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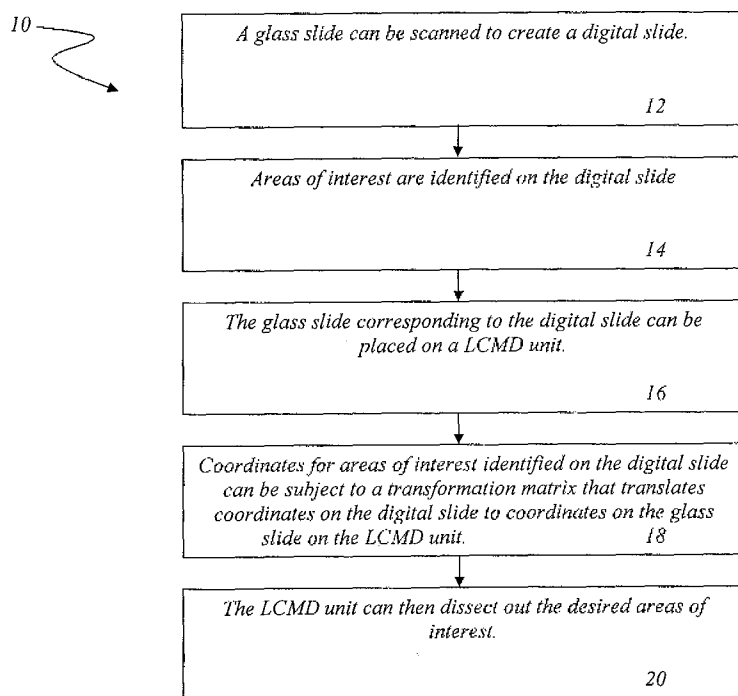
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(54) Title: SYSTEM, DEVICE, AND METHOD FOR LASER CAPTURE MICRODISSECTION



(57) Abstract: A system, device, and method for obtaining samples from a laser capture microdissection system. A slide can be scanned to create a digital slide. The digital slide can then be annotated by a user. The coordinates of the annotations can then be subject to a transformation, such that the designated area is laser dissected out on a laser capture microdissection device.

Fig. 1



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SYSTEM, DEVICE, AND METHOD FOR LASER CAPTURE MICRODISSECTION

RELATED APPLICATIONS

5 This application claims the benefit of U.S. Provisional Application No. 61/017,353, filed December 28, 2007, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

10 The disclosure relates generally to microdissection. More particularly, the disclosure relates to a system, device, and method for designating and capturing targets of interest for microdissection.

BACKGROUND OF THE INVENTION

15 Laser Capture Microdissection ("LCMD") is a technology for isolating individual cells or specific cells of interest from microscopic regions of a sample. One method of performing LCMD is to apply a transfer film to the surface of a tissue section. Under a microscope, the thin tissue section is viewed through a glass slide on which it is mounted and individual cells or clusters of cells are identified for isolation. When the isolated cells are in the field of view, the microscope operator activates a near IR laser diode integral with the microscope optics. The pulsed laser beam activates a precise spot on the transfer film, 20 fusing the film with the underlying isolated cells. The transfer film with the bonded cells is then lifted off the thin tissue section, leaving the other, non-isolated cells on the glass slide.

25 LCMD can be performed on a variety of tissue samples including blood smears, cytologic preparations, cell cultures, aliquots of solid tissues, and frozen and paraffin embedded archival tissues. These individual cells can then be analyzed using a variety of techniques to analyze their various constituents by such techniques as Polymerase Chain Reaction ("PCR"), immunoassays, microarrays, or the like. This has proven valuable in research by enabling very precise molecular assays to be performed without compromising the ability to target particular cells. Further, because LCMD does not alter or damage the 30 morphology and chemistry of the sample collected, nor the surrounding cells, LCMD is a useful method of collecting selected cells for DNA, RNA, and protein analyses.

However, the process of identifying cells can be very tedious requiring an individual to sit at the microscope and manually identify each cell. If multiple people want to use the system, they have to each schedule time on the unit. Furthermore, the individual performing LCMD must be trained in the identification of the cells of interest.

5 This can make higher volume applications much less practical and much more expensive, as well as creating a constraint on experts whose time and location limitations might not be amenable to such a workflow.

There remains a need for a system that allows identification of the specified cells of interest to be performed independently, and optionally remotely, from the LCMD
10 process.

SUMMARY OF THE INVENTION

Embodiments of the present invention resolve many of the above-described deficiencies and drawbacks, and are directed to a system, device, and method for obtaining samples from a laser capture microdissection system. A slide, such as a glass slide,
15 containing a tissue or the like sample can be scanned to create a digital slide. The digital slide can then be annotated by a user, such as an expert in cell identification. The coordinates of the annotations can then be subject to a transformation, such that the designated area is laser dissected out on a laser capture microdissection device, independently and discretely from the cell identification process.

20 In an embodiment of the invention, the digital slide having a first annotation representing an area of interest is compared to an image produced by the laser capture microdissection unit having a second annotation representing a portion of the biological sample before LCMD is performed. The image comparison is done via side-by-side comparison or transparent overlay. The first and second annotations are initially
25 registered based on the coordinate transformation. The first and second annotations can then be precisely registered by either movement of the second annotation or movement of the image produced by the laser capture microdissection unit until the portion of biological sample represented by the second annotation substantially corresponds to the area of interest previously selected on the digital slide.

30 The above summary of the invention is not intended to describe each illustrated embodiment or every implementation of the present invention. The figures and the detailed description that follow more particularly exemplify these embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a flow diagram of a method of utilizing a digital slide to identify regions of interest according to an embodiment.

FIG. 2 is a block diagram of a laser capture microdissection system according to an
5 embodiment of the invention.

FIG. 3 is a schematic of a microscope imaging system according to an embodiment of the invention.

FIG. 4 is a front view of a microscope of the microscope imaging system of FIG. 3.

FIG. 5a is a screen shot of a side-by-side comparison of an initial registration of
10 the digital slide and the LCMD unit field of view.

FIG. 5b is a screen shot of the side-by-side comparison of FIG. 5a after moving the annotation on the LCMD unit field of view.

FIG. 6a is a screen shot of a side-by-side comparison of an initial registration of the digital slide and the LCMD unit field of view.

FIG. 6b is a screen shot of the side-by-side comparison of FIG. 6a after moving the
15 image on the LCMD unit.

