EXHIBIT 23



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EXAMINER	
BRUMBACK, BRENDA G	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Transmittal of Communication to Third Party Requester Inter Partes Reexamination	**Control No.** 95/001,292	**Patent Under Reexamination** 6,654,505 B2 ET AL.	
	Examiner BRENDA BRUMBACK	**Art Unit** 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

OFFICE ACTION IN* INTER PARTES *REEXAMINATION	**Control No.**	**Patent Under Reexamination**	
	95/001,292	6,654,505 B2 ET AL.	
	Examiner	**Art Unit**	
	BRENDA BRUMBACK	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

Responsive to the communication(s) filed by:
Patent Owner on _____
Third Party(ies) on 31 December 2009

RESPONSE TIMES ARE SET TO EXPIRE AS FOLLOWS:

For Patent Owner's Response:
2 MONTH(S) from the mailing date of this action. 37 CFR 1.945. EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.956.
For Third Party Requester's Comments on the Patent Owner Response:
30 DAYS from the date of service of any patent owner's response. 37 CFR 1.947. NO EXTENSIONS OF TIME ARE PERMITTED. 35 U.S.C. 314(b)(2).

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

This action is not an Action Closing Prosecution under 37 CFR 1.949, nor is it a Right of Appeal Notice under 37 CFR 1.953.

PART I. THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892
2. ☐ Information Disclosure Citation, PTO/SB/08
3. ☐ _____

PART II. SUMMARY OF ACTION:

1a. ☒ Claims 1-6 are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled.
3. ☐ Claims _____ are confirmed. [Unamended patent claims]
4. ☐ Claims _____ are patentable. [Amended or new claims]
5. ☒ Claims 1-6 are rejected.
6. ☐ Claims _____ are objected to.
7. ☐ The drawings filed on _____ ☐ are acceptable ☐ are not acceptable.
8. ☐ The drawing correction request filed on _____ is: ☐ approved. ☐ disapproved.
9. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119 (a)-(d). The certified copy has: ☐ been received. ☐ not been received. ☐ been filed in Application/Control No 95001292.
10. ☐ Other _____

INTER PARTES REEXAMINATION

Detailed Action

1. Claims 1-6 of U.S. Patent 6,654,505 to Bridgham *et al.* are currently under reexamination in the present *inter partes* proceeding.

Documents Cited

2. WO 96/12014, 04/25/1996 to Brenner (hereinafter, "Brenner").

Gelles *et al. Tracking kinesin-driven movements with nanometer-scale precision.* Nature, 331:450-453 (1988) (hereinafter, "Gelles").

U.S. Patent No. 6,057,150 issued 05/02/2000 to Lee *et al.* (hereinafter "Lee").

Schmidt *et al. Integrin-Cytoskeletal Interactions in Migrating Fibroblasts are Dynamic, Asymmetric, and Regulated.* J. Cell Biology, 123(4):977-991 (1993) (hereinafter, "Schmidt").

Wilson *et al. Single particle tracking of cell-surface HLA-DR molecules using R-phycoerythrin labeled monoclonal antibodies and fluorescent digital imaging.* J.Cell Science, 109:2101-2109 (1996) (hereinafter "Wilson").

Dow *et al. A simple microcomputer-based system for real-time analysis of cell behaviour.* J. Cell Science, 87:171-182 (1987) (hereinafter "Dow").

NIH Image Version 1.58 Manual 1995 (hereinafter, "NIH").

Wernet *et al. Particle displacement tracking technique and Cramer-Rao lower bound error in centroid estimates from CCD imagery.* Experiments in Fluids, 15:295-307 (1993) (hereinafter "Wernet").

U.S. Patent No. 5,415,839 issued 05/16/1995 to Zaun *et al.* (hereinafter, "Zaun").

U.S. Patent No. 5,599,668 issued 02/04/1997 to Stimpson *et al.* (hereinafter, "Stimpson").

U.S. Patent No. 5,556,764 issued 09/17/1996 to Sizto *et al.* (hereinafter, "Sizto).

WO 97/43611, 11/20/1997 to Stern (hereinafter, "Stern").

U.S. Patent No. 6,151,405 issued 11/21/2000 to Douglass *et al.* (hereinafter "Douglass").

DiMilla *et al. Maximal Migration of Human Smooth Muscle Cells on Fibronectin and Type IV collagen Occurs at an Intermediate Attachment Strength.* J. Cell Biology, 122(3):729-737 (1993) (hereinafter "DiMilla").

U.S. Patent No. 5,257,182 issued 10/26/0993 to Luck et al. (hereinafter "Luck").

U.S. Patent No. 6,122,396 issued 09/19/2000 to King et al. (hereinafter "King").

