spherical, ellipsoidal or cylindrical manner with any base area. In the lower portion, the cross section of the hollow space tapers continuously in the direction of the opening 4. As a result of this funnel-shaped section 2, the transfer to the cartridge is facilitated. Arranged at the tip of the funnel there is a section 5 in the shape of a small tube which together with the opening 4 forms the interface 14a to the cartridge. For the input of samples the preparation module is provided with a closable cover 8.

In the alternative embodiment of Figure 2 the sample is drawn up and/or output through the opening 4 with the aid of a plunger 6. This can be displaced along the arrow P as in the case of a medical syringe.

Figure 3 shows an embodiment in which magnetic beads 10 are provided in the hollow space 3 of the preparation module 1. The beads are used to bind and concentrate the target substance, for example those cells that are sought, if applicable after an incubation period. Furthermore, the passage of the sample into the cartridge can be achieved by applying a magnetic field.

In Figure 4, the preparation module 1 of Figure 1 is shown whilst in fluid connection with a cartridge 16. In this case, the module with the interface 14a is set downwards onto a corresponding interface 14b of the cartridge 16 so that the sample 12 can penetrate into the microfluidics system of the cartridge 16. If applicable, further preparation steps can also take place within the cartridge 16. The interface 14 can be formed as a plug-, bayonet- or screw-connection.

A special embodiment of the interface 14 is shown in Figures 5 and 6. In the case of this embodiment, the small tube-shaped section 5 that leads to the opening 4 of the preparation module is closed by a flexible membrane or partition wall 20. This can consist, for example, of an elastomer material. Viewed from the outside, provided behind the membrane or partition wall 20 there is a spike 18, whose tip is either, as in the example shown, embedded in the membrane or partition wall 20 or contacts the latter or is arranged at a short distance from it. The spike 18 is provided with a hollow bore which is connected to the hollow space 3 of the preparation module 1. This whole section is referred to as the interface 14a of the preparation module. The corresponding interface 14b of the cartridge likewise has a section in the shape of a small tube that is closed by a further flexible membrane or partition wall 22 closing off the cartridge in the unconnected state in a fluid-tight manner. If the interfaces 14a and 14b are now pressed onto each other in the direction of the arrow, the spike 18 pierces both membranes or partition walls and thus

establishes a fluidic connection between the preparation module 1 and the cartridge 16, as shown in Figure 6. The prepared sample, for example molecules deposited on magnetic beads, can thus reach the input opening of the cartridge from the hollow space 3.

After the transfer of the prepared sample into the cartridge, if applicable the connection can be undone again. In this case, the spike 18 of the preparation module is drawn out of both membranes or partition walls 20, 22 which thereupon close again. In this case as well, a situation where liquids unintentionally flow out of the preparation module or cartridge is thus precluded. The arrangement of the spike 18 as a lower extension of the hollow space 3 in a particularly advantageous way permits a consequently funnel-shaped configuration of the same, as a result of which a situation is avoided where magnetic beads get caught when emerging from the preparation module.

So that the sample and any reagents can react together in an optimum way in the hollow space 3, the module can be shaken manually or mechanically before carrying out the analysis assay in the cartridge. Figures 7 and 8 therefore show embodiments in which a stirring body 24 is provided in the hollow space of the preparation module.

The stirring body 24 that is shown in Figure 7 is formed in the manner of a cage rotor of a three-phase asynchronous motor. For this, it has a plurality of conductors 26 that are orientated in a longitudinal direction and are connected at the end faces by way of

a respective annular conductor 27. These elements are preferably made from conductive metal, for example copper or aluminium. Currents are induced in such a cage rotor by means of an external, rotating magnetic field and these currents for their part can result in further magnetic fields and in this way generate a torque in the cage rotor 24. Alternatively, the rotor can also be completely or partly filled with conductive metal, in which case here as well the torque is generated by eddy currents in the conductive material. In both cases, the stirring body 24 is preferably coated in such a way that the conductors do not affect the chemical reactions that occur in the interior of the preparation module. In the example of Figure 7, the conductors 26 that are aligned in the longitudinal direction are simultaneously used to stir the sample.