DETAILED DESCRIPTION OF THE DRAWINGS

Embodiments of the present disclosure provide a mechanism to utilize a digital slide to identify regions of interest. The glass slide corresponding to the digital slide can
20 be placed on a LCMD unit. Coordinates for areas of interest identified on the digital slide can be subject to a transformation matrix that translates coordinates on the digital slide to coordinates on the glass slide on the LCMD unit. The LCMD unit can then dissect out the desired areas.

FIG. 1 illustrates a flow diagram 10 of an LCMD method, utilizing a digital slide.
25 At 12, a glass slide is scanned to create a digital slide. The digital slide is stored locally, or remotely, such as in a database on a remote server, or both. The digital slide is then analyzed at 14 to identify cells of interest for further analysis. The analysis can be done either on the same microscope system, or remotely. At 14, areas of interest are identified on the digital slide and optionally annotated. In one embodiment of the invention, cell
30 identification 14 is performed manually by a pathologist, lab technician, or other such

individual trained in the identification of cells. In another embodiment of the invention, cell identification 14 is performed automatically, as discussed in U.S. Patent No. 6,215,892 entitled "Method and Apparatus for Automated Image Analysis of Biological Specimens" incorporated herein by reference in its entirety.

5 To perform LCMD, the glass slide corresponding to the digital slide is placed on a stage of the LCMD unit at 16. At 18, the coordinates of the identified areas of interest are then subject to a transformation matrix, transforming the coordinates of the digital slide, i.e. pixel information, to the corresponding coordinates, i.e. X-Y coordinates, on the stage of the LCMD unit. At 20, the LCMD unit is activated by an individual that is the same as
10 or separate from the individual who performed the cell identification to dissect out the desired areas or cells of interest.

FIG. 2 illustrates a laser capture microdissection system 200, according to embodiments of the present invention, including a microscope imaging unit 202, a storage medium 204 such as a database, a visualization unit 206, and an LCMD unit 208.
15 Microscope imaging unit 202 and LCMD unit 208 can be one in the same unit, i.e. a microscope comprising both a scanning feature and an LCMD feature, or separate and distinct units. Storage medium 204 can be located locally, such as on the microscope imaging unit 202 and/or LCMD unit 208, or can comprise a remote server that is networked to microscope imaging unit 202, visualization unit 206, and LCMD unit 208,
20 such that visualization unit 206 can be positioned remotely from at least one of microscope imaging unit 202 and visualization unit 206, and can be used to access and view the image data stored in storage medium 204.

Each unit of system 200 is described in more detail below.

Microscope imaging unit

25 FIG. 3 illustrates an exemplary high-level functional diagram of a microscope imaging unit 202, according to an embodiment of the invention. Microscope imaging unit 202 includes a microscope 110 electrically connected to a controller 112 having a display device 114. Controller 112 in FIG. 3 can be any special-purpose or conventional computer, such as a desktop, laptop, or host computer. Controller 112 is loaded with the
30 appropriate software for controlling microscope imaging unit 202, such as software for running image-processing algorithms, LCMD algorithms, and/or image analysis algorithms. Display device 114 can be any special-purpose or conventional computer

display device that outputs graphical images to a user. Microscope 110 can further include a barcode reader 116, a camera 118, a serial interface 120, one or more sensors 122, one or more motors 124, a light source 126, a turret 128, and a data interface 130.

Camera 118 can be a digital camera having selectable resolution capabilities. Furthermore, camera 118 can comprise any type of device suitable for gathering an image. Camera 118 is mounted upon a turret 128 of microscope 110 such that an aperture of camera 118 is aligned with the field of view (FOV) of any lens associated with turret 128. Camera 118 is electrically coupled to a serial interface such that they can feed electrical inputs to a serial interface 120, which facilitates a serial communication link between camera 118 and controller 112. In an embodiment of the invention, serial interface 120 provides a USB connection to controller 112. It should be appreciated that camera 118 can be communicatively coupled to controller 112 in other manners.

Controller 112 can include one or more components for facilitating its functions. In an embodiment, controller includes a video card 112. Camera 118 provides a direct video output to the video card within controller 112. The video card gathers the image data from camera 118 for processing in a well-known manner.

The sensors can include one or more sensors for sensing various aspects of microscope imaging unit 202. For example, sensors 122 include, but are not limited to, position sensors, temperature sensors, and light intensity sensors or optical encoders. Motors 124 can be any type of motors for providing motion to the microscope or any portion of the microscope. In an embodiment, motors 124 are conventional servomotors associated with the motion control of microscope 110, such as those for rotating the appropriately powered lens within the optical path of microscope 110, for adjusting focus, or for controlling an automated X,Y stage (shown in FIG. 4).

Light source 126 can be any suitable light source for appropriately illuminating the FOV of microscope 110 sufficient to create a digital image of that FOV. Turret 128 is a conventional motor-driven microscope turret upon which is mounted a set of lenses of varying power that may be rotated into the optical path of microscope 110. Turret 128 is also suitably controlled to provide the desired focus. Sensors 122, motors 124, light source 126, and turret 128 feed to the electrical inputs of data interface 130. Data interface 130 can be a conventional system driver card, which facilitates a data

communication link between these elements and a motion control card within controller 112.

FIG. 4 shows a front view of an exemplary microscope 110 of microscope imaging unit 202. A set of viewing oculars 173 of microscope 110 are optionally located on microscope 110 for operator viewing. As mentioned, microscope 110 further includes a camera 118 for acquiring images. Illumination light source 126 in FIG. 4 projects light onto X-Y stage 177, which is subsequently imaged through microscope 110 and acquired through CCD camera 118 for processing in an image processor. A Z stage or focus stage 179 under control of microscope controller 112 provides displacement in the Z plane for focusing. Microscope 110 further includes motorized objective turret 128 for selection of objectives. In one embodiment of the invention, microscope 110 comprises a LCMD unit, such as a near IR laser diode integral with the microscope optics, such that microscope imaging unit 202 and LCMD unit 208 comprise a single piece of equipment.

Digital Slide Area Designation

Referring back to FIG. 1, at 12, a glass slide is scanned to create a digital slide. In particular, a standard microscope slide having at least one biological sample deposited thereon and optionally stained with one or more chromogenic dyes is positioned on automated X-Y stage 177 of microscope 110, depicted in FIG. 4.

