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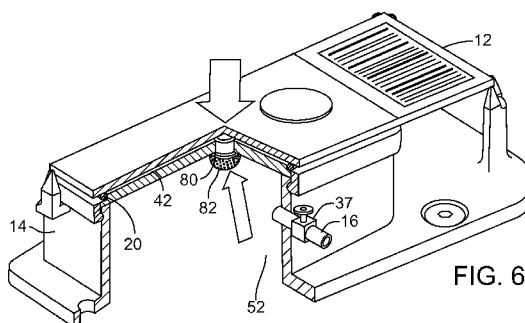


FIG. 6

(57) Abstract: During automated processing of microscope slides, a microscope slide containing a sample on one side can be placed on a platform with a sample side of the slide facing upwardly. Previously, a fluid employed in slide processing could spill over the edges of a slide and work its way under the slide, contaminating a backside of the slide. Disclosed systems overcome such difficulties by sealing a region of the slide that engages a platform. Disclosed systems can comprise a platform configured to receive a microscope slide and a seal circumscribing the platform. When the bottom surface of the microscope slide contacts the seal, a pressure reducer can be actuated and fluidically coupled to a volume bounded, in part, by the platform and the bottom surface of the microscope slide.



APPARATUS FOR SEALING SLIDE BOTTOM

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to and benefit of U.S. Provisional Patent
5 Application No. 61/138,365, filed December 17, 2008, which is incorporated herein
in its entirety.

FIELD

The present disclosure concerns an automated microscope slide processing
10 apparatus and method for its use.

BACKGROUND

Molecular pathology is the molecular level examination of DNA, mRNA and
proteins that cause or otherwise are associated with disease. This examination can
15 elucidate important information about patient diagnosis, prognosis, and treatment
options. Molecular pathology generally is divided into two main areas: (i) analysis
of DNA, mRNA, and proteins in intact cells (*in-situ*), and (ii) analysis of these
biological materials after they have been extracted from tissues. The first category
allows the pathologist or scientist to study the histopathologic architecture or
20 morphology of the tissue specimen microscopically while the nucleic acid or
proteins are assayed. These techniques include immunohistochemistry (IHC), for
analyzing proteins; *in-situ* hybridization (ISH), for analyzing nucleic acids;
histochemistry (HC), for analyzing carbohydrates; and enzyme histochemistry
(EHC), for analyzing enzyme chemistry. For example, one can use ISH to look for
25 the presence of a genetic abnormality or condition, such as amplification of cancer-
causing genes specifically in cells that morphologically appear to be malignant when
viewed under a microscope. ISH allows detection not only of a microbial sequence
but also of precisely which cells are infected, rendering it useful for diagnosing
infectious diseases. This may have important clinicopathologic implications and is
30 an effective means to rule out the possibility that a positive hybridization signal may
have come from an adjacent tissue of no clinical concern or from blood or outside
contamination.

IHC utilizes antibodies that bind specifically with unique epitopes present only in certain types of diseased cellular tissue. IHC highlights morphological indicators of disease states by selective staining; this requires a series of treatment steps conducted on a tissue section or cells (e.g. blood or bone marrow) mounted on a glass. Typical steps include pretreating the tissue section to remove paraffin and to reduce non-specific binding; retrieval of antigens masked by cross-linking of proteins by chemical fixatives; antibody treatment and incubation; enzyme-labeled, secondary antibody treatment and incubation; substrate reaction with the enzyme to produce a fluorophore or chromophore, thereby highlighting areas of the tissue section having epitopes binding with the antibody; counterstaining; and the like. Most of these steps are followed by rinse steps to remove unreacted residual reagent from the prior step. Incubations generally occur at elevated temperatures, usually around 37 °C, while cell conditioning steps typically are conducted at somewhat higher temperatures, e.g. 90-100 °C. Moreover, the tissue continuously must be protected from dehydration. ISH analysis, which relies upon the specific binding affinity of probes with unique or repetitive nucleotide sequences, requires a similar series of process steps with many different reagents. Varying temperature requirements further complicate ISH analysis.

In view of the large number of repetitive treatment steps required for both IHC and ISH, automated systems have been developed to introduce uniformity and to reduce human labor and its associated costs and error rate. For example, U.S. Patent No. 5,654,200 to Copeland *et al.* describes an automated biological processing system comprising a reagent carousel cooperating with a sample support carousel to apply a sequence of preselected reagents to each of the samples with interposed mixing, incubating, and rinsing steps. This patented automated biological processing system, which is available from Ventana Medical Systems, Inc. of Tucson, Arizona, includes a slide support carousel having a plurality of slide supports. A drive mechanism engages the slide support carousel for consecutively positioning each of a plurality of slide supports in a reagent receiving zone. The reagent carousel comprises a plurality of reagent container supports. The drive mechanism engages the reagent carousel to rotate the carousel to position a preselected reagent container support and associated reagent container in a reagent

supply zone. The apparatus has a reagent delivery actuator mechanism configured to engage a reagent container positioned on a container support in the reagent supply zone and to initiate reagent delivery from the reagent container to a slide that is on a slide support in the reagent receiving zone.

5 The slide support comprises a metal plate mounted on a molded plastic base. An electrical resistance heater is mounted in direct contact to the underside of the metal plate. Corner pins locate a specimen carrying glass slide on the surface of the metal plate. The metal plate has a top surface that is essentially flat and smooth. Flatness and smoothness facilitate glass plate position stability and thermal
10 conduction uniformity. This slide support allows for occasional processing failures, and further refinement is needed to alleviate these processing failures.

SUMMARY

 The disclosure concerns an automated slide processing device, and more
15 particularly to an improved slide support. A microscope slide containing a sample, usually a tissue sample, on one side is placed on a platform, sample side up. In practice, water and other fluids used to process the sample may contaminate the backside of the slide, inhibiting analysis of the processed slide and necessitating post processing backside cleaning. Additionally, such fluids may contact the hot metal
20 plate and boil, causing localized high pressure between the slide support and the slide, thereby dislocating the slide. Slide dislocation may compromise further processing of that one slide, or worse yet, result in a domino effect where a first dislocated slide contacts a neighboring slide, thereby causing that slide to dislocate, and so forth.

25 Disclosed embodiments of the present apparatus and method for its use address these deficiencies by sealing the area of the slide that is over the plate, thereby preventing processing fluids from entering the area between the slide and the plate. This provides several advantages, including: mitigating the need to clean the backside of the slides after processing; preventing slide dislocation from
30 unwanted vaporization; and improving the contact between the slide and the plate, thereby affording more efficient conductive heat transfer.

To achieve this result the apparatus is equipped with a platform, shaped and sized to receive the microscope slide, and a seal circumscribing the platform upon which the microscope slide rests. When the bottom surface of the microscope slide contacts the seal, a pressure reducer is actuated to at least partially, if not

5 substantially completely, evacuate the volume defined by the space between the platform and the bottom surface of the microscope slide. The resultant pressure differential between the ambient pressure conditions above the microscope slide and the space between the microscope slide and the platform create a net force urging the microscope slide toward the platform, compressing the seal and forcing the

10 sample-free area into tight contact with the platform.

In one embodiment, the pressure reducer may engage only when a microscope slide is placed on the platform. For instance, the apparatus may include a sensor for sensing the microscope slide and a mechanism for fluidly connecting the pressure reducer with the volume defined by the slide bottom surface, the seal,

15 and the plate, thereby sealing the slide bottom surface.

Upon sensing a microscope slide, the sensor may signal actuation of the pressure reducer. For example, the sensor may send an electronic signal to a controller or a relay that, in turn, opens a valve or otherwise engages the pressure reducer, thereby fluidly connecting the pressure reducer with the volume between

20 the plate and slide. Alternatively, a sensor may be a normally-closed, mechanically actuatable valve, such as a poppet valve, actuated by placing the slide on the platform.

In one embodiment, the seal is formed from a pliable, waterproof, heat-resistant, and chemical resistant material. Exemplary seal materials include Viton®,

25 Kalrez®, Chemraz®, Viton® Extreme™ ETP, Simriz®, nitrile (buna-n), neoprene, silicone, polyurethane, and Teflon encapsulated elastomers. The physical design of the seal may be a custom-engineered, continuous ridge sized to circumscribe the plate and extend vertically above the top of the plate. Alternatively, the seal may be an off-the-shelf design, such as an O-ring.

30 The platform may incorporate a thermally conductive plate operatively associated with a temperature control unit for controlling the temperature of the slide

and sample during processing. The temperature control unit may comprise a heater and temperature sensor.

In order to thermally isolate the platform from nearby platforms, the plate may rest on a housing formed from a thermally insulating material. For example, the thermally insulating material may be thermoset plastic or vulcanized rubber. The housing may also define a cavity to contain any electrical components or other connections necessary for device operation, such as for operation of the temperature control unit. To seal this cavity to the automated processing unit, the housing may contain a groove, circumscribing the cavity, for holding a seal, such as an O-ring. The housing also may include a fastening mechanism to fasten the housing to the automated processing unit. For instance, it may contain a clamping mechanism or plural apertures for receiving fasteners.