Alternatively, the stirring body 24 can also be provided with one or more permanent magnets, likewise set rotating by rotating magnetic fields applied from the outside.

In accordance with Figure 8, the function of the stirring body can be extended by equipping it with one or more blades 28. These blades can chop up a sample in the solid state. In this way, homogenization of the sample can be achieved in connection with corresponding pre-stored solution buffers.

The rotating magnetic fields are preferably produced externally. For this purpose, in addition to the preparation module 1 and the cartridge 16 it is possible to provide a sample-preparation unit 30 by

means of which, for example, the reactions are also controlled within the cartridge. For this, an electronics module, if applicable with a connected monitor, keyboard, mouse and/or a connected PC, can be provided.

An exemplary embodiment of such a sample-preparation unit 30 is shown in Figure 9. The unit has a plug-in space for the preparation module 1 into which the latter is plugged, for example before the assay is carried out. In the plug-in space the preparation module 1 is optionally surrounded by a heating element 32. Heating such as this can promote biochemical processes, such as, for example, the dissolution of cell membranes and conglomerates (for example sputum liquefaction). The incubation of liquids (blood, urine, liquor) proves to be particularly advantageous for the enrichment or multiplication of pathogens that are only present in a low concentration. This pre-incubation in the preparation module 1 replaces an external primary culture. After a defined incubation period, automatic further processing of the sample material can be effected in the preparation module 1 or in the cartridge 16. If a previously defined pathogen concentration in the culture medium is required, the process can be controlled visually, for example by nephelometry or turbidimetry.

Furthermore, provided in the sample-preparation unit shown in Figure 9 there are electromagnets 34 for the generation of a rotating magnetic field with which a stirring body 24 or a rotor belonging to it can be rotated in the preparation module.

The embodiments of the invention that have been described have the advantage that it is possible to process larger sample volumes than before, something which could not be realized on a cartridge. The cartridge can be constructed in a simple way and thus so that it is miniaturized, since no additional chambers, fluidic channels or even plungers and valves have to be accommodated on it in order to render possible complex sample-preparation.

The same media that are also used for further processing in the cartridge, in particular magnetic beads, can be used in the preparation module.

Claims

1. Module (1) for preparing a biological sample (12) for an examination in which a target substance in the sample is to be detected or quantified, in which module one or more preparation steps may be carried out; the preparation module comprising a hollow space (3) and an interface (14a) including means for connecting the preparation module to a cartridge (16) with a miniaturized laboratory ("lab-on-a-chip"), in which cartridge the steps of analysis that are necessary to detect or to quantify the target substance can be carried out.

2. Preparation module according to claim 1, characterised in that the preparation of the sample includes any of the steps of concentration, extraction and/or multiplication of cells, preferably of viruses or bacteria, concentration, extraction and/or amplification of molecules, homogenization or liquefaction of the sample, cell-lysis or combinations of these steps.

3. Preparation module according to claim 1 or 2, characterised in that the hollow space (3) has a tapering end (2), preferably a funnel-shaped end (2), located at whose tip (5) as an interface to the cartridge there is an opening (4).

4. Preparation module according to any of the preceding claims, characterised in that a displaceable plunger (6) is arranged in the hollow space (3) for drawing up the sample.

5. Preparation module according to one of the preceding claims, characterised in that the hollow space (3) contains spherules (10) which on their surface are provided with binding partners of the target substance.

6. Preparation module according to claim 5, characterised in that the spherules are magnetic beads (10) which by means of a magnetic field can be transferred from the preparation module (1) through the interface (14a) into the cartridge (16).

7. Preparation module according to any of the preceding claims, characterised in that the connection means (14a) comprise a plug-, screw-, hose- or bayonet-connection to the cartridge.

8. Preparation module according to one of the preceding claims, characterised in that at the interface (14a) it has an opening (4) that is closed by a membrane or a partition wall (20).

9. Preparation module according to claim 8, characterised in that furthermore on the inside of the membrane or the partition wall it has a spike (18) arranged to pierce the membrane (20) when set upon the cartridge (16) and as a result establish a connection between the cartridge and the preparation module.