Once the slide is positioned in the FOV of microscope 110, an image scan operation is performed wherein the slide can be scanned at one or more resolutions and magnifications based upon image-processing algorithms and image analysis algorithms executed by controller 112. Examples of such image acquisition can be found in U.S. Patent Publication Applications 2006/0002636 entitled "Data Structure of an Image Storage and Retrieval System" and 2005/0089208 entitled "System and Method for Generating Digital Images of a Microscope Slide," both of which are incorporated herein by reference in their entirety. Upon completion of the image scan operation, the slide image data for that particular slide is transmitted to controller 112 and stored in memory or storage medium 204, such as in a database, for example. In one embodiment of the invention, the slide image data file is stored in a database on a remotely available server such that remote users networked to the server can access the slide image data.

It should be appreciated that microscope imaging unit 202 can be configured to operate autonomously. That is, a clinician can initiate microscope imaging unit 202 such

that microscope imaging unit 202 thereafter operates automatically without the need for human intervention as long as a supply of microscope slides is available at its in-feed stage and no system errors occur. Alternately, the clinician and/or the controller can manually feed slides into the microscope imaging system.

5 The digital slide is a digital representation of the slide image data of all or substantially all of a sample on a glass slide that was captured during scanning. In one embodiment, the slide image data is digitized such that mechanical stage coordinates of the captured area(s) are represented. This coordinate information can be stored inside the image data file (.TIFF or .JPG) or can be a separate file for example located in storage
10 medium 204, such as on a database. Other methods of storing positional information are also possible. This provides sufficient information such that a particular pixel coordinate on a digital slide can be converted to mechanical stage, i.e. real world x-y coordinates. Other information may also be contained in storage medium 204, such as, for example,
15 patient and health care provider information, including, but not limited to, the patient's name, age, and address, and the physician's name and location of practice, slide identification such as barcode information, microscope identification, and any of a variety of information.

As mentioned above, storage medium 204 can also include coordinates with respect to a coordinate system, such as a Cartesian coordinate system comprised of x and y
20 coordinates that are oriented relative to a reference point on the slide. The process of capturing and inserting these coordinates into storage medium 204 is referred to as the "registration" process. The registration process of these coordinates can occur either during the image capture process 12 (referred to as "online") or after the image capture process is complete (referred to as "offline").

25 **Visualization unit and identification of areas of interest**

Referring back to FIG. 1, after digitization of the slide at 12, a user such as a pathologist views the slide at 14 using visualization unit 206. Visualization unit 206 can include, for example, a computer with access to storage medium 204, such as a computer networked to a remote database. The computer can have software installed thereon to
30 access, view, and edit the image data stored in storage medium 204.

The user can either view the digital slide locally on LCMD unit 208 if LCMD unit 208 comprises an integrated visualization unit 206, or can optionally access storage

medium 204 remotely, and view the digital slide on any of a number of networked computers having a visualization unit 206. The user then identifies cells or areas of interest, using a selection tool. The corresponding digital coordinates describing this area of interest, such as pixel and/or rectangular coordinates, can then be stored to storage medium 204.

In another embodiment of the invention, the user can annotate the digital slide on top or in the slide area(s) of interest of the digital slide while viewing the slide. The digital slide can be annotated with a variety of drawing tools such as freehand drawing, text boxes, circle, rectangle, and polygon, and the like. The annotation data, such as the coordinates describing the annotation, are stored to a persistent mechanism or storage medium 204, such as in the database, an xml file, and/or as metadata inside the digital slide file.

In yet another embodiment, visualization unit 206 can provide automated or semi-automated assistance to the user. For example, unit 206 can separate epithelium from stroma and auto-generate an annotation. This semi-automated or automated assistance is explained, for example, in previously referenced U.S. Patent No. 6,215,892 entitled "Method and Apparatus for Automated Image Analysis of Biological Specimens." The user can then edit this annotation. Such edits can include change the shape of the annotation or alternatively drawing an exclusionary annotation the deletes a certain portion of the area in the annotation. For example, if the semi-automated system created a free hand drawing, the user can draw another free hand drawing. The area defined by this second freehand drawing is subtracted from the area of the first such that the overlap is eliminated from the first and only the non-overlapping area of the first is left.

Coordinate Transform/ Registration

Referring back to FIG. 1 at 18, in order to perform LCMD on the areas of interest identified in 16, the annotations generally must be converted to coordinates readable by LCMD unit 208. In some embodiments, LCMD unit 208 understands mechanical coordinates, such as Cartesian coordinates or rectangular coordinates, corresponding to its x-y stage system. A stage mapping calibration that would be performed periodically on microscope imaging unit 202, or the digital slide scanning system, and LCMD unit 208 provides the transformation information necessary to construct a transform matrix. This transform matrix can be combined with a digital slide pixel to scanner stage matrix in

order to provide transformation of the annotation pixel coordinates to LCMD stage coordinates.

At the completion of the cell identification, system 100 transposes the positions into actual stage coordinates for the LCMD procedure. A program running on LCMD unit 208 controls the operation by communicating with a stage controller, similar to the stage controller of microscope imaging unit 202.

LCMD

Before LCMD is performed, embodiments of the present disclosure can also include a step to perform a manual or dynamic, automated registration or alignment of the digital slide and the field of view of the LCMD using the transformed coordinates as a starting point. Because LCMD unit 208 typically has a camera on the unit, such as when microscope imaging unit 202 and LCMD unit 208 comprise the same unit, an image of the specified area on the glass slide can be captured before LCMD is performed. This image can then be compared to the original annotated area of the digital slide.

In one embodiment of the invention, the comparison is done automatically. This automatic comparison can be done by doing a normalized cross correlation. This comparison can be repeated using a sliding window of a predetermined amount to find the best match. Once the coordinates of the best match are determined, the stage coordinates for transfer can then be adjusted. Stage coordinates describing the area to be captured can be optionally padded by a predetermined amount in order to compensate for any mechanical inaccuracies that can be in the system. Such padding can be different in each axis to reflect the potentially different accuracies of each axis.

In another embodiment of the invention, the comparison is done manually by the LCMD operator. The manual registration of the digital slide can be accomplished via a side-by-side comparison of the digital slide and LCMD unit field of view, a transparent overlay comparison, or a combination of both. Registration of the images using either the side-by-side and overlay techniques, such as transparent overlay, can be accomplished by a user interface and a user input device, such as a mouse, joystick, keyboard, and the like, which allows an operator to adjust any of a variety of parameters on the LCMD unit field of view including movement, sizing, and/or scaling of the annotation, movement of the image, adjustment of scale or magnification of the image, and any combination thereof.