The plate may be sealably associated with the housing. The seal between the housing and the plate may be accomplished by coupling a plate border to the plate edges, thereby inhibiting processing fluids from flowing into the cavity. To afford such a seal the plate border may comprise a pliable, substantially waterproof material with features designed to seal against the housing. Because the plate may reach a temperature of up to 300 °C, it may be desirable for the plate border to be heat resistant up to at least 300 °C as well, more typically heat resistant up to about 200 °C, and even more typically heat resistant up to a temperature of about 100 °C or less.

In one embodiment, the housing has an indentation extending continuously around the upper outer wall of the cavity defined by the housing. The plate border has a lip extending downward with a ridge on the inner surface for sealing against the indentation in the housing.

In another embodiment, the housing may include physical restraints for preventing lateral movement of a microscope slide relative to the plate. In one disclosed embodiment, such restraints may be plural posts extending upwardly and substantially orthogonally from the bottom surface of the slide support. To prevent capillary forces from wicking reagents or other fluids from the slide top surface, it may be desirable for the posts to have a height less than the cross-sectional thickness of the microscope slide.

In yet another embodiment, the pressure reducer may be operatively connected to a manifold. The manifold may be a separate piece, incorporated in the housing, or incorporated in the plate. The manifold is contained within the area defined by the seal and provides a path for fluidly connecting the pressure reducer
5 and the volume to be evacuated.

In another embodiment, the pressure reducer may be fluidly connected to the cavity and the cavity may be fluidly connected to the volume to be evacuated via one or more apertures in the housing or the plate. The aperture(s) may contain a valve(s) for controlling the fluid connectivity between the cavity and the volume to
10 be evacuated, or a valve may control the pressure reducer itself. When a slide is placed on the slide support platform, the sensor detects the slide and causes the valve to open, thereby fluidly connecting the pressure reducer with the volume to be evacuated. This causes the microscope slide to compress against the seal, thereby sealing the area of the microscope slide circumscribed by the seal.

15 When removing the sealed slide, it may be necessary to vent the partially evacuated volume; however, only a small pressure differential may be necessary to affect an adequate seal, in which case the slides may be lifted from the slide support platform without venting the volume.

The foregoing and other objects, features, and advantages of the invention
20 will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective view of one embodiment of a disclosed slide support
25 with a microscope slide in place.

FIG. 2 is a plan view of one embodiment of a disclosed slide support without the microscope slide.

FIG. 3A is a cross-sectional view of one embodiment of a disclosed slide support with a microscope slide in place, showing the volume to be evacuated
30 between the slide and the plate.

FIG. 3B is a cross-sectional view of one embodiment of a disclosed slide support with the volume evacuated.

FIG. 4 is a cross-sectional view of one disclosed embodiment of a plate.

FIG 5 is a plan view of one embodiment of a plate and manifold.

FIG. 6 is a perspective view of one embodiment of the apparatus having a poppet valve.

5 FIG. 7 is a side view of one embodiment of the apparatus having a clamping mechanism.

FIG. 8 is a perspective assembly view of the automated processing unit.

DETAILED DESCRIPTION

10 A. Definitions

"Automated" or "Automatic" refers to activity substantially computer or machine driven and substantially free of human intervention.

"Lateral movement of the microscope slide" refers to movement in the direction of the microscope slide edges.

15 "Pressure reducer" refers to any device, utility, or resource capable of reducing the pressure of a substantially bounded fixed volume. Exemplary pressure reducers include vacuum pumps and flowing liquid aspirators.

"Poppet valve" refers to a normally closed valve that rises perpendicularly to its seat.

20 "Sensor" refers to a component or feature that responds to a physical stimulus with a mechanical action and/or electric, electronic, or pneumatic signal. Physical stimulus, as used in this definition, includes mechanical stimulus, optical stimulus, capacitive stimulus, or other stimulus effective to achieve disclosed functions.

25 "Stain" refers to any biological or chemical entity that, when applied to targeted molecules in tissue, renders the molecules detectable under a microscope.

"Substantial portion of a surface" refers to a continuous area of a surface containing about 50% or more of the total area of the surface.

30 "Targeted molecules" refers to detectable molecules found in cells including, without limitation, nucleic acids, proteins, carbohydrates, lipids, and small molecules.

"Tissue" refers to any collection of cells that can be mounted on a standard glass microscope slide including, without limitation, sections of organs, tumors sections, bodily fluids, smears, frozen sections, cytology preps, and cell lines.

"Treating" or "Treatment" refers to application of a stain or other detectable label to a tissue as well as other processes associated with such application including, without limitation, heating, cooling, washing, rinsing, drying, evaporation inhibition, deparaffinization, cell conditioning, mixing, incubating, and evaporation.

B. Disclosed Apparatus Embodiments

FIG. 1 shows a perspective view of one embodiment of the presently disclosed apparatus 10. FIG. 1 shows microscope slide 12 resting on the apparatus 10. Apparatus 10 comprises a slide support 14 and a pressure reducer 16 operatively associated with the slide support. Slide support 14 has a top surface 18 for receiving the microscope slide 12. Top surface 18 is circumscribed by a seal 20. When a microscope slide 12 is placed on the slide support 14, a substantial portion 22 of the bottom surface 24 of the microscope slide rests on the seal 20 and the top surface 18.

To prevent lateral movement of the slides and to afford accurate and repeatable alignment of the slides on the apparatus 10, the slide support 14 may include physical restraints for locating and preventing lateral movement of a microscope slide relative to the plate. FIG. 1 shows plural posts 26 extending upwardly and substantially orthogonally from the bottom surface 28 of the slide support 14. To prevent capillary forces from wicking reagents or other fluids from the microscope slide 12, it may be desirable for the height of the posts 26 to be less than the cross-sectional thickness of the microscope slide when the slides rest on the slide support 14.

FIG. 1 shows an apparatus 10 sized and shaped to accommodate a rectangular microscope slide 12. Slides are not limited to rectangular slides. The size and/or shape of the apparatus can be modified to accommodate whatever size and/or shape slide is used or needed in a given system.

FIG. 1 shows the apparatus 10 having fastening mechanism 30 for mounting the apparatus to the automated processing unit (not shown). The fastening mechanism 30 shown in FIG. 1 comprises plural apertures 32 and fasteners 34.

With reference to FIG. 2, one embodiment of apparatus 10 further comprises a sensor 36. When a microscope slide 12 is placed on the slide support 14, sensor 36 detects the microscope slide, thereby actuating the pressure reducer 16. Any appropriate sensor capable of detecting the physical presence of an object may be employed. Such sensors include, without limitation, optical sensors, ultrasonic sensors, inductive sensors, capacitive sensors, mechanical, or mechanical/electrical sensors.

In the embodiment illustrated in FIG. 2, the pressure reducer 16 is controlled by valve 37. The sensor 36, when sensing a microscope slide 12, may send an electronic signal to a controller or a relay which, in turn, opens valve 37. Other methods for engaging the pressure reducer 16 are possible. For instance, sensor 36 may be a normally-closed, mechanically actuatable valve, actuated by the microscope slide 12 when it is placed on the slide support 14. Such a sensor may be a poppet valve.

With reference to FIG. 3A, the slide support 14 includes a housing 38 and a plate 40. The pressure reducer 16 is fluidly connected with the volume 42 defined by the bottom surface 24, the top surface 18 and the seal 20. Consequently, when the pressure reducer 16 is actuated, the volume 42 is evacuated to an extent sufficient to create a pressure differential, forcing the seal 20 to compress between the plate 40 and the microscope slide 12, thereby sealing a substantial portion 22 of the bottom surface 24 and forcing the bottom surface of the microscope slide into tight contact with the top surface 18 of the slide support, as shown in FIG. 3B.

It can be desirable to re-pressurize the evacuated volume to facilitate removing a microscope slide 12 from slide support 14. Such mechanisms may include, without limitation, a three-way valve vented to ambient air or connected to a positive pressure source. Re-pressurization may be controlled automatically, semi-automatically, or manually.

The seal 20 desirably seals against smooth, hard surfaces, such as the glass surface of most microscope slides. Additionally, the slide processing environment is a wet environment that uses various chemical reagents. Tissue processing also may be facilitated by heating the microscope slide. The seal 20 can be formed from a pliable, substantially waterproof, heat-resistant, and chemical-resistant material.

Substances for making such seals can include, without limitation, Viton®, Kalrez®, Chemraz®, Viton® Extreme™ ETP, Simriz®, nitrile (buna-n), neoprene, silicone, polyurethane, and Teflon encapsulated elastomers. The physical design of the seal 20 may be a custom engineered continuous ridge, sized to circumscribe the top surface 14 and extend vertically above the top surface. Alternatively, seal 20 may be an off-the-shelf design, such as an O-ring.