10. Preparation module according to any of the preceding claims, characterised in that the reagents

that are required for the preparation steps are held in the module in a liquid or dry state.

11. Preparation module according to any of the preceding claims, characterised in that the hollow space (3) contains a stirring body (24).

12. Preparation module according to claim 11, characterised in that the stirring body can be driven by magnetic fields that are applied from the outside.

13. Preparation module according to claim 11 or 12, characterised in that the stirring body (24) is provided, furthermore, with cutting blades (28) for homogenizing the sample.

14. Preparation module according to any of the preceding claims, characterised in that connection of the preparation module to the cartridge allows establishment of a fluidic connection for the transfer of the prepared sample from the preparation module (1) into the cartridge (16).

15. Preparation module according to any of claims 5 to 13, characterised in that the interface (14) is configured in such a way that when the preparation module is connected to the cartridge a conveyance of spherules for the transfer of the prepared sample from the preparation module (1) into the cartridge (16) is rendered possible.

16. Biochip-assembly for carrying out an examination, in which a target substance in a biological sample is to be detected or quantified, comprising

- a preparation module (1) according to any of the preceding claims,
- a cartridge (16) with a miniaturized laboratory ("lab-on-a-chip"), in which cartridge the steps of analysis that are necessary to detect or to quantify the target substance can be carried out and which has an interface (14b) for connection to the preparation module.

17. Biochip-assembly according to claim 16, including a plurality of preparation modules (1) that are adapted in terms of their dimensioning and/or other features to different sample materials and can be connected to the same cartridge (16).

18. Biochip-assembly according to claim 16, including a universal preparation module (1) that is suitable for the preparation of different sample materials.

19. Biochip-assembly according to any of claims 16 to 18, including a plurality of cartridges (16) that are suitable for carrying out different detection or quantification examinations.

20. Biochip-assembly according to any of claims 16 to 18, including a universal cartridge (16) that is suitable for diverse examinations and different sample materials.

21. Biochip-assembly according to any of claims 16 to 20, in which at least one cartridge or the cartridge at its interface (14b) has an opening that is closed by a membrane or a partition wall (22), with a spike being arranged on the inside of the membrane or partition wall (22) that pierces the membrane (22) when the preparation module (1) is set upon the cartridge (16).

22. Biochip-assembly according to any of claims 16 to 21, including a sample-preparation unit (30) which is equipped with a heating element (32) and/or with electric motors (34) for the generation of rotating magnetic fields in the preparation module (1) and/or with a control module to control the steps of preparation and/or analysis.

23. Use of the preparation module (1) according to any of claims 1 to 15 for the preparation of a biological sample (12) for an examination in a cartridge (16) with a miniaturized laboratory ("lab-on-a-chip"), in which cartridge the steps of analysis that are necessary to detect or to quantify a target substance can be carried out.

24. A preparation module or biochip-assembly substantially according to any of the embodiments shown in the drawings and/or set out in the description.

Application No: GB0700586.1 **Examiner:** Dr Jonathan Corden

Claims searched: 1-23 **Date of search:** 14 May 2007

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1-3, 7-10, 14	US 2004/157343 A1 (APPLERA CORP) see figures especially 3 and paragraphs [0003]-[0036]
X	1-3, 7, 10, 14	US 2006/234243 A1 (BESTMANN et al) see abstract and figures especially
X	1-3, 5, 7, 10, 16	WO 2006/032044 A2 (MICROCHIP BIOTECHNOLOGIES) see whole document and Figure 4 especially
X	1, 2	US 2005/105077 A1 (PADMANABHAN et al) see whole document especially paragraphs [0061]-[0063]
X	1, 2	WO 03/104772 A1 (CHEMPAQ) see abstract and figures especially
X	1, 2	DE 102006024149 A1 (SIEMENS) and also WPI Abstract Acc. No. 2007-126137

Categories:

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The following online and other databases have been used in the preparation of this search report

WPI, EPODOC

International Classification:

Subclass	Subgroup	Valid From
G01N	0033/50	01/01/2006
B01L	0003/00	01/01/2006
G01N	0001/38	01/01/2006
G01N	0001/40	01/01/2006