The movement of the annotation, image, or both can include x-y translation, as well as rotational movement.

According to one embodiment of the invention, FIGS. 5a and 5b represent an example of manual registration 500 using a side-by-side comparison technique in which the annotation, i.e. the boxed area in this case, can be moved. FIG. 5a illustrates a side-by-side screen shot 500a of an initial registration of digital slide image 506 having annotation 502 and LCMD unit image 508 having annotation 504. As apparent in FIG. 5a, the initial registration of annotation 502 and 504 is poor, and does not represent the same or similar selected area of interest. The user, through a user interface, moves and/or sizes annotation 504 to improve the registration, as illustrated in FIG. 5b in screen shot 500b, such that the selected areas of interest are the same or similar in both images 506 and 508. Movement of annotation 504 can include x-y translation as well as rotational movement.

In another embodiment of the invention, the scale of the annotation can be adjusted. If the initial scale of the annotation of the LCMD unit image is different from the scale of the annotation of the digital slide, the user can adjust the scale of the annotation using a user input device, such as a mouse, until the scale of the two views are substantially similar.

According to an alternative embodiment of the invention, FIGS. 6a and 6b represent an example of manual registration 600 using a side-by-side comparison technique in which LCMD unit image 608 can be moved to register annotations 602 and 604. FIG. 6a illustrates a side-by-side screen shot 600a of an initial registration of digital slide image 606 having annotation 602 and LCMD unit image 608 having annotation 604. As apparent in FIG. 6a, the initial registration of annotation 602 and 604 is poor, and does not represent the same or similar selected area of interest. The user, through a user interface, moves LCMD unit image 608 to improve the registration, as illustrated in FIG. 5b in screen shot 600b, such that the selected areas of interest are the same or similar in both images 606 and 608. Movement of LCMD unit image 608 can include x-y translation as well as rotational movement. In addition, the scale or magnification of LCMD unit image 608 can be made smaller or larger such that LCMD unit image 608 is approximately the same magnification of digital slide image 606.

In another embodiment of the invention, the scale between the digital slide and the LCMD unit image can be automatically adjusted such that it is not dependent upon the

user's manual adjustment. This automatic scale adjustment can be accomplished via a distance/pixel calibration, for example. The scale of the one or both of the digital slide and the LCMD unit image can be adjusted so that one screen pixel corresponds to the same distance, such as a μm distance, in both images. This automatic scale adjustment
5 can be incorporated in the registration system in which the annotation is moved or adjusted and the registration system in which the LCMD unit image is moved or adjusted.

Referring back to FIG. 1 at 20, when the isolated cells are in the field of view, and the user is satisfied with the annotation registration and scale, the microscope operator activates LCMD unit 208. LCMD unit 208 can comprise, for example, a near IR laser
10 diode integral with the microscope optics. The pulsed laser beam activates a precise spot on the transfer film, fusing the film with the underlying isolated cells. The transfer film with the bonded cells is then lifted off the thin tissue section, leaving the other, non-isolated cells on the glass slide. The isolated cells can then be analyzed as discussed in the Background section.

The microscope operator activating LCMD unit 208 need not be an expert in the area of cell identification, and can be a lab technician as compared to a pathologist. Therefore, the system and method of the present invention does not constrain an expert, such as a pathologist, to an LCMD unit for long periods of time. Rather, the pathologist or expert can identify areas of interest at their leisure, and at any location in which they have
15 editing and selecting access to storage medium 204 and the digital slide image data.

The embodiments above are intended to be illustrative and not limiting. In addition, although the present disclosure has been described with reference to particular embodiments, those skilled in the art will appreciate that changes can be made in form and detail without departing from the spirit and scope.

CLAIMS

What is claimed is:

1. A system for designating and capturing targets of interest on a slide having a biological sample contained thereon, the system comprising:

a microscope imaging unit including a microscope having a stage for positioning the slide thereon, and an image capturing apparatus, wherein the image capturing apparatus generates a digital image representation of at least a portion of the biological sample;

a visualization unit including a computer having a display screen, the computer having a selection tool installed thereon, the selection tool being adapted to enable a user to select at least one area of interest from the digital image representation;

a laser capture microdissection unit adapted to dissect a portion from the biological sample,

wherein a first set of coordinates is generated by the visualization unit upon selection of the at least one area of interest, and wherein the first set of coordinates is transformed to a second set of coordinates corresponding to positions on the slide and readable by the laser capture microdissection unit such that the dissected portion of the biological sample corresponds to the at least one area of interest selected from the digital image representation.

2. The system of claim 1, further comprising a storage medium adapted to store the digital image representation, the first set of coordinates, and the second set of coordinates.

3. The system of claim 2, wherein the storage medium comprises a remote server, selectively in communication with the microscope imaging unit, the visualization unit, and the laser capture microdissection unit.

4. The system of claim 1, wherein the first set of coordinates comprise pixel coordinates, and wherein the second set of coordinates comprise Cartesian coordinates corresponding to positions on a stage of the laser capture microdissection unit.

5. The system of claim 1, wherein the image capture apparatus comprises a digital camera in communication with a video card.
6. The system of claim 1, wherein the system further comprises an executable task adapted to transform the first set of coordinates to the second set of coordinates.
7. The system of claim 6, wherein the executable task is stored to the storage medium.
8. A method for designating and capturing targets of interest on a slide having a biological sample contained thereon, the method comprising:
 - providing a slide having a biological sample thereon;
 - generating a digital image representation of at least a portion of the biological sample;
 - selecting at least one area of interest from the digital image representation, thereby generating a first set of coordinates;
 - placing the slide having the biological sample thereon on a laser capture microdissection unit;
 - transforming the first set of coordinates to a second set of coordinates readable by the laser capture microdissection unit; and
 - dissecting a portion of the biological sample corresponding to the at least one area of interest selected from the digital image representation.
9. The method of claim 8, further comprising:
 - storing the digital image representation to a storage medium.
10. The method of claim 9, wherein the storage medium comprises a remote server.

11. The method of claim 10, wherein selecting the at least one area of interest comprises:

- accessing remotely the digital image representation stored on the remote server;
- viewing the digital image representation at a remote location; and
- storing the first set of coordinates to the remote server.

12. The method of claim 11, wherein transforming the first set of coordinates to a second set of coordinates comprises:

- accessing the first set of coordinates stored on the storage medium; and
- executing a program for transforming the first set of coordinates to the second set of coordinates.