To accommodate the need to heat the slides in a controlled fashion, the plate 40 can be thermally conductive and operatively associated with a temperature control unit. A thermally conductive plate may comprise any material with sufficient thermal conductivity to afford efficient and uniform heat transfer to the microscope slide 12. Such materials include, without limitation, copper, silver, aluminum, iron, and alloys thereof, such as brass and stainless steel. The plate also may have a plurality of slots or channels in the top surface of the plate as disclosed in U.S. Patent No. 7,425,306, which is incorporated by reference.

FIGS. 3A and 3B show plate 40 operatively associated with temperature control unit 44. Temperature control unit 44 comprises heater 46 and temperature sensor 48. Temperature control units for such purposes have been described in detail in U.S. Patent No. 6,296,809, which is incorporated herein by reference. A variety of commercially available heaters and temperature sensors may be employed for this purpose.

In an embodiment containing a temperature control unit, the neighboring slide supports can be thermally isolated and the electrical components can be protected. In order to thermally isolate the slide supports from nearby slide supports, the plate 40 may rest on a housing formed from thermally insulating material. Further, the temperature control unit and electrical connections can be protected from processing fluids. For example, FIG. 3A shows temperature control unit 44 and electrical connections 50 contained in a sealed volume. In the embodiment shown in FIG. 3A, the slide support 14 comprises a housing 38 and a plate 40. The housing 38 defines a cavity 52. The plate 40 is sealably associated with the housing 38. To accomplish this, a plate border 54 is coupled to the plate edges 55. The plate border 54 may be or include a pliable, heat resistant, water-resistant material, such as Viton®, Kalrez®, Chemraz®, Viton® Extreme™ ETP,

Simriz®, nitrile (buna-n), neoprene, silicone, polyurethane, and Teflon encapsulated elastomers. Because the plate 40 may reach temperatures up to 100 °C, plate border 54 also can be heat-resistant up to 100 °C. The plate border 54 has a lip 56 extending downwardly with a ridge 58 on the bottom inner surface 60 of the lip.

5 Ridge 58 coordinates with an indentation 62 in the housing 38, thereby substantially sealing the plate to the housing. The housing bottom 64 has a groove 66 circumscribing the cavity 52, for receiving a seal 68. When the housing 38 is mounted on an automated processing unit 70, the seal 68 is compressed in the groove 66 against the automated processing unit, thereby sealing the volume defined
10 by the housing, the plate 40, and the automated processing unit.

Moreover, the plate 40 can be protected from the processing environment. One method for protecting plate 40 is to coat the thermally conductive plate at least partially or substantially completely with a protective coating. Such coatings include, without limitation, ceramic, hard anodization, epoxy, Teflon, and silicone.

15 FIG. 4 is a cross-sectional view of coated plate 72 comprising thermally conductive plate 40 and protective coating 74.

In yet another embodiment, the pressure reducer may be operatively associated with a manifold. FIG. 5 shows plate 40 with manifold 76. Manifold 76 may be a separate piece, incorporated in the housing 38 or in the plate 40, and
20 contained within the area defined by the seal 20. Manifold 76 comprises orifices 78 that are fluidly connected to the pressure reducer 16. Using a manifold has the advantage of improving temperature uniformity in plate 40 by minimizing localized effects on the heat conduction profile.

FIG. 6 illustrates an embodiment where the pressure reducer 16 is fluidly
25 connected to the cavity 52 and the cavity is fluidly connected to the volume 42 to be evacuated via an aperture 80 in the plate. A poppet valve 82 is positioned in aperture 80 for controlling the fluid connectivity between the cavity 52 and the volume 42 to be evacuated. When a slide 12 is placed on slide support 14, poppet valve 82 opens, thereby fluidly connecting the pressure reducer 16 with the volume
30 42 to be evacuated. This causes microscope slide 12 to compress against the seal 20, thereby sealing a substantial portion 22 of the microscope slide 12 circumscribed by the seal.

FIG. 7 is a side view showing an alternate mechanism for fastening the apparatus 10 to the automated procession unit 70. FIG. 7 shows a lip 84 coordinating with the apparatus 10 and a latch 86 for holding the apparatus to automated processing unit 70. However, other mounting mechanisms known, in the art and capable of exerting adequate force to compress the seal 68, may be employed.

C. Automated Slide Processing

1. Apparatus

Disclosed slide support embodiments can be components of an automated processing device. Embodiments of automated staining devices are disclosed in various patents assigned to Ventana Medical Systems, Inc., including 5,595,707, 5,654,200, 6,296,809, 6,582,962, 7,270,785, 7,303,725, 7,396,508, each of which is incorporated herein by reference. A brief, general description of suitable automated processing devices follows.

The automated processing unit 70 is designed to automatically stain or otherwise treat tissue mounted on microscope slides with nucleic acid probes, antibodies, and/or reagents associated therewith in the desired sequence, time, and temperature. Tissue sections so stained or treated are then to be viewed under a microscope by a medical practitioner who reads the slide for purposes of patient diagnosis, prognosis, or treatment selection. In one embodiment, the automated processing unit functions as a module of a system further comprising a host computer, a monitor, a keyboard, a mouse, bulk fluid containers, a waste container, and related equipment. Additional staining modules or other instruments may be added to such a system to form a network with the computer functioning as a server. Alternatively, some or all of these separate components could be incorporated into the automated processing unit, making it a stand-alone instrument.

In brief, the automated processing unit is a microprocessor-controlled staining instrument that automatically applies chemical and biological reagents to tissue mounted on standard glass microscope slides. A carousel supporting radially positioned glass slides is revolved by a stepper motor to place each slide under one of a series of reagent dispensers. The automated processing unit controls

dispensing, washing, mixing, and heating to optimize reaction kinetics. The computer controlled automation permits use of the automated processing unit in a walk-away manner, i.e. with little manual labor.

More particularly, as shown in FIG. 8, automated processing unit 70
5 comprises a housing formed of a lower section 90 removably mounted or hinged to an upper section 92. A slide carousel 94 is mounted within lower section 90 for rotation about its central axis A-A. A plurality of thermal platforms 10 are mounted radially about the perimeter of carousel 94 upon which standard glass slides with tissue samples may be placed. The carousel 94 is preferably constructed of stainless
10 steel. The temperature of each slide may be individually controlled by means of various sensors and microprocessors. Also housed within the automated processing unit 70 are wash dispense nozzles 96, CoverslipTM dispense nozzle 98, a fluid knife 100, a wash volume adjust nozzle 102, bar code reader mirror 104, and air vortex mixers 106.

15 The automated devices typically include a rotatable reagent carousel 108. Dispensers 110 are removably mounted to a reagent tray 112 which, in turn, is adapted to engage the carousel 108. Reagents may include any chemical or biological material conventionally applied to slides including nucleic acid probes or primers, polymerase, primary and secondary antibodies, digestion enzymes, pre-
20 fixatives, post-fixatives, readout chemistry, and counterstains. Reagent dispensers 110 are preferably bar code labeled 114 for identification by the computer. For each slide, a single reagent is applied and then incubated for a precise period of time in a temperature-controlled environment. In certain embodiments, compressed air jets 106 aimed along the edge of the slide cause rotation of the reagent, thereby mixing
25 the reagents. After the appropriate incubation, the reagent is washed off the slide using the nozzles 96. Then the remaining wash buffer volume is adjusted using the volume adjust nozzle 102. CoverslipTM solution, to inhibit evaporation, is then applied to the slide via nozzle 98. Air knife 100 divides the pool of CoverslipTM solution followed by the application of the next reagent. These steps are repeated as
30 the carousels turn until the protocol is completed.

In addition to a host computer, the automated processing unit 70 preferably includes its own microprocessor to which information from the host computer is

downloaded. In particular, the computer downloads to the microprocessor both the sequence of steps in a run program and the sensor monitoring and control logic called the "run rules" as well as the temperature parameters of the protocol. Model No. DS2251T 128K from Dallas Semiconductor, Dallas, Texas, is an example of a
5 microprocessor that can perform this function.

The automated processing unit 70 generally comprises about twenty thermal platforms 10, radially mounted to a carousel 94, for heating the slides and monitoring the temperature thereof, and a control electronics printed circuit board also mounted to the slide carousel 94 for monitoring the sensors 48 and controlling
10 the heaters 46. The control electronics are mounted under the rotating slide carousel 94. Information and power are transferred from the fixed instrument platform to the rotating carousel 94 via a slip ring assembly. This information includes the temperature parameters needed for heating the slides (upper and lower) communicated from the microprocessor 116 (after having been downloaded from
15 the computer) to the control electronics as described below. If, during a run, the slide temperature is determined to be below the programmed lower limit, the thermal platform 10 heats the slide. Likewise, if the slide temperature is found to be above the upper limit, heating is stopped. A power supply of sufficient capacity to provide about eight watts per heater is provided to meet the requisite rate of
20 temperature rise (a/k/a "ramp up").