Scope of claims

3. In reexamination, patent claims are construed broadly. *In re Yamamoto*, 740 F.2d 1569, 1571,222 USPQ 934, 936 (Fed. Cir. 1984) (claims given "their broadest reasonable interpretation consistent with the specification"). The '505 patent consists of claims 1-6 drawn to a device-readable medium embodying a program to generate images of a planar array of microparticles and to track positions of the microparticles during processing steps.

Claim 1 is representative.

1. A device-readable medium embodying a program of instructions for execution by said device to perform a method of generating images of a planar array of microparticles and tracking positions of the microparticles during a sequence of processing steps, said program of instructions comprising instructions for:

rendering a plurality of digital images of the planar array of the microparticles during the sequence of processing steps, based on optical signals generated at the microparticles; and

processing the plurality of digital images, wherein said processing includes correlating the optical signals generated at each microparticle with its corresponding image in each of the plurality of digital images.

Statutory Basis for Claim Rejections - 35 U.S.C §§102 & 103

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains Patentability shall not be negatived by the manner in which the invention was made

Proposed Rejections

6. **GROUND A (SNQ 1):**

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Brenner.

This rejection of claim 1 was proposed by the third party requester (see pages 32-34 of the request and exhibit CC-A) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Brenner teaches a computer based apparatus for generating images of a planar array of microparticles comprising a microscope for observing optical signals generated at the sight of the microparticles and software (a computer-readable set of instructions) for generating digital images corresponding to the microparticles during steps of chemical or enzymatic processes (*e.g.* polynucleotide sequencing) (page 25, line 27 through page 26, line 23, and page 28, lines 6-10). Brenner teaches that the scanning system is able to reproducibly scan the substrate and define the position of each microparticle by way of a coordinate system (page 26, lines 7-9, and page 27, lines 4-16). Brenner teaches that the system comprises computer software for table translation and data collection functions (page 26, lines 21-23). The computer readable program of instructions designed to generate images of the planar array of microparticles and define the positions of individual particles disclosed by Brenner anticipates the device-readable medium of patented claim 1.

7. **GROUND B (SNQ 2):**

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Gelles.

This rejection of claims 1-6 was proposed by the third party requester (see pages 34-36) of the request and Exhibit CC-B) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Regarding ***claim 1***, Gelles teaches a device readable medium employing a program of instructions for execution by the device (a video-image processing computer) as a monochrome high resolution optical disk recorder under the control of the computer and as custom software designed to process the optical signals (Page 451, Fig. 2, column 1). Gelles teaches using the

system for recording, analyzing, and determining precise positional information of microscopic plastic beads (*i.e.*, microparticles) on a glass coverslip (*i.e.*, a planar array) as the microparticles, driven by kinesin, attach to and move along microtubules *in vitro* (*i.e.*, a sequence of processing steps; see page 450, abstract, and column 2 in its entirety, through page 451, first partial paragraph, and Fig. 2). Gelles teaches generating a plurality of digital images and correlating the signals by generation of optical signals using video-enhanced differential interference contrast microscopy and digitization of the signals by the video-image processing computer (page 451, Fig. 2).

Regarding ***claim 2***, Gelles teaches determining the approximate center of each microparticle by teaching calculation of the centroid (see page 450, Fig. 1).

With respect to ***claim 3***, Gelles teaches assigning a plurality of pixels to each microparticle by analyzing a kernel consisting of a single bead image obtained through differential interference microscopy, in which a plurality of pixels are assigned to the kernel image (see page 450, Fig. 1). Gelles discloses using pixel information to analyze the position (*i.e.,* at least one property) of the beads within a plurality of digital images based on the pixels assigned to each bead (Fig. 1 and the paragraph bridging pages 450 and 451).

As for ***claim 4***, Gelles teaches using cross-correlation analysis as a template to search for and identify other beads within the digital images, the beads identified as areas where the pixel intensity distribution most closely matches those of the kernel (*i.e*, uniformity of diameter and shape). The cross-correlation method determines the number of pixels assigned to each bead by comparing the digital images or pixels occupied by each of the other beads with the pixels of the bead used to generate the kernel (see page 450, Fig. 1).

Regarding ***claim 5***, Gelles teaches assigning an initial pixel to the center of the particle by teaching assigning the center of the bead to be the point (0,0) (Fig. 1).

With respect to ***claim 6***, Gelles teaches that the kernel comprises pixels immediately adjacent to the centroid by teaching that positional information is derived from the entire bead image rather than from an individual point or edge in order to maximize precision. Thus, Gelles teaches additional pixels immediately adjacent to the initial pixel (Fig. 1).

8. **GROUND C (SNQ 3):**

Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee.