13. The method of claim 12, wherein the executable program is stored on the remote server.

14. The method of claim 8, further comprising analyzing the dissected portion of the biological sample.

15. The method of claim 14, wherein analyzing the dissected portion of the biological sample comprises at least one technique selected from the group consisting of Polymerase Chain Reaction ("PCR"), immunoassays, microarrays, and combinations thereof.

16. The method of claim 8, wherein the first set of coordinates comprise pixel coordinates, and wherein the second set of coordinates comprise Cartesian coordinates corresponding to positions on a stage of the laser capture microdissection unit.

17. A system for designating and capturing targets of interest on a slide having a biological sample contained thereon, the system comprising:

microscope imaging means for generating a digital image representation of at least a portion of the biological sample;

visualization and selection means for viewing and selecting at least one area of interest from the digital image representation, wherein a first set of coordinates is generated upon selection of the at least one area of interest;

transformation means for transforming a first set of coordinates to a second set of coordinates readable by laser capture microdissection means; and

laser capture microdissection means for dissecting a portion of the biological sample corresponding to the at least one area of interest selected from the digital image representation.

18. A device for designating and capturing targets of interest on a slide having a biological sample contained thereon, the device comprising:

a microscope having a stage for positioning a slide thereon, ;

a digital image acquisition unit operably coupled to the microscope, wherein the digital image acquisition unit is adapted to capture and digitize at least a portion of the slide forming a digital slide;

a laser capture microdissection unit operably coupled to the microscope; and

a controller, wherein the controller comprises an executable task for transforming a first set of coordinates representing at least one area of interest from the digital slide to a second set of coordinates readable by the laser capture microdissection unit, and wherein the laser capture microdissection unit is adapted to dissect a portion of the biological sample based on the second set of coordinates, such that the dissected portion of the biological sample corresponds to the at least one area of interest selected from the digital slide.

19. A method for designating and capturing targets of interest on a slide having a biological sample contained thereon, the method comprising:

providing a slide having a biological sample thereon;

generating a digital image representation of at least a portion of the biological sample;

selecting an area of interest from the digital image representation, thereby generating a first annotation representing the area of interest;

placing the slide having the biological sample thereon on a laser capture microdissection unit and generating a laser capture microdissection unit image having a second annotation representing a portion of the biological sample;

registering the first annotation and the second annotation such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation; and

dissecting the portion of the biological sample represented by the second annotation.

20. The method of claim 19, wherein registering the first annotation and the second annotation comprises:

presenting a side-by-side comparison of the digital image representation having the first annotation and the laser capture microdissection unit image having the second annotation;

moving the second annotation on the microdissection unit image using a user input device such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation.

21. The method of claim 20, wherein moving the second annotation includes at least one of x-y translation and rotational movement.

22. The method of claim 19, wherein registering the first annotation and the second annotation comprises:

presenting a side-by-side comparison of the digital image representation having the first annotation and the laser capture microdissection unit image having the second annotation;

moving the laser capture microdissection unit image having the second annotation using a user input device such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation.

23. The method of claim 22, wherein moving the laser capture microdissection unit image includes at least one of x-y translation and rotational movement

24. The method of claim 22, wherein registering the first annotation and the second annotation further comprises:

changing a magnification of the laser capture microdissection unit image such that the magnification substantially similar to a magnification of the digital image representation.

25. The method of claim 19, wherein registering the first annotation and the second annotation comprises:

presenting a transparent overlay comparison of the digital image representation having the first annotation and the laser capture microdissection unit image having the second annotation;

moving the second annotation on the microdissection unit image using a user input device such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation.

26. The method of claim 25, wherein moving the second annotation includes at least one of x-y translation and rotational movement.

27. The method of claim 19, wherein registering the first annotation and the second annotation comprises:

presenting a transparent overlay comparison of the digital image representation having the first annotation and the laser capture microdissection unit image having the second annotation;

moving the laser capture microdissection unit image having the second annotation using a user input device such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation.

28. The method of claim 27, wherein moving the laser capture microdissection unit image includes at least one of x-y translation and rotational movement

29. The method of claim 27, wherein registering the first annotation and the second annotation further comprises:

changing a magnification of the laser capture microdissection unit image such that the magnification substantially similar to a magnification of the digital image representation.

30. A system for designating and capturing targets of interest on a slide having a biological sample contained thereon, the system comprising:

a microscope imaging unit including a microscope having a stage for positioning the slide thereon, and an image capturing apparatus, wherein the image capturing apparatus generates a digital image representation of at least a portion of the biological sample;

a visualization unit including a computer having a display screen, the computer having a selection tool installed thereon, the selection tool being adapted to enable a user to select at least one area of interest from the digital image representation thereby forming a first annotation representing the at least one area of interest;

a laser capture microdissection unit adapted to generate a slide image having a second annotation representing a portion from the biological sample, and to dissect the portion from the biological sample,

wherein the first annotation and the second annotation are registered such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation.