Slide cooling may be likewise controlled, as described subsequently. In one alternate embodiment, cooling platforms are mounted below the slide. The cooling platforms may comprise Peltier-type thermal transducers. In an alternative embodiment, a cooling device, such as a fan, optionally may be provided if rapid
25 cooling of the slides is required for particular applications.

Certain disclosed slide heating system use conduction heating and heats slides individually. The system provides more accurate on-slide temperature and allows for temperature settings on a slide-by-slide basis. The heater/sensor unit should have the ability to rapidly heat the useful area of the slide from 37 °C to 95
30 °C in under two minutes and to cool down over same range in under four minutes so as to permit DNA denaturation without over-denaturation and loss of cell morphology due to excess heating.

Certain disclosed embodiments include control electronics. For example, certain control electronics include an annular printed circuit board with the components necessary to receive temperature setpoint information from the automated processing unit's microprocessor 116 via a serial digital protocol. This information is used to maintain each heater 46 at its setpoint. Heater control may be performed in a variety of methods. In a preferred embodiment, the heaters 46 may be individually controlled by an integrated circuit driver or individual transistors capable of switching the heater current on and off. Thus, the processor may control the duty cycle of the heaters 46, as described subsequently. In an alternate embodiment, the amount of power to the heaters 46 may be regulated by a processor so that the heaters may be performed at a percentage of total capacity (e.g., 50% of maximum heating power). The control electronics functions to both monitor the temperature sensors 48 and control the heaters 46. Central to control electronics is a microprocessor (which is in communication with memory) or other digital circuitry of sufficient capability to communicate with the automated processing unit's microprocessor 116 via a serial bus, monitor the heater temperature sensors 48, and power the heaters 46 when the slide temperature needs to be raised at a particular time. An example of such a microprocessor is PIC16C64A available from Microchip Technology Inc., Chandler, Ariz. The program controls each heater 46 in response to the heater temperature sensor 48 when compared with the setpoint temperature (or target temperature) provided by the automated processing unit's microcontroller. The microprocessor determines the setpoint temperatures in the memory to control the heaters 46. The setpoint temperatures in a look-up table are received from the serial communication with the automated processing unit's microprocessor 116. The control electronics microprocessor obtains the actual temperatures from the temperature sensors 48, and thereafter modifies the control of the heaters 46 based on the difference in actual temperature and setpoint temperature. This control of the heaters 46 may be strictly on-off (i.e., turn the heater on if its sensor 48 temperature is below setpoint, and turn the heater off if its sensor temperature is above setpoint) or it may use proportional, integral, and/or derivative control system algorithms to provide a more controlled and accurate response.

2. Use and Operation

In operation, the automated processing unit may be used to perform *in-situ* hybridization (ISH), *in-situ* PCR, immunohistochemistry (IHC), as well as a variety of chemical (non-biological) tissue staining techniques. Moreover, two or more of the above techniques may be employed during a single run despite their differing temperature requirements by using individual slide heating systems.

In-situ hybridization is clearly a technique that may be advantageously employed with the present invention, either alone or in combination with other techniques, since many of the steps in ISH must be carefully temperature controlled for a precise period of time. The precise amount of heat for a specific period of time is necessary to sufficiently denature DNA so that subsequent hybridization may occur without over-heating to the point where cell morphology is degraded. Different specimens may require different temperatures for denaturation depending on how the tissue was prepared and fixed. The steps of denaturation, hybridization, and posthybridization washes each have unique temperature requirements that depend on the particulars of the probe and tissue being tested. These temperature requirements can be controlled through the individualized control of heaters. DNA probes require and are typically hybridized at between 30 °-55 °C while RNA probes are typically hybridized at higher temperatures with the time for hybridization varying from 30 minutes to 24 hours depending on target copy number, probe size and specimen type. Standard denaturation for cytogenetic preparations is performed at about 72 °C for 2 minutes while for tissue sections the conditions may vary from 55 °C to 95 °C from 2 to 30 minutes. Post hybridization wash temperatures may vary from about 37 °C to 72 °C for 2 minutes to 15 minutes. Salt concentration may vary from 0.1x to 2x SSC. Probe detection temperatures may vary from ambient to 42°C for 2 minutes to 30 minutes.

The low mass of the plate and heater enables the rapid heating and cooling of the slide and consequently the tissue on the slide (i.e. from 37 °C to 95 °C in 180 seconds). The increased rapidity of heating and cooling increases the efficiency of *in situ* hybridization. The rapid annealing of the probe to the target facilitated by rapid temperature ramping increases the specificity of the probe. Concomitantly, the

background is decreased and the quality of the resulting test is vastly improved. ISH may be employed to detect DNA, cDNA, and high copy mRNA. It can be applied to smears, tissue, cell lines, and frozen sections. Typically, the specimen is mounted on a 1"x3" glass slide.

5 An automated processing unit permits the placement of multiple types of specimens and ISH tests in the same run without compromising the unique requirements of each ISH test requirement (i.e., hybridization temperature 37-45 °C stringency, and wash concentrations). The system may run more than one detection chemistry in the same run on different slides. As used herein "ISH" includes both
10 fluorescent detection (FISH) and non-fluorescent detection (e.g. brightfield detection).

 The automated processing unit also may be employed for simultaneous application of ISH and IHC staining to certain tissue sections to allow both genetic and protein abnormalities to be viewed at the same time. This may be advantageous,
15 for example, in assaying breast tumor sections for both gene amplification and protein expression of HER-2/neu as both have been deemed to have clinical significance.

 The rapid heating and cooling by the thermal platform make the automated processing unit amenable for *in-situ* PCR (polymerase chain reaction), which
20 requires repeated cycles of higher and lower temperatures. A limitation of PCR is the need to extract the target DNA or RNA prior to amplification that precludes correlation of the molecular results with the cytological or histological features of the sample. *In situ* PCR obviates that limitation by combining the cell localizing ability of ISH with the extreme sensitivity of PCR. The technique is described in
25 U.S. Pat. No. 5,538,871 to Nuovo et. al, which is incorporated herein by reference.

 Sections embedded in paraffin require as a first step deparaffinization of the embedded tissue. Using a thermal platform eliminates the use of harsh chemicals, such as xylene, because precisely controlled heating of individual slides allows the paraffin embedded in the tissue to melt out and float in aqueous solution where it
30 can be rinsed away. Liquid paraffin can then be removed from the microscope slide and away from the tissue sample by passing a fluid stream, either liquid or gaseous, over the liquid paraffin. A similar technique may be employed to remove

embedding materials other than paraffin such as plastics although the addition of etching reagents may be required.

Typical *in-situ* Hybridization (ISH), *in-situ* PCR, Immunohistochemical (IHC), Histochemical (HC), or Enzymehistochemical (EHC) methods as carried out
5 with the apparatus of this invention includes the following steps.

1) Slides are prepared by applying a bar code to the slide indicating the *in-situ* Hybridization, *in-situ* PCR Immunohistochemical, Histochemical, or Enzymehistochemical process to be used with the sample.

10 2) Inserting a batch of slides in the apparatus, mounting each slide into a slide support.

3) Closing the apparatus and beginning the treatment process.

4) If the slides are to be deparaffinized in the apparatus as a pretreatment, each slide will be dry heated to temperatures above 60 °C. Following the dry heat, the slides are washed with about 7 ml of DI water leaving a residual aqueous volume
15 of about 300 µl. The slides are then covered with about 600 µl of evaporation inhibiting liquid. The slides remain at temperatures above 60 °C for an additional 6 minutes and are then rinsed again with about 7 ml DI water and covered with 600 µl of evaporation inhibiting liquid. The temperature of lowered to 37 °C. The slides are deparaffinized and ready for the next phase of the indicated process.

20 5) Slides that are to be cell conditioned will be rinsed with about 7 ml DI water. A volume-reducing fixture within the apparatus will lower the residual volume from about 300 µl to about 100 µl. Using a volume-adjusting fixture within the apparatus 200 µl of cell conditioning solution will be added to the slide. The slide will then receive about 600 µl of evaporation inhibiting liquid. The slide
25 temperature will be raised to the assigned temperature in a range of 37 °C to 100 °C, and fluid cycling will commence and be repeated every 6-8 minutes for a period of time up to 2 hours as set in the protocol. Slides are cooled to 37 °C and rinsed with about 7 ml of APK wash solution. At this point the slides are ready for the next phase of the indicated process.

30 6) As each slide pauses in the reagent application zone, the appropriate reagent vessel is moved by the reagent carousel to the reagent application station. A

metered volume of reagent is applied to the slide. The reagent liquid passes through the evaporation inhibiting liquid layer to the underlying liquid layer.

7) The slide carousel then proceeds, moving slides directly in front of vortex mixing stations. The vortex mixer jets stir the reagents on the slide surface below
5 the evaporation inhibiting liquid layer.