This rejection of claims 1-3 was proposed by the third party requester (see pages 37-38 of the request and Exhibit CC-C) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Regarding ***claim 1***, Lee teaches a microscope equipped with a charge-coupled device video camera and video frame grabber for recording images of fluorescent microparticles seeded in a planar array on the surface of a collagen-coated substrate having cells cultured thereon. Lee teaches transferring the recorded images to a computer for image processing and finite strain analysis. Lee teaches measurement of marker coordinates before and after stretch (*i.e.*, processing steps) using NIH-1 image software (a device readable medium with a program of instructions for generating images). Lee teaches tracking the positions of the microparticles before and after stretch by correlating the optical signals of the microparticles to their locations (column 9, line 22, through column 10, line 14).

Regarding ***claim 2***, the processing would necessarily encompass determining the centroid or approximate center of the microparticles so as to enable measurement of positions before and after stretch (see also NIH at page 2, second paragraph).

With respect to ***claim 3***, the NIH system assigns pixels to the fluorescent microparticles in order to determine location before and after stretch.

9. **GROUND D (SNQ 4):**

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmidt.

This rejection of claims 1-6 was proposed by the third party requester (see pages 38-41 of the request and Exhibit CC-E) and **is adopted** for the reasons stated in the request and those reasons set forth below.

Regarding ***claim 1***, Schmidt teaches a video camera for capturing images of cells mounted in a planar array on a coverslip and coated with either polystyrene or colloidal gold micropartices (page 977, abstract, and page 979, the paragraph bridging columns 1 and 2 and column 2, second full paragraph). Schmidt teaches that captured images were digitized from a video tape using an image processor, a computer, and a real time storage system. Thus, Schmidt teaches a device-readable medium employing a program of instructions for generating images of a planar array of microparticles. Schmidt teaches processing the digital images for tracking the positions of the microparticles in order to study cellular motility (see page 977, title and abstract, and page 979, last full and partial paragraphs). Schmidt teaches tracking the positions of the gold beads in the digitized images using the cross-correlation method of Gelles (page 979, column 2, last full paragraph).

With respect to ***claim 2***, Schmidt teaches determining the centroid of the DIC image, which is the approximate center of the microparticle. Additionally, as was set forth *supra* in Ground 2, the method disclosed by Gelles and used by Schmidt determines the approximate center of each microparticle by calculating the centroid (see Gelles at page 450, Fig. 1).

With respect to ***claim 3***, the method of Gelles, used by Schmidt, assigns a plurality of pixels to each microparticle by analyzing a kernel consisting of a single bead image obtained through differential interference microscopy in which a plurality of pixels are assigned to the kernel image (see page 450, Fig. 1). Pixel information is then used to analyze the position (*i.e.*, at least one property) of the beads from digital images based on the pixels assigned to each bead (Gelles at Fig. 1 and the paragraph bridging pages 5450 and 451).

As for ***claim 4***, the Gelles method, used and referenced by Schmidt, uses cross-correlation analysis as a template to search for and identify other beads within the digital images, the beads identified as areas where the pixel intensity distribution most closely matches those of the kernel (*i.e*, uniformity of diameter and shape). The cross-correlation method determines the number of pixels assigned to each bead by comparing the digital images or pixels occupied by each of the other beads with the pixels of the bead used to generate the kernel (see Gelles at page 450, Fig. 1).

Regarding ***claim 5***, the method of Gelles, used by Schmidt, assigns an initial pixel to the center of the particle by assigning the center of the bead to be the point (0,0) (see Gelles at Fig. 1).

With respect to ***claim 6***, the method disclosed by Gelles, referenced and used by Schmidt, derives positional information from the entire bead image rather than from an individual point or

edge in order to maximize precision. Thus, Schmidt, by reference to Gelles, teaches additional pixels immediately adjacent to the initial pixel (Gelles at Fig. 1).

10. **GROUND E (SNQ 5):**

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Wilson.

This rejection of claim 1 was proposed by the third party requester (see pages 41-42 of the request and Exhibit CC-E) and **is adopted** for the reasons stated in the request and those reasons set forth below.

Wilson teaches a system for sequentially imaging microparticles (either fluorescent particles or colloidal gold particles) via time-lapse images over a period of time, typically 30 minutes, to track their movement on cells as an indication of the mobility of cell surface MHC (HLA DR) molecules (see the abstract and the paragraph bridging pages 2101-2102). Wilson teaches seeding the cells onto slides (*i.e.*, placing the cells into a planar array), treating the cells with HLA DR specific monoclonal antibody coupled to the fluorescent phycobiliprotein, R-phycoerythrin, and visualizing optical signals generated by the particle tracks using fluorescence digital imaging microscopy (see the abstract and page 2102, column 2, second from last full paragraph, through page 2103, column 1, first four full paragraphs). Thus, Wilson teaches processing a plurality of images of a planar array of microparticles. Wilson teaches a camera attached to the video port of microscope and a detector to digitize the images. Wilson teaches that the particles appear as diffraction limited spots covering a number of pixels. Wilson teaches identifying the microparticle positions by an image analysis algorithm and quantifying them, based on the pixels recorded (see page 2103 first and second full paragraphs). Thus, Wilson

teaches a device-readable medium with a program of instructions for generating images of a planar array of microparticles to track their positions during a sequence of processing steps.