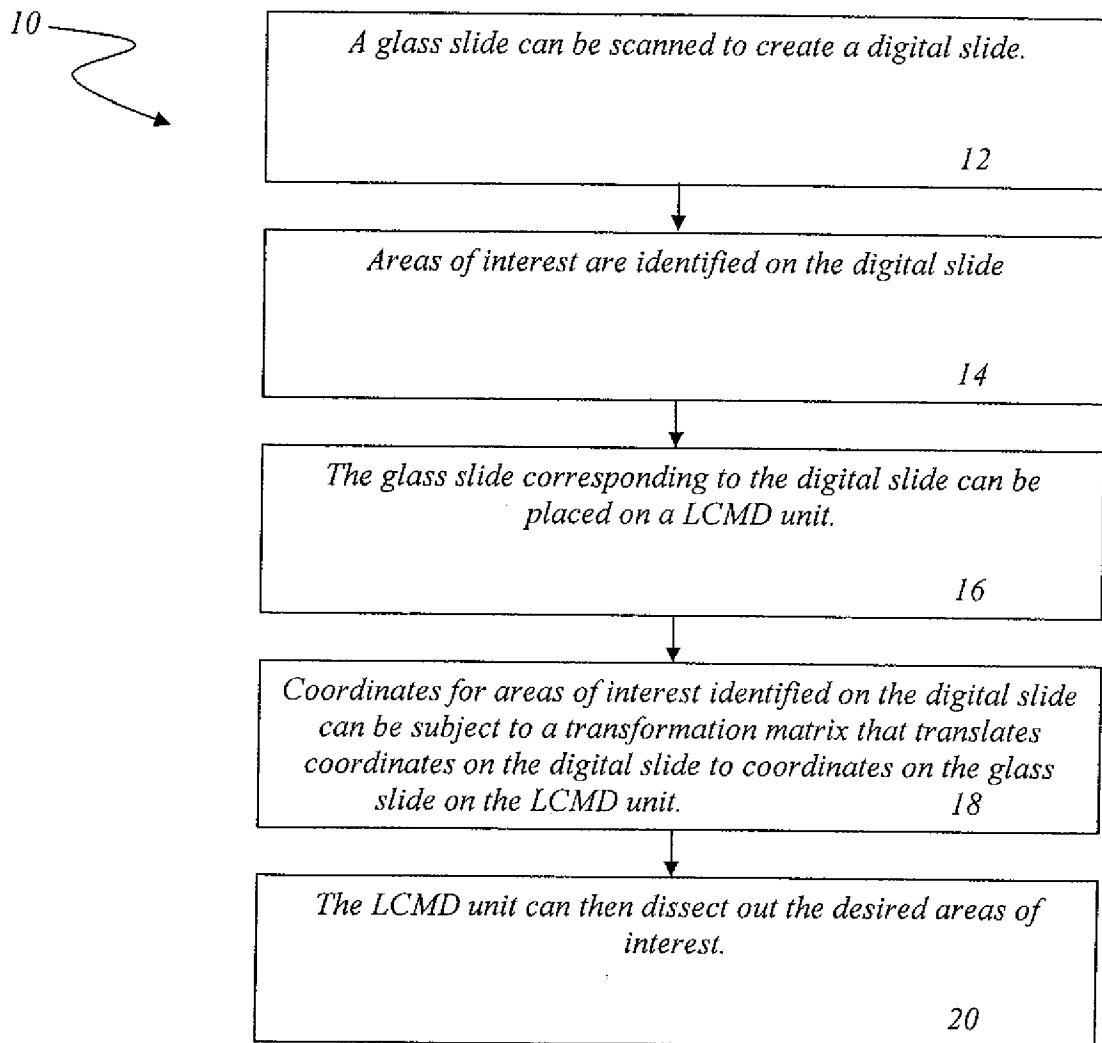
31. The system of claim 30, wherein the laser capture microdissection unit is adapted to generate a side-by-side comparison of the digital image representation having the first annotation and the slide image having the second annotation, and includes a user input device to register the first annotation and the second annotation by movement of the second annotation such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation.

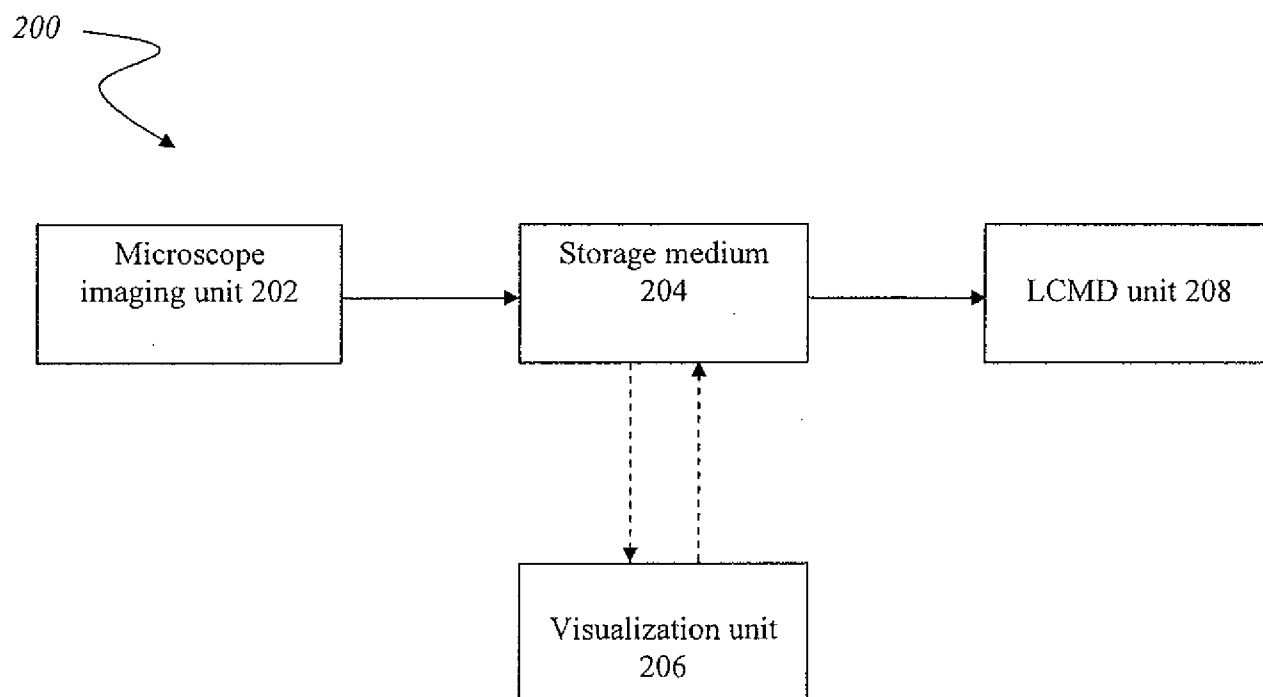
32. The system of claim 30, wherein the laser capture microdissection unit is adapted to generate a side-by-side comparison of the digital image representation having the first annotation and the slide image having the second annotation, and includes a user input device to register the first annotation and the second annotation by movement of the slide image such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation.