8a) For *in-situ* Hybridization

If process requires protein digestion, slides can be rinsed with about 7 ml of APK wash solution leaving a residual volume of about 300 µl of buffer. The slide will then receive about 600 µl of evaporation inhibiting liquid. Steps as described in
10 steps 6 and 7 are repeated for digestive enzyme application. Selectable incubation times range from 2 min through to 32 minutes at 37 °C. The slides are rinsed with about 7 ml of 2x SSC buffer, leaving a residual volume of about 300 µl of buffer. A volume reducing fixture is used to shift the volume from about 300 µl to about 100 µl. Steps as described in 6 and 7 are repeated for probe application. The slide will
15 then receive about 600 µl of evaporation inhibiting liquid. Raise slide temperature to specified temperature in a range of 37 °C to 95 °C for denaturization or unfolding respectively of target and/or probe. Selectable incubation times range from 2 min through to 18 hrs. Rinsing occurs after hybridization employing user selectable stringency, which includes selectable salt concentrations of 2x, 1x, 0.5x, 0.1x SSC
20 and temperature range 37 °C to 75 °C. Following the probe step, the slides are washed with 1x APK wash buffer, and then receive about 600 µl of evaporation inhibiting liquid. Probes are detected directly as in the case of some labeled probes as in FISH, and indirectly for ISH using anti hapten antibody followed an appropriate detection technology. If clearing is desired, following the detection
25 steps for the probe, slides will be rinsed with DI water and a detergent will be applied to clear the slides of the evaporation inhibiting liquid. Again the slides will be rinsed with DI water and the residual volume will be removed with the use of the volume reducing fixture. The slides will be dry heated at temperatures at or above 37 °C until all aqueous is evaporated from the tissue, cells or smears.

30 8b) For *in-situ* PCR If process requires protein digestion, slides are rinsed with about 7 ml of APK wash solution leaving a residual volume of about 300 µl of buffer. The slide will then receive about 600 µl of evaporation inhibiting liquid.

Steps as described in steps 6 and 7 are repeated for digestive enzyme application. Selectable incubation times range from 2 minutes through to 32 minutes at 37 °C. The slides are rinsed with about 7 ml of DI water, leaving a residual volume of about 300 µl of buffer. A volume reducing fixture is used to shift the volume from about 300 µl to about 100 µl. Steps as described in step 7 are repeated for amplification reagent application. Amplification reagents are formulated for delivery to 100 µl residual slide volume at temperatures at or above 37°C. The slide will then receive about 600 µl of evaporation inhibiting liquid. Raise slide temperature to specified temperature in a range of 37 °C to 95 °C for greater than 2 minutes to start PCR reaction. Heat cycling, up to 30 cycles, will commence from 55 °C for 1.5 minutes to 89 °C for 45 seconds. Following In-Situ PCR the slides will be subjected to *in-situ* Hybridization.

8c) For IHC, HC, EHC protocols, the slides are rinsed with about 7 ml of 1x APK wash or appropriate buffer, leaving a residual volume of about 300 µl of buffer. A volume reducing fixture may or may not be used to shift the volume from about 300 µl to about 100 µl. The slide will then receive about 600 µl of evaporation inhibiting liquid. Steps as described in step 7 are repeated for antibody or other reagent application.

Selectable incubation times range from 2 minutes to 32 minutes. Selectable incubation temperatures range from 37 °C to 95 °C depending on whether cell conditioning or deparaffinization is required. Throughout the procedure, the slides are washed with 1x APK wash or appropriate buffer, and then receive about 600 µl of evaporation inhibiting liquid. Proteins, carbohydrates, and enzymes are directly labeled, as in fluorescence, or indirectly using an appropriate detection technology. At the conclusion of the designated staining procedures, the slides are prepared for coverslipping with the automated clearing procedure, coverslipped, and reviewed microscopically for appropriate staining, be it DNA/RNA, protein, carbohydrate or enzyme.

The procedures set forth above, including sequence of steps, application of reagents, and temperature parameters above are preferably pre-programmed into the host computer by the manufacturer. Certain parameters, such as the reaction time, may optionally be modifiable by the user. Initial programming of the test is flexible

enough to allow complex manipulation of the protocol and addition of multiple reagents (5-6 reagents) both before and after addition of the probe to the target tissue or specimen.

Within-run and between run temperature control is $\pm 1\%$ of the target temperature and may be controlled as described previously. The operator may run multiple complex ISH protocols in the same run. This includes ability to program protocols for ISH methods that run at the same denaturation temperatures. Likewise, the system is accessible for slide temperature calibration by the operator without tedious dismantling of the instrument. The protocol changes for user-defined ISH protocols are protected by a security access. The system is barcode driven for both the slide and reagent system. There is also the option for operator manual control of all major hardware functions including reagent dispense, wash dispense, coverslip (high and low temperature) dispense, slide indexing and temperature control. This enables the user to help troubleshoot problems. User defined protocols allow the operator to control the temperature of all phases of the reaction except detection temperature. The software includes pre-programmed optimized protocols resident in the software to allow continuous introduction of the optimized turnkey probes.

In view of the many possible embodiments to which the principles of the disclosed apparatus may be applied, it will be recognized that the illustrated embodiments are only examples and should not be construed as limiting the claims to a scope narrower than would be appreciated by a person of ordinary skill in the art. Rather, the scope is defined by the following claims. We therefore claim as all that comes within the scope and spirit of these claims.

25

We claim:

1. A system, comprising:
a slide support having a top surface configured to receive a microscope slide,
wherein the microscope slide defines a slide top surface configured to receive a
5 sample and a slide bottom surface devoid of any sample;
a seal operatively associated with the slide support and configured to engage
the bottom surface; and
a pressure reducer operatively associated with the slide support and
configured to seal a substantial portion of the slide bottom surface against the slide
10 support, wherein the pressure reducer is actuable, at least in part, in response to the
slide being received by the slide support.
2. The system according to claim 1, wherein the system comprises an
automated slide processing system.
15
3. The system according to claim 2, wherein the sample comprises a
biological sample.
4. The system according to claim 3, wherein the biological sample
20 comprises a tissue sample.
5. The system according to claim 1, wherein the slide support comprises
a housing defining a housing bottom surface and a recessed region configured to
enclose one or more electrical connections.
25
6. The system according to claim 5, wherein the housing comprises a
plurality of lateral restraints configured to limit lateral movement of the microscope
slide relative to the top surface.
- 30 7. The system according to claim 6, wherein the plurality of lateral
restraints comprises a corresponding plurality of posts extending upwardly from and
substantially orthogonally to the housing bottom surface.

8. The system according to claim 7, wherein the plurality of posts is configured to substantially preclude wicking of a fluid from the microscope slide.

5 9. The system according to claim 5, wherein the housing comprises a thermally insulating material.

10 10. The system according to claim 5, wherein the housing bottom surface defines a periphery of the recessed region and a groove circumscribing the recessed region, wherein the groove is configured to receive a bottom seal for sealing the periphery of the recessed region.

11. The system according to claim 1, wherein the slide support comprises a plate for supporting the slide.

15

12. The system according to claim 11, wherein the plate comprises a thermally conductive material.

13. The system according to claim 11, wherein the slide support further comprises a temperature control unit operatively associated with the plate for controlling a temperature of the plate.

20

14. The system according to claim 13, wherein the temperature control unit comprises a heater and a temperature sensor.

25

15. The system according to claim 12, wherein the plate comprises a metal alloy.

16. The system according to claim 15, wherein the metal alloy comprises a ferrous metal alloy.

30

17. The system according to claim 15, wherein the metal alloy comprises an alloy of one or more of copper, silver, brass, aluminum, steel, and stainless steel.

5 18. The system according to claim 15, wherein the plate comprises a protective coating.

19. The system according to claim 18, wherein the protective coating comprises Teflon.

10 20. The apparatus according to claim 5, further comprising a plate sealably associated with the housing, whereby the plate covers the recessed region opposite the housing bottom surface, the plate being configured to support the microscope slide.

15 21. The apparatus according to claim 20, wherein the housing bottom surface is sealably associated with an automated processing unit, thereby forming a substantially sealed volume bounded by the plate, the housing, and the automated processing unit.

20 22. The system according to claim 1, wherein the seal comprises a pliable, heat resistant and substantially waterproof material.

23. The system according to claim 22, wherein the seal comprises a compressible O-ring.

25

24. The system according to claim 1, further comprising a valve configured to control the pressure reducer.

25. The system according to claim 24, further comprising a sensor,
30 wherein the valve is operatively associated with the slide support such that the valve opens, at least in part, in response to the sensor detecting a presence of a microscope slide on the slide support.

26. The system according to claim 25, wherein the valve is further operatively associated with the slide support such that the valve closes, at least in part, in response to the sensor detecting the absence of a slide.