11. **GROUND F (SNQ 6):**

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Dow.

This rejection of claims 1-4 was proposed by the third party requester (see pages 42-44 of the request and Exhibit CC-F) and **is adopted** for the reasons stated in the request and those reasons set forth below.

Regarding ***claim 1***, Dow teaches an image analysis package based on a microcomputer, which tracks moving cells in a focal plane (or planar array) *in vitro*. Absent a limiting definition in the '505 patent specification, the term "microparticle" in interpreted herein for prior art purposes as encompassing the biological cells disclosed by Dow. Thus, Dow teaches an image analysis package for tracking the positions of microparticles during a sequence of processing steps. Dow teaches a monochrome TV camera for viewing the cells under phase optics. Dow teaches digitizing the signal via a video digitizer unit, so that successive frames are acquired by the computer as a pixel array (page 171, abstract, and page 173, second full paragraph). Dow teaches that a digitizing pad allows for measurements and calculations to be performed by a microcomputer based on a frame grabber (see page 172, first and second full paragraphs). Thus, Dow teaches a device readable medium employing a program of instructions to generate images of a planar array of microparticles for tracking the positions of the cells during real time while they are moving (*i.e.*, a sequence of processing steps).

Regarding ***claim 2***, Dow teaches finding the centroid, or approximate center, of the cells by dividing the *x* and *y* coordinates by the number of pixels found in the area adjacent to the cell (referred to by Dow as the "box") (page 173, column 2, first full paragraph).

Regarding ***claim 3***, the system assigns a number of pixels to the particle or box. The system of Dow applies search algorithms to the assigned pixel data in the area around each cell's centroid for correlating data from a previous digital image (abstract and page 173).

As for ***claim 4***, Dow describes assigning the number of pixels according to the magnification (a 10x microscopic lens) used in the system and the size of biological cells. The 10x magnification would ensure relative uniformity in the size and shape of the biological cells. Dow teaches a pixel size of around 1-5 μm (page 173, column 1, second full paragraph, last sentence of the paragraph)..

12. **GROUND G (SNQ 7):**

Claims 1-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Douglass.

This rejection of claims 1-6 was proposed by the third party requester (see pages 44-46 of the request and Exhibit CC-G) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Regarding ***claim 1***, Douglass teaches a system for generating digitized images of biological cells on a microscope slide (*i.e.*, a planar array) for tracking and selecting candidate cells which exhibit a particular marker of interest (*e.g.*, a tumor marker) for further analysis (see the abstract and column 6, line 65, through column 7, line 3). The marker of interest is visualized by a colored insoluble precipitate, which is generated by an enzymatic reaction

employing specific antibodies to locate and label a specific targeted cellular marker (see the abstract and column 1, lines 26-31). Douglass teaches that the system comprises a microscope; a camera; and a computer with a system processor, an image processor, and a communications modem (see column 5, line 66, through column 7, line 65). As was set forth above in Ground F for Dow, the "microparticles" of the present claims are interpreted to encompass the biological cells disclosed by Douglass, absent a limiting definition in the '505 patent specification. Thus, Douglass teaches a device readable medium employing a program of instructions for generating and recording a plurality of digitized images of microparticles during a series of processing or scanning steps and correlating each of the optical signals with its corresponding image.

Regarding ***claim 2***, Douglass teaches computing the centroid, or approximate center, of each cell and storing the data for evaluation of marker-identifying precipitate (column 7, lines 8-10 and 26-31).

Regarding ***claim 3***, Douglass teaches assigning pixel data to the area centered about the centroid for determining the amount of marker identifying precipitate (column 7, lines 3-26).

With respect to ***claim 4***, Douglass teaches that two colors of pixels are assigned and the system computes a ratio of two color components for the pixels in a regularly shaped area around the identified centroid. The system bases the size of the area on the size of the cells and the likelihood that the approximate center of the cell correlates to the geometric center (column 7, lines 11-51).

Regarding ***claim 5,*** Douglass discloses assigning the pixels to the area surrounding the centroid after assigning a pixel to the centroid (column 4, lines 11-51, and column 7, lines 4-26).

Lastly, with respect to ***claim 6***, Douglass teaches assigning additional pixels to each microparticle in the area immediately surrounding the centroid (column 4, lines 11-32, and column 7, lines 4-26).

13. **GROUND H1 (SNQ 8):**

Claims 1-3 and 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brenner in view of Wernet.

This proposed rejection is ***adopted*** for claims 2-3 and 5-6 and is ***not adopted*** for claim 1.