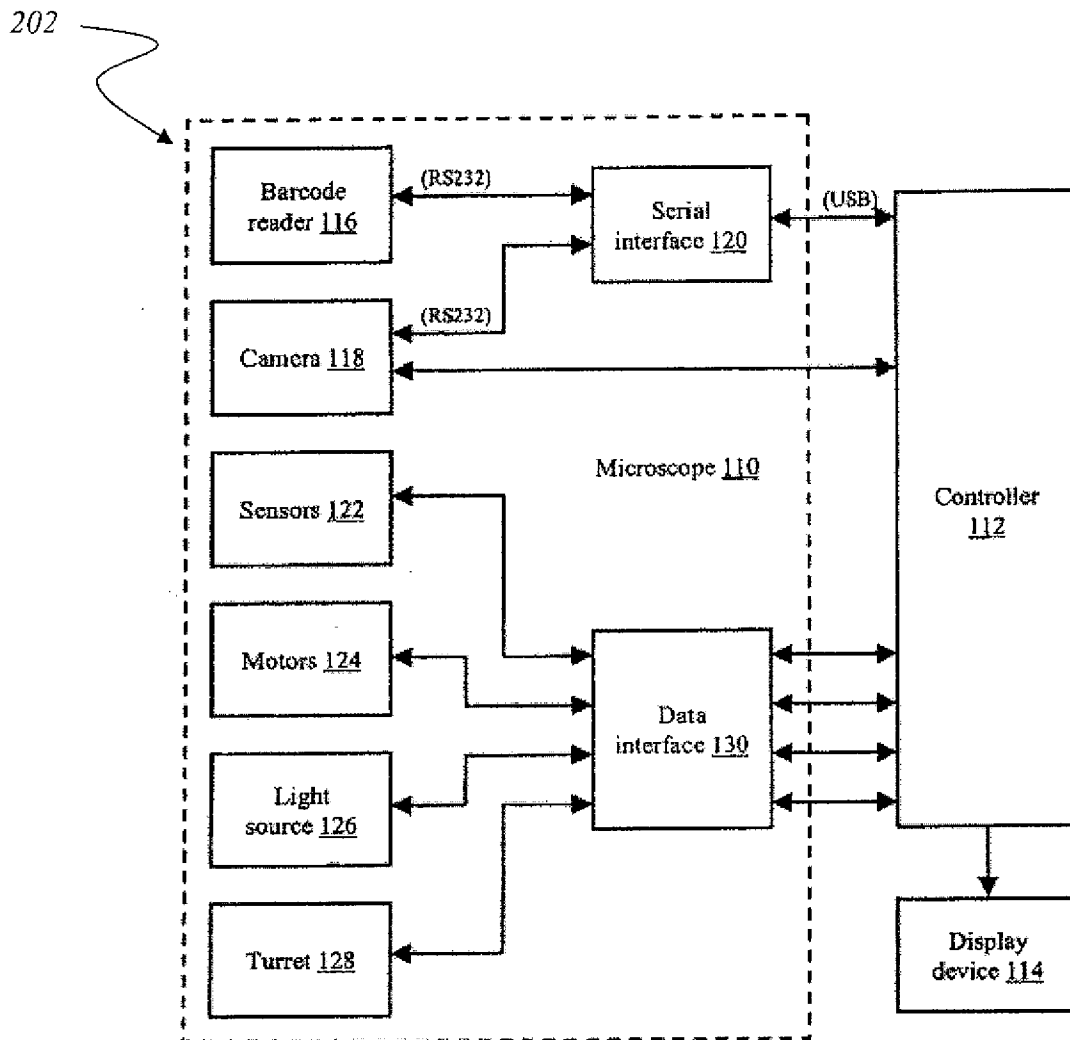
33. The system of claim 30, wherein the laser capture microdissection unit is adapted to generate a transparent overlay comparison of the digital image representation having the first annotation and the slide image having the second annotation, and includes a user input device to register the first annotation and the second annotation by movement of the second annotation such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation.

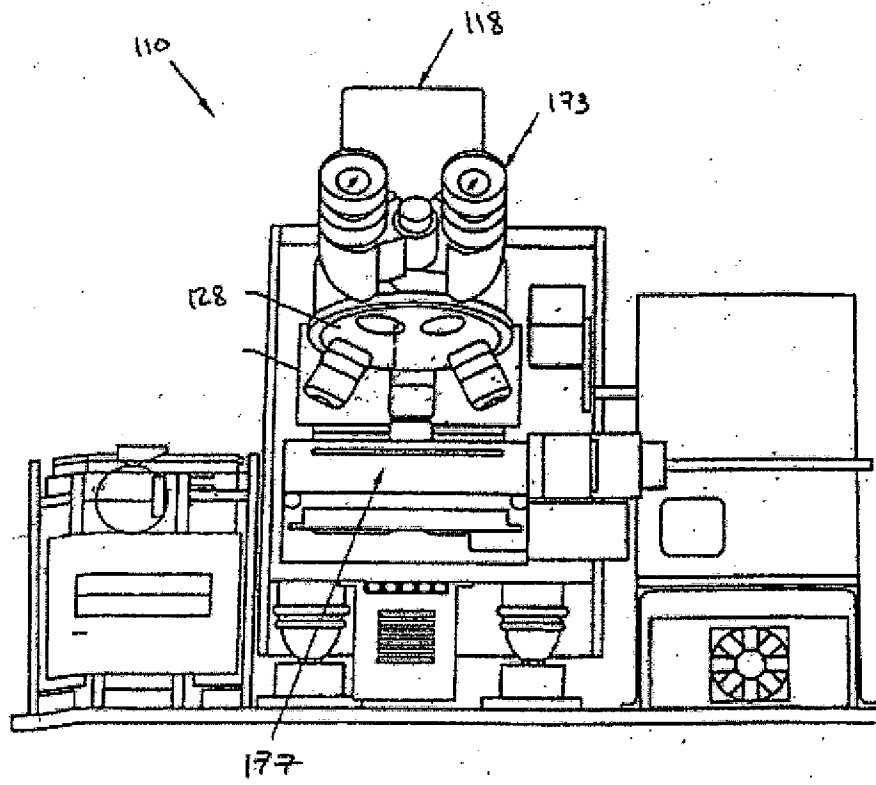
34. The system of claim 30, wherein the laser capture microdissection unit is adapted to generate a transparent overlay comparison of the digital image representation having the first annotation and the slide image having the second annotation, and includes a user