5

27. The system according to claim 1, wherein the slide support comprises a manifold.

28. The apparatus according to claim 26, wherein the manifold is operatively associated with the pressure reducer for fluidicly coupling the recessed region and the pressure reducer.

29. The system according to claim 1, further comprising a sensor wherein the sensor comprises a mechanically actuable valve being operatively associated with the pressure reducer and being configured to open, at least in part, in response to a microscope slide being placed in contact with the slide support.

30. The system according to claim 29, wherein the sensor comprises a poppet valve.

20

31. The system according to claim 1, further comprising an electronic sensor.

32. The system according to claim 1, further comprising a sensor configured to detect the presence of the microscope slide when the microscope slide is positioned on the slide support.

25

33. The system according to claim 32, wherein the sensor is configured to emit a signal for actuating the pressure reducer.

30

34. The system according to claim 33, wherein the pressure reducer and the sensor are configured such that the pressure reducer is substantially simultaneously actuable with emission of the signal.

5 35. The system according to claim 33, wherein the pressure reducer is responsively actuable in response and subsequent to a signal emitted from the sensor.

10 36. The system according to claim 1, wherein the pressure reducer is responsively actuable in response to a mechanical valve being urged against.

37. The system according to claim 36, wherein the mechanical valve is configured such that a slide placed on the slide support sufficiently urges the mechanical valve so as to actuate the pressure reducer.

15

38. A platform for holding a microscope slide during automated processing, the platform comprising:

20 a housing defining a housing cavity configured to receive a microscope slide, the housing having a housing bottom defining a bottom surface, the housing cavity having an upper outer wall having an indentation continuously extending around the upper outer wall, the housing further comprising a plurality of posts extending upwardly from and substantially orthogonally to the bottom surface and being configured to limit lateral movement of a microscope slide, the housing bottom sealably associated with an automated processing unit, the housing further having a fastening mechanism configured to fasten the housing to an automated processing unit;

25 a thermally conductive plate sealably associated with the housing, the plate defining a top plate surface, a bottom plate surface, and plate edges;

30 a heater operatively associated with the bottom plate surface and comprising a heat source and a temperature sensor;

a continuous, pliable plate ridge circumscribing the plate and extending from the top plate surface;

a pressure reducer operatively associated with the housing; and
a valve operatively associated with the pressure reducer such that, when open, the valve fluidically couples the cavity and the top plate surface for evacuating a volume bounded by the top plate surface, the plate ridge, and the microscope slide.

5

39. The platform according to claim 38, wherein the housing bottom defines a groove circumscribing the housing cavity and being configured to receive a compressible O-ring for sealing the housing to the automated processing unit.

10

40. The platform according to claim 38, wherein the fastening mechanism defines a plurality of apertures configured to receive a corresponding plurality of fasteners for fastening the housing to the automated processing unit.

15

41. The platform according to claim 38, wherein the fastening mechanism comprises a clamping mechanism.

20

42. The platform according to claim 38, wherein the plate edges are coupled to a pliable, heat resistant, waterproof plate border configured to inhibit fluid flow at the plate edges, the plate border defining a downwardly extending lip having a bottom inner surface comprising a border ridge configured to matingly engage the indentation in the upper outer wall of the cavity.

25

43. The platform according to claim 38, wherein the plate ridge is heat resistant up to at least 100 °C and substantially waterproof.

44. The platform according to claim 43, wherein the plate ridge comprises a compressible O-ring.

30

45. The platform according to claim 38, wherein the valve is configured to be opened in response to placement of the microscope slide on the plate.

46. The platform according to claim 38, further comprising a manifold operatively connected to the pressure reducer for fluidically coupling the pressure reducer and the housing.

5 47. The platform according to 38, wherein the plate ridge is resistant to chemical damage.

48. A platform for holding a microscope slide during automated processing, the platform comprising:

10 a housing defining a cavity configured to receive a microscope slide, the housing having a housing bottom defining a bottom surface, the housing cavity having an upper outer wall defining a recessed region extending continuously around the upper outer wall, the housing further comprising a plurality of posts extending upwardly from and substantially orthogonally to the bottom surface and
15 being configured to inhibit lateral movement of a microscope slide, the housing bottom defining a groove circumscribing the cavity and being configured to receive a compressible O-ring in the groove for sealing the housing to an automated processing unit, the housing further defining a plurality of apertures configured to receive a corresponding plurality of fasteners for fastening the housing the
20 automated processing unit;

a thermally conductive plate comprising a top plate surface, a bottom plate surface, and plate edges;

a pliable, heat resistant, waterproof plate border so coupled to the plate edges as to be configured to inhibit a fluid flow at the plate edges, the plate border having
25 a downwardly extending lip having a bottom inner surface, the bottom inner surface defining a border ridge configured to seal against the indentation in the upper outer walls of the cavity;

a heater operatively associated with the bottom plate surface and comprising a heat source and a temperature sensor so as to control a temperature of the bottom
30 plate;

a unitary, compressible, heat resistant up to at least 100 °C, chemical resistant, and substantially waterproof O-ring positioned in the groove so as to circumscribe the plate and extend from the top plate surface;

a pressure reducer operatively associated with the housing; and

- 5 a valve operatively associated with the pressure reducer and mechanically actuable by placement of a microscope slide on the plate, wherein, when open, the valve fluidically couples the cavity and the top plate surface for evacuating a volume bounded at least in part by the top plate surface, the plate ridge, and the microscope slide.

10

49. A method, comprising:

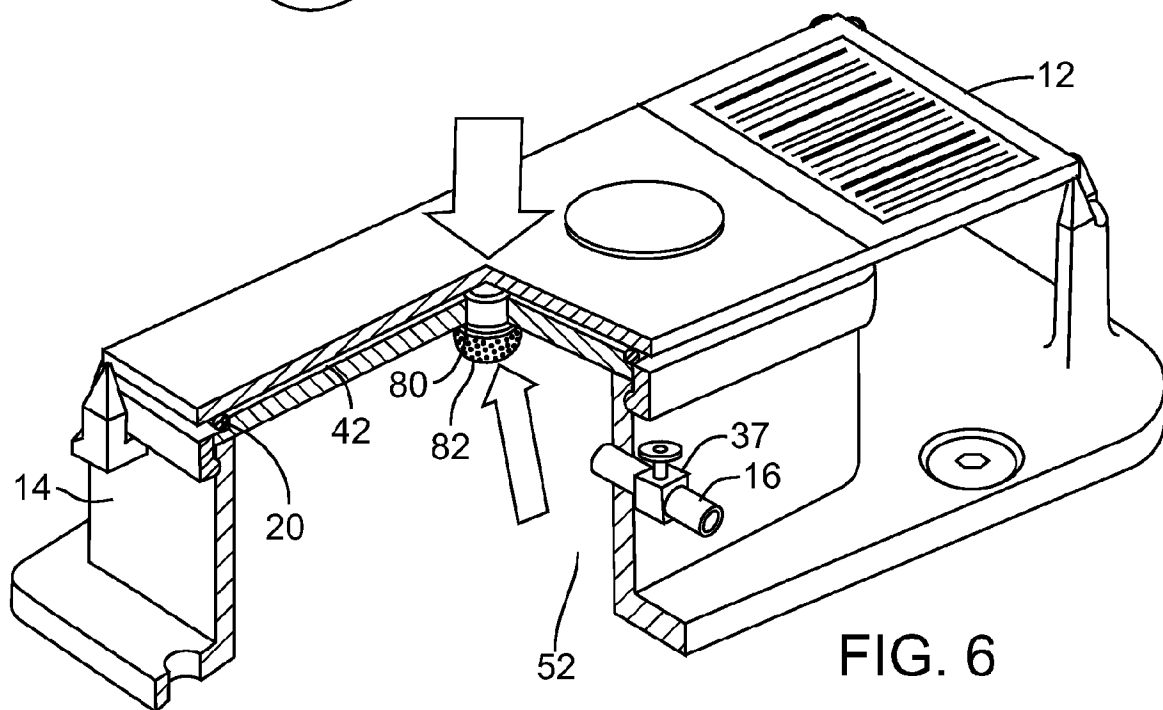
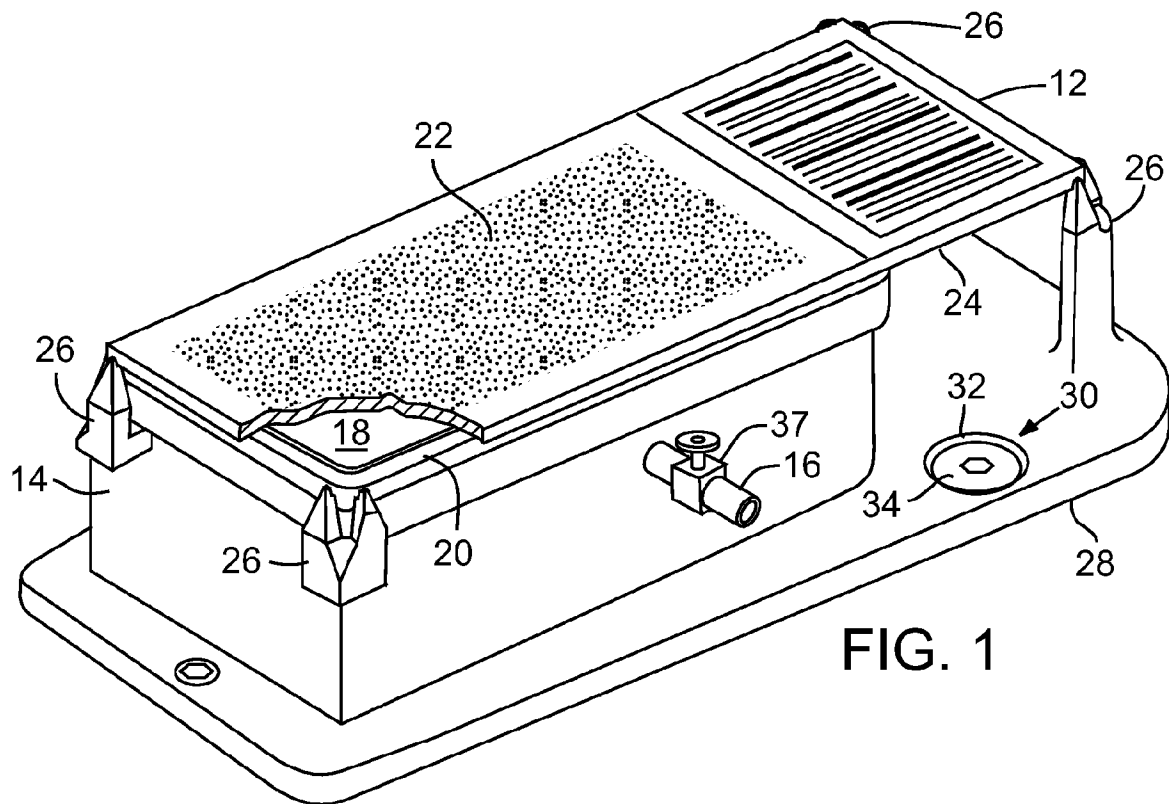
placing a microscope slide having a bottom surface on a slide support top surface configured to receive the slide, wherein a seal is operatively associated with the slide support top surface and configured to engage the bottom surface of the microscope slide;