The rejection of claims 1-3 and 5-6 was proposed by the third party requester (see pages 46-50 of the request and Exhibit CC-H-1) and **is adopted for claims 2-3 and 5-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground A, which is incorporated herein by reference in its entirety, Brenner teaches a computer readable program of instructions designed to generate images of a planar array of microparticles and to define the positions of individual particles during a sequence of processing steps. Brenner contemplates using a charge coupled device (CCD) array for scanning the particles (page 26, lines 11-15), but does not specify the steps of determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel, as in patented claims 2-3 and 5-6.

Regarding ***claim 2***, Wernet teaches a particle displacement tracking method used in combination with a charge-coupled device (CCD) array. Wernet teaches calculating the centroid of the particles using images from the CCD (see page 295, Title, and page 296, the paragraph bridging columns 1 and 2 and column 2, two full paragraphs).

With respect to ***claim 3,*** Wernet teaches that spreading the image over many pixels produces accurate centroid estimates. Wernet exemplifies imaged particle diameters at 5 or 6 pixels in diameter, which indicates that pixels in addition to the to the centroid pixel are assigned to the particles (page 300 column 1, second full paragraph, the paragraph bridging columns 1 and 2, and column 2, full paragraph, second from last sentence).

Regarding ***claims 5 and 6***, Wernet teaches that the particle centroids are determined by first locating the particle image boundary and then computing the intensity weighted mean location. Wernet teaches assigning an initial pixel to the centroid by stating that the centroids are estimated to subpixel accuracy (page 286, column 2, first full paragraph). Wernet teaches additional pixels immediately adjacent to the centroid by teaching that the "particle centroid estimate is very sensitive to the ratio of number of counts in two adjoining pixels" and by teaching that "subpixel particle centroids can be accurately determined when the particle image straddles two adjacent particles" (page 299, column 2, last three sentences of the first partial paragraph).

Wernet teaches that particle tracking techniques in combination with CCD imagery are more accurate than other methods; for example, auto or cross-correlation methods (see the abstract).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to have used the particle displacement tracking technique with CCD imagery disclosed by Wernet to accurately define the positions of individual microparticles within the planar array of Brenner because Brenner suggests using CCD and Wernet teaches a high degree of accuracy associated with particle displacement tracking.

14. The proposed rejection of claims 1-3 and 5-6 under 35 U.S.C. 103(a) as being unpatentable over **Brenner in view of Wernet is not adopted with respect to claim 1** for the reasons set forth below.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted herein (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. The distinction between rejections based on 35 U.S.C. 102 and those based on 35 U.S.C. 103 should be kept in mind. Under the former, the claim is anticipated by the reference. No question of obviousness is present. In other words, for anticipation under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present; whereas, in a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made. MPEP 706.02. Because Brenner anticipates claim 1, there are no differences between patented claim 1 and Brenner which would require modification by Wernet, in order to meet the limitations of the

claims. Requester has not pointed out any such differences in the request between the claimed invention and Brenner, which would require modification in the proposed obviousness rejection..

15. GROUND H2 (SNQ 9):

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brenner in view of Luck.

The proposed rejection is ***adopted*** for claims 2-6 and is ***not adopted*** for claim 1.

This rejection of claims 1-6 was proposed by the third party requester (see pages 50-54 of the request and Exhibit CC-H-2) and **is adopted for claims 2-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground A, which is incorporated herein by reference in its entirety, Brenner teaches a computer readable program of instructions designed to generate digital images of the planar array of microparticles and to define the positions of individual particles during a series of processing steps. Brenner does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle.

Luck teaches a system for classification of biological cells comprising a computer readable program of instructions for generating images of the cells in a planar array on a microscopic slide (a "PAP smear") for classification of the cells as benign, premalignant or malignant (see the abstract). The system disclosed by Luck comprises an automated microscope,

a computer, a camera for capturing images of the cells, an image processor, and a digitizer (column 4, line 6-58, and column 5, line 25, through column 6, line 22). The system disclosed by Luck utilizes software to perform the functions (column 6, lines 23-32). Thus, Luck teaches a device-readable medium having a program of instructions for generating images of a planar array of cells. Absent a limiting definition in the '505 patent disclosure, "microparticles" is interpreted herein for prior art purposes as encompassing the cells described by Luck.

Regarding ***claims 2 and 5***, Luck teaches that the processing system performs a primary classification of the image and determines the centroids of biological objects in the image having attributes of the cell class for which screening is being performed (column 4, lines 11-26, and column 8, lines 58-62).

Regarding ***claim 3 and 6***, Luck teaches an array of pixels surrounding the centroid called a net image. Thus, Luck teaches that additional pixels are assigned immediately adjacent to the centroid. The net image is used to determine characteristics of a premalignant or malignant cell based on the gray scale density (*i.e.*, determines at least one property of the optical signals generated at each microparticle) (see column 7, lines 49-59).

With respect to ***claim 4***, Luck teaches that the assigned array of pixels corresponds to a one micron per pixel resolution during the high resolution rescan pass (column 6, lines 44-53). Luck also teaches that the system initially classifies cells by size based on the pixels recorded (column 8, lines 42-62). Thus, Luck teaches that the number of pixels assigned to each cell corresponds to the size of the cell (microparticle).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used Luck's image processing system with the device-readable medium

and program disclosed by Brenner in order to more efficiently track the particles within Brenner's planar array during a sequence of processing steps. The person of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success because both Brenner and Luck disclose automated systems for visualizing microparticles within a planar array by digitizing optical signals and analyzing the digitized signals using a computer with software embodying a program of instructions for doing so.

16. The rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over **Brenner in view of Luck is not adopted with respect to claim 1.**

As was set forth above, the proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted herein (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Brenner anticipates claim 1, there are no differences between patented claim 1 and Brenner which would require modification by Luck.

17. **GROUND H3 (SNQ 10):**

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brenner in view of Stimpson.

The proposed rejection is ***adopted*** for claims 2-3 and ***not adopted*** for claim 1.

This rejection of claims 1-3 was proposed by the third party requester (see pages 54-57 of the request and Exhibit CC-H-3) and **is adopted for claims 2-3** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground A, which is incorporated herein by reference in its entirety, Brenner teaches a computer readable program of instructions designed to generate images of the planar array of microparticles and to define the positions of individual particles during a series of processing steps. Brenner teaches that the system can be used to track, identify, and sort polynucleotides in large scale operations, where many polynucleotides or many segments of a polynucleotide are sequenced or identified simultaneously (see the abstract). Brenner contemplates a scanning system comprising a CCD, but does not specify determining the approximate center of each microparticle or assigning a plurality of pixels to each microparticle, as in patented claims 2 and 3.

Stimpson teaches that for large scale detection of specific binding analytes (e.g., oligonucleotide hybridization) immobilized on a high density array, light scattering labels (*e.g.* colloidal gold particles) may be used. Stimpson teaches that real-time binding and dissociation can be monitored by video imaging of optical signals with a CCD camera and frame grabber software (see the abstract; column 2, line 47, through column 3, line 3; column 22, lines 5-43; and Example 4 at column 26, line 48, through column 28, line 57). Stimpson teaches that with the CCD camera and frame grabber software, hybridization mismatches of as few as one base can be distinguished by real-time melting curves.

Regarding ***claim 2***, Stimpson teaches that the digitized data is analyzed using Image Pro Plus software, wherein a circular area approximately the size of a signal spot is used to measure

the numerical grayscale values of the image data. The digital values within the circular measuring area are averaged for the capture situs and then compared to a representative background (column 25, lines 22-32). Absent evidence to the contrary, in order to assign this circular area, the software must first determine the approximate center of the microparticle.

With respect to ***claim 3***, Stimpson teaches that a digital video image is acquired using a frame grabber and a CCD video camera, which consists of a series of 8-bit grayscale number values. The digital file consists of a series of the number values, each number corresponding to a particular and unique pixel location of the image (column 25, lines 8–21). Thus, Stimpson teaches assigning a plurality of pixels to each of the microparticles.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the apparatus, software, and method of center determination and pixel assignment disclosed in Stimpson in the system of Brenner, in order to accurately and efficiently sequence oligonucleotides in large scale operations. The person of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success because Brenner suggests using a CCD and Stimpson teaches that mismatches of as few as one base can be distinguished using a CCD and video camera.

18. The proposed rejection of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over **Brenner in view of Stimpson is not adopted with respect to claim 1.**

As was set forth above, the proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted herein (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. In a rejection based on 35 U.S.C.

103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Brenner anticipates claim 1, there are no differences between patented claim 1 and Brenner, which would require modification by Stimpson.

19. **GROUND H4 (SNQ 11).**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brenner in view of Sizto.

The proposed rejection is ***adopted*** for claims 2-6 and is ***not adopted*** for claim 1.

This rejection of claims 1-6 was proposed by the third party requester (see pages 58-62 of the request and Exhibit CC-H-4) and **is adopted for claims 2-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground 1, which is incorporated herein by reference in its entirety, Brenner teaches a computer readable program of instructions designed to generate images of a planar array of microparticles and define the positions of individual particles during a series of processing steps. Brenner teaches that the system may be used for manipulating and sorting polynucleotides or other molecules in large-scale operations (see the abstract). Brenner does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle.

Sizto teaches a computerized method with software to analyze cells within a cellular sample in a container, such as a blood sample, by generating a plurality of digital images of the cells and processing the images by correlating optical signals generated at the site of each of the cells with its corresponding digital image (see the abstract and column 2, lines 42-67).

Regarding ***claims 2 and 5***, Sizto teaches detecting a cell or cell constituent using an algorithm based on the average of two images. A 5 x 5 pixel map surrounding each pixel is defined in sequence, the center pixel is then determined, and the *x* and *y* coordinates for the center pixel are saved (see column 14, lines 35-58). As has been set forth previously herein, the "microparticles" of the patent claims are determined to encompass the cells disclosed by Sizto for prior art purposes, absent a limiting definition to the contrary in the '505 patent disclosure. Thus, Sizto teaches determining the approximate center of each of the cells or microparticles and assigning an initial pixel which encloses the center of particle.

With respect to ***claims 3 and 6,*** once the *x* and *y* coordinates for the center pixel are saved, a 7 x 7 pixel map, or neighborhood, surrounding the center pixel is saved. Thus, Sizto teaches assigning a plurality of pixels to each microparticle, wherein the additional pixels are immediately adjacent to the initial center pixel. Sizto teaches that the system is used to generate information relevant to detectable characteristics of the cells or cellular constituents (column 2, lines 53-57).

Regarding ***claim 4***, a neighborhood of pixels is defined for each of a plurality of identified segments in the scanned images, which is larger than the expected size of a target cell. The perimeter of the neighborhood is determined based on the expected shape of the target cell or cellular constituents within the neighborhood (column 3, lines 14-37). This is equivalent to

assigning the number of pixels to a given microparticle based on the size and uniformity of the diameter and shape of the cell or microparticle.

Sizto teaches that this system is robust and accurate and allows for continuous scans of large volumes of data. Sizto further teaches that it allows for concurrent data collection and analysis, as well as analysis of data after collection. Lastly, Sizto teaches that the system allows for completion of data analysis very rapidly (column 15, lines 44-58).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have employed the system described by Sizto to efficiently track the particles within Brenner's planar array during a sequence of processing steps. The person of ordinary skill in the art at the time of the invention would have been motivated to combine the references because Brenner contemplates analyzing many polynucleotides or other molecules simultaneously and Sizto teaches that his system is able to process large volumes of data rapidly and accurately.

20. The rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over **Brenner in view of Sizto is not adopted with respect to claim 1.**

As was set forth above, the proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted herein (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Brenner

anticipates claim 1, there are no differences between patented claim 1 and Brenner, which would require modification by Sizto to meet the limitations of the claim.

21. **GROUND H5 (SNQ 12):**

Claim 1 is rejected under 35 U.S.C. 103(a) as unpatentable over Brenner in view of Stern.

This **rejection of claim 1**, proposed by the third party requester (SNQ 12; see pages 62-65 of the request and Exhibit CC-H-5) **is not adopted.**

As was set forth above, the proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted herein (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Brenner anticipates claim 1, there are no differences between patented claim 1 and Brenner, which would require modification by Stern to meet the limitation of the claim.

22. **GROUND H6 (SNQ 13).**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brenner in view of Douglass.

The proposed rejection is ***adopted*** for claims 2-6 and ***not adopted*** for claim 1.

This rejection of claims 1-6 was proposed by the third party requester (see pages 65-69 of the request and Exhibit CC-H-6) and **is adopted with respect to claims 2-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground A, which is incorporated herein by reference in its entirety, Brenner teaches a computer readable program of instructions designed to generate images of a planar array of microparticles and define the positions of individual particles during a series of processing steps. Brenner teaches using the system for tracking, identifying, and/or sorting classes or subpopulations of oligonucleotides or other molecules (see the abstract). Brenner does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle.

As was set forth *supra* in Ground G, which is incorporated herein by reference in its entirety, Douglass teaches a system for generating digitized images of biological cells on a microscope slide (*i.e.*, a planar array) for tracking and selecting candidate cells which exhibit a particular marker of interest (*e.g.*, a tumor marker) for further analysis (see the abstract and column 6, line 65, through column 7, line 3).

Regarding ***claim 2***, Douglass teaches computing the centroid, or approximate center, of each cell and storing the data for evaluation of marker-identifying precipitate (column 7, lines 8-10 and 26-31).

Regarding ***claim 3***, Douglass teaches assigning pixel data to the area centered about the centroid for determining the amount of marker identifying precipitate (column 7, lines 3-26).

With respect to ***claim 4***, Douglass teaches that two colors of pixels are assigned and the system computes a ratio of two color components for the pixels in a regularly shaped area around the identified centroid (column 7, lines 11-51).

Regarding ***claim 5,*** Douglass discloses assigning the pixels to the area surrounding the centroid after assigning an initial pixel to the centroid (column 4, lines 11-51, and column 7, lines 4-26).

With respect to ***claim 6***, Douglass teaches assigning additional pixels to each microparticle in an area surrounding the centroid (column 4, lines 11-32, and column 7, lines 4-26).

Douglass teaches that his system offers advantages over other systems which are used to track cells or microparticles in that it identifies individual cells within a specimen, even when the cells overlap; uses a regularly shaped area to effectively identify only those pixels representing the areas of interest in the cells without the necessity to locate and traverse the perimeter of the object of interest; and reduces electronic noise for improved accuracy (column 3, lines 55-58, column 4, line 66, through column 5, line 40).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to have used the methods described by Douglass to determine the approximate center of each microparticle, assign an initial pixel to the center, and assign additional pixels adjacent to the initial pixel in the Brenner system of tracking and identifying classes or subpopulations of polynucleotides or other molecules. The person of ordinary skill in the art at

the time of the invention would have been motivated to combine the Douglass and Brenner references in order to ensure precision and accuracy in the system disclosed by Brenner, as is suggested by Douglass.

23. The rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over **Brenner in view of Douglass is not adopted with respect to claim 1.**

As has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted herein (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. If the claim is anticipated by the reference, no question of obviousness is present. Because Brenner anticipates claim 1, there are no differences between patented claim 1 and Brenner which would require modification by Douglass to meet the limitations of claim 1.

24. **GROUND H7 (SNQ 14):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as being unpatentable over Brenner in view of Douglass and Stern.

This rejection of claims 1-6, which was set forth by Requester (see pages 69-74 of the request and Exhibit CC-H-7) is **not adopted** for the reasons which follow.

Regarding claim 1, as has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to

meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Brenner anticipates claim 1, there are no differences between patented claim 1 and Brenner which would require modification by Douglass to meet the limitations of claim 1.

With respect to claims 2-6, the proposed rejection of claims 1-6 under 103(s) as unpatentable over Brenner in view of Douglass has been adopted with respect to claims 2-6 (see Ground H6). Once again, for the additional obviousness rejection over Brenner in view of Douglass and Stern, the combination of Brenner and Douglass must be modified in order to meet the claims. Requester has failed to point to any deficiencies in the combination of Brenner and Douglass which would necessitate the addition of Stern.

25. **GROUND H8 (SNQ 15):**

Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brenner in view of DiMilla.

The proposed rejection is ***adopted*** for claim 2 and is ***not adopted*** for claim 1.

This rejection of claims 1-2 was proposed by the third party requester (see pages 74-77 of the request and Exhibit CC-H-8) and **is adopted for claim 2** for the reasons as stated in the request and those reasons set forth below.

As was set forth *supra* in Ground A, which is incorporated herein by reference in its entirety, Brenner teaches a computer readable program of instructions designed to generate images of a planar array of microparticles and to define the positions of individual particles during a series of process steps. Brenner does not teach determining the approximate center of each microparticle, as in patented ***claim 2***.

DiMilla teaches a method of tracking individual cells in a planar array on the bottom of a 35 mm diameter cell culture dish using time-lapse videomicroscopy and digital-image analysis. DiMilla teaches determining the centroids of individual cells and tracking the centroids (center of the microparticles) at intervals of 15 minutes for up to 36 hours using a semiautomated algorithm, in which a single field is analyzed at a time. DiMilla teaches determining pixel coordinates as a function of elapsed tracking time for each cell tracked. DiMilla teaches converting the pixel coordinates to real physical displacements for a qualitative description of the path traveled by each individual cell (page 731, column 2, third, fourth and fifth full paragraphs).

The person of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to have used the DiMilla method and system encompassing centroid determination for accurate tracking of individual migration of a target object as a convenient and accurate means of tracking the individual microparticles in the series of processing steps disclosed by Brenner.

26. The proposed rejection of claims 1-2 under 35 U.S.C. 103(a) as being unpatentable over **Brenner in view of DiMilla is not adopted for claim 1.**

As was set forth above, the proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted herein (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Brenner

anticipates claim 1, there are no differences between patented claim 1 and Brenner, which would require modification by DiMilla to meet the limitations of the claim.

27. **Ground H9 (SNQ 16):**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brenner in view of Gelles.

The proposed rejection is ***adopted*** for claims 2-6 and ***not adopted*** for claim 1.

This rejection of claims 1-6 was proposed by the third party requester (see pages 78-82 of the request and Exhibit CC-H-9) and **is adopted with respect to claims 2-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground A, which is incorporated herein by reference in its entirety, Brenner teaches a computer readable program of instructions designed to generate images of the planar array of microparticles and to define the positions of individual particles during a series of processing steps. Brenner does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle.

As was set forth supra in Ground B, which is also incorporated by reference herein in its entirety, Gelles teaches a system for recording, analyzing, and determining precise positional information of microparticles as they attach to and move along microtubules *in vitro*. Gelles teaches determining the approximate center of each microparticle (***claim 2***), assigning a plurality

of pixels to each microparticle (***claim 3***) by analyzing a kernel, using cross-correlation analysis