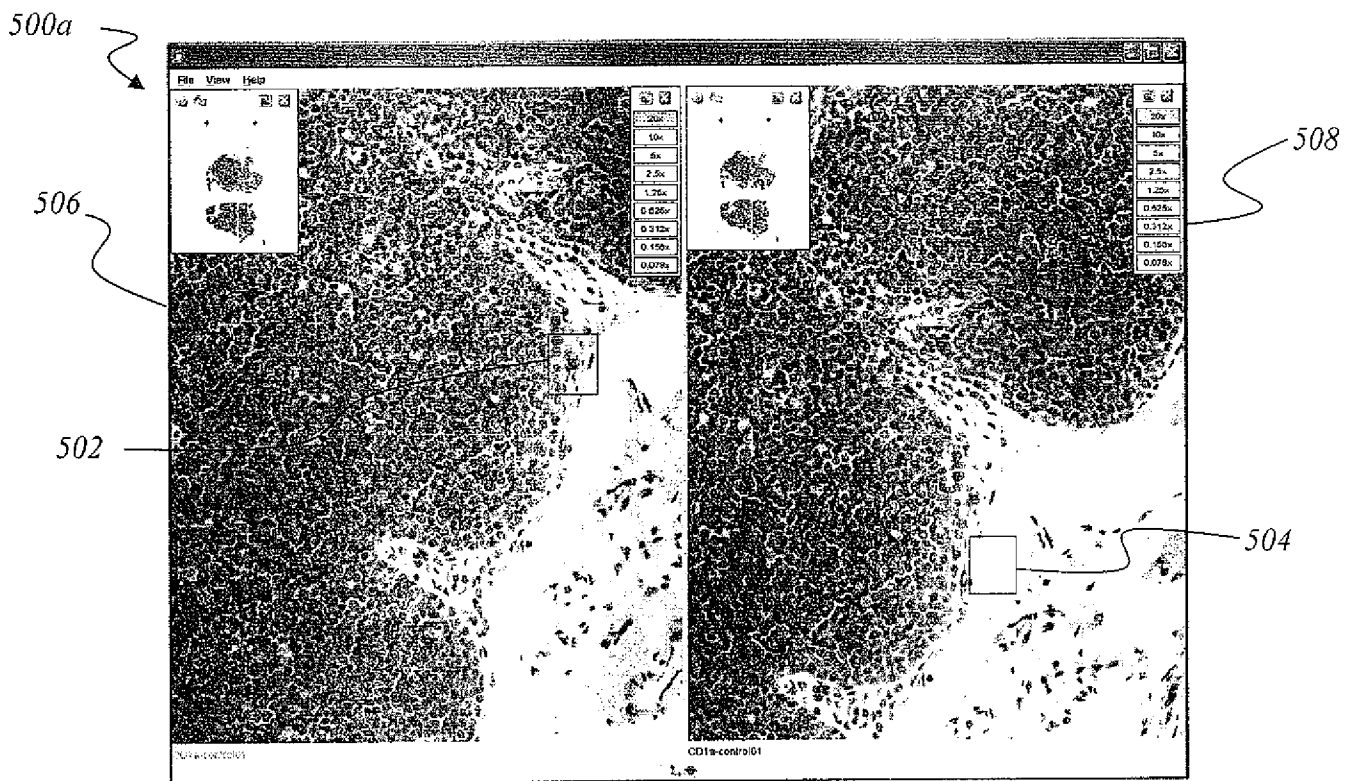
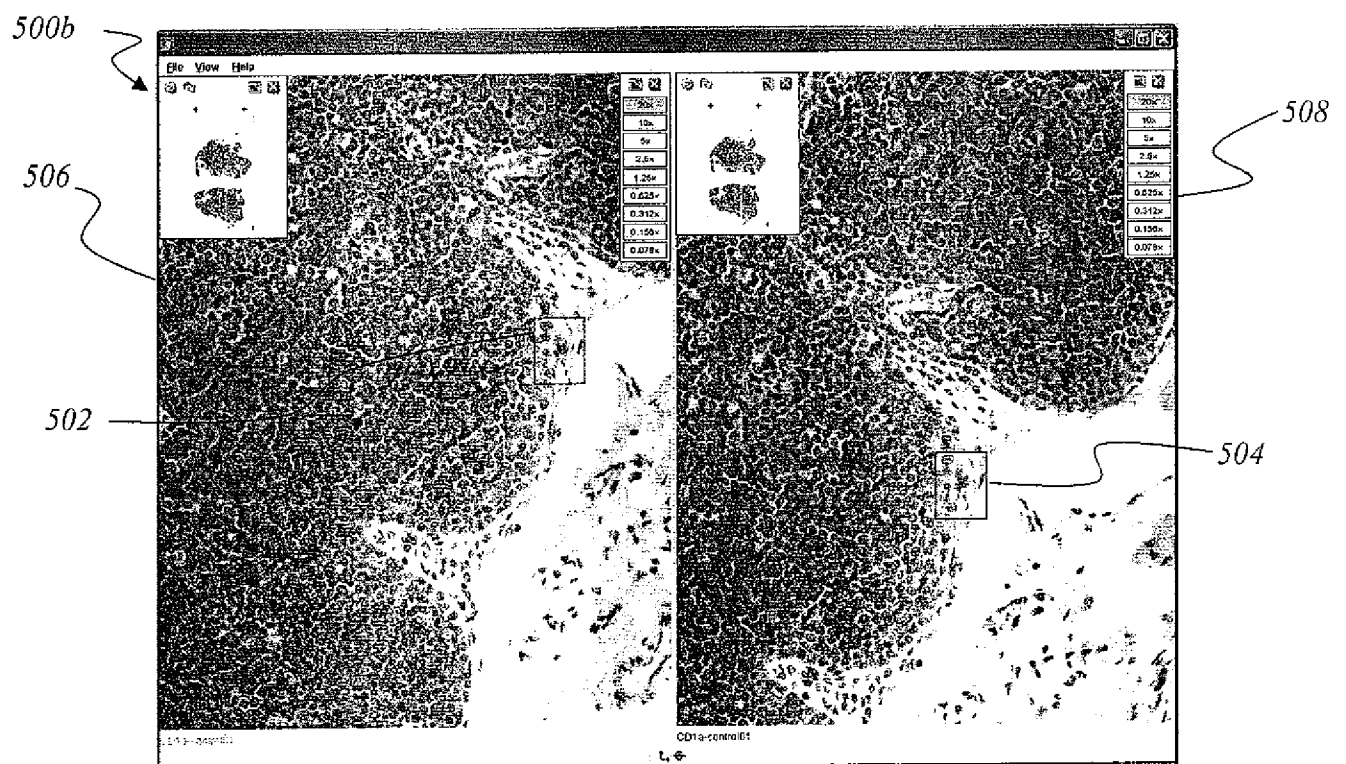
input device to register the first annotation and the second annotation by movement of the slide image such that the portion of the biological sample represented by the second annotation corresponds to the area of interest represented by the first annotation.

**Fig. 1**

***Fig. 2***

*Fig. 3*

*Fig. 4*

*Fig. 5a**Fig. 5b*