15

detecting the presence of the microscope slide on the slide support with a sensor; and

substantially evacuating a fluid within in a volume bounded at least in part by the bottom surface of the microscope slide, the top surface of the slide support, and the seal.

20



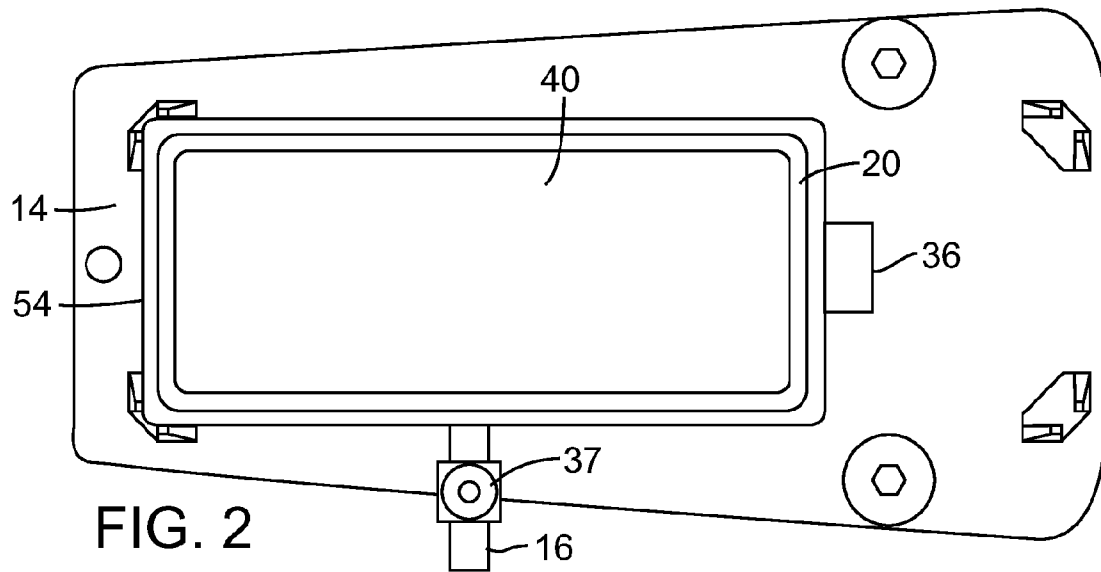


FIG. 2

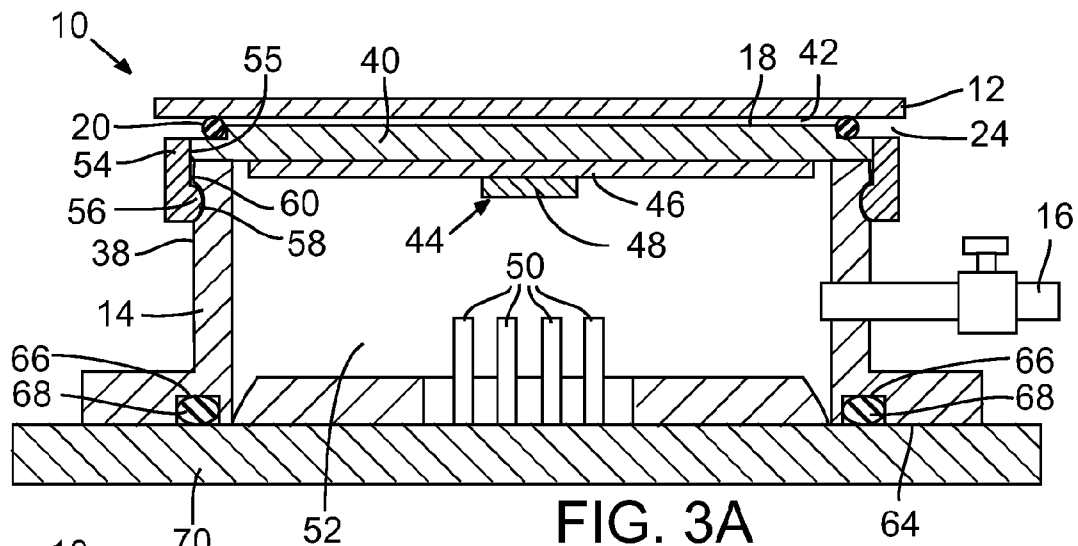


FIG. 3A

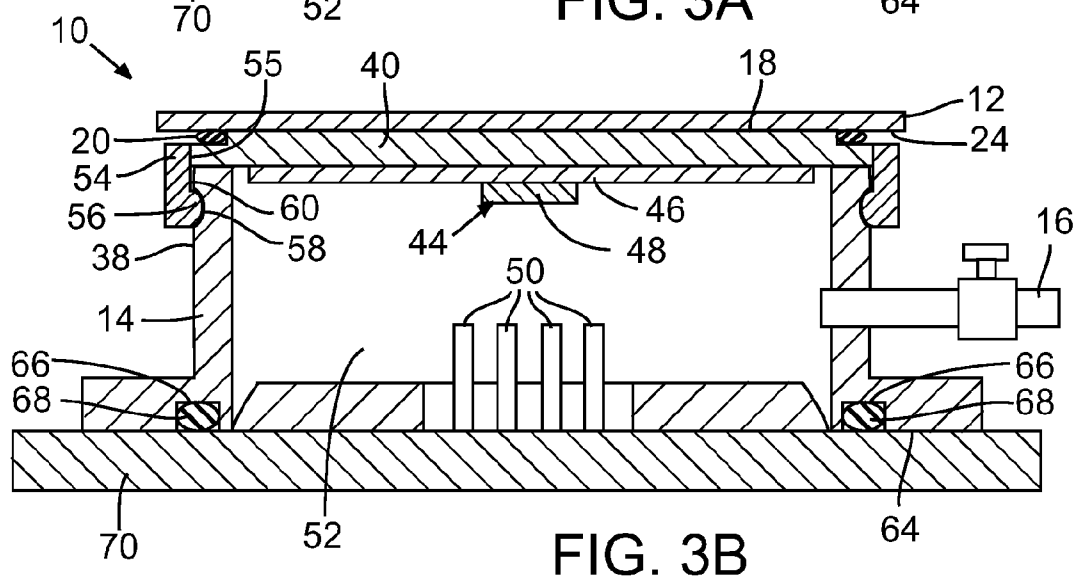


FIG. 3B



FIG. 4

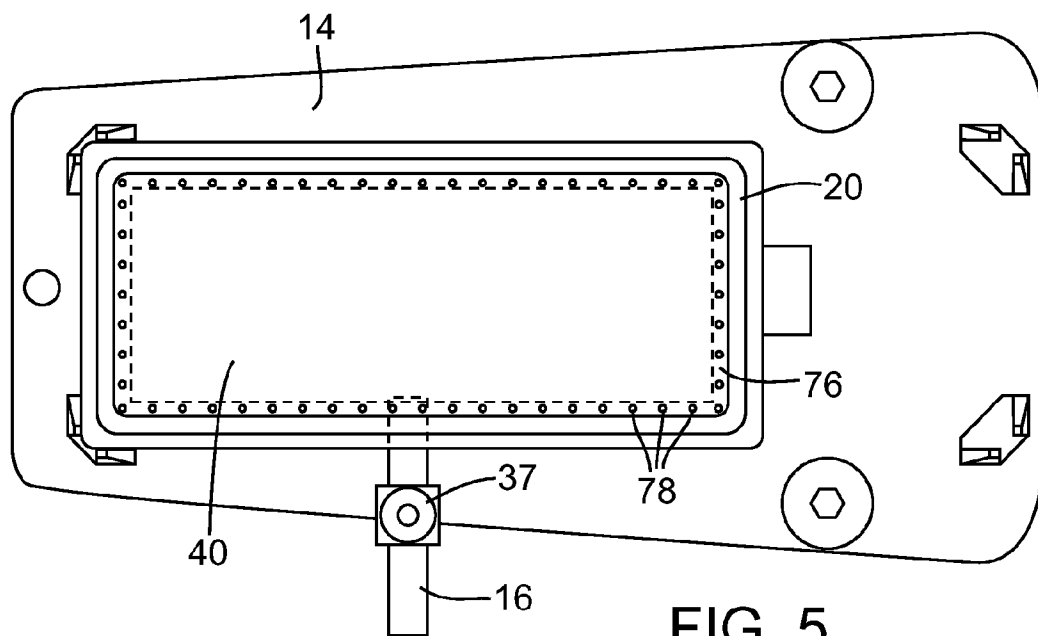


FIG. 5

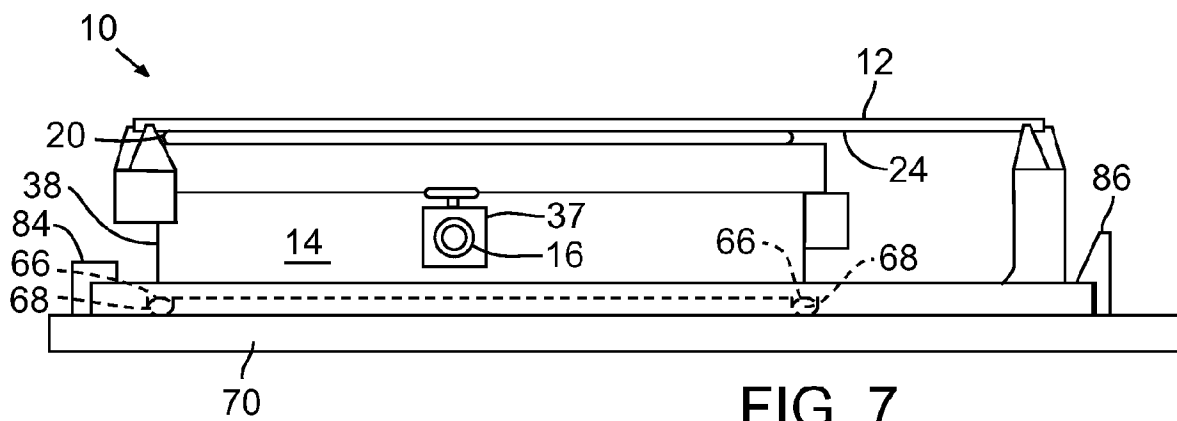
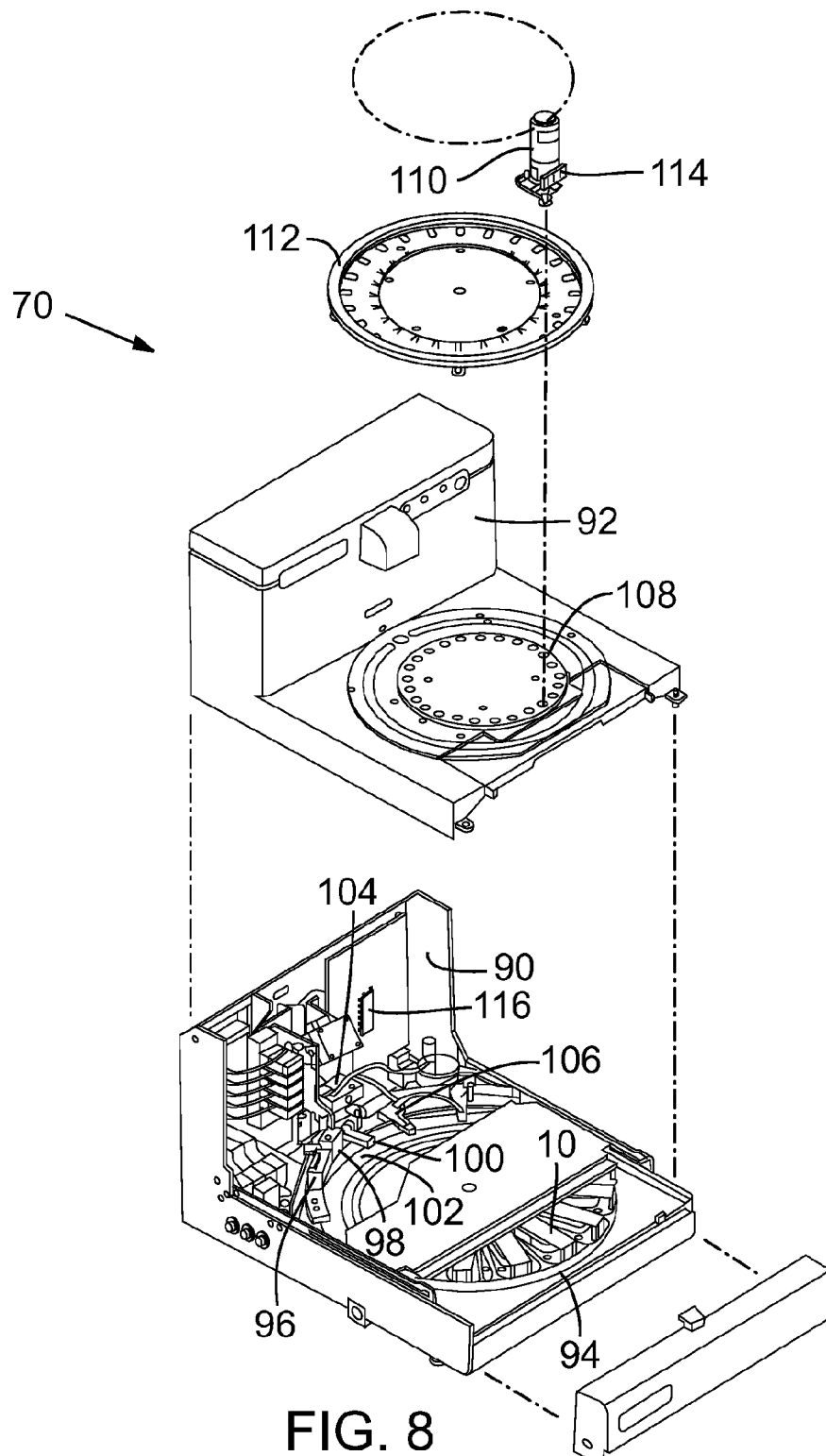


FIG. 7



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/068303

A. CLASSIFICATION OF SUBJECT MATTER

G02B 21/26(2006.01)i, G02B 21/34(2006.01)i, G01N 1/28(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

G02B 21/26; B01L 11/00; G01N 1/10; G01N 1/28; G02B 21/24

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

Korean utility models and applications for utility models
Japanese utility models and applications for utility models
(Chinese Patents and application for patent)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: "slide", "vacuum", "holder", "support"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4508435 A1 (GRAHAM, M. D. et al.) 02 April 1985 See figures 1-3; column 3, line 12-column4, line 68.	1-4, 22-37, 49 5-21
X Y	US 5659421 A1 (RAHMEL, R. J. et al.) 19 August 1997 See figures 1-3; column 2, line 32-column 4, line 65.	1-4, 22-37, 49 5-21
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A	US 3848962 A (NELSON, J. R. et al.) 19 November 1974 See figure 1, claims.	1-49

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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"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

31 MARCH 2010 (31.03.2010)

Date of mailing of the international search report

01 APRIL 2010 (01.04.2010)

Name and mailing address of the ISA/KR



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Telephone No. 82-42-481-8435



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2009/068303

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2009/068303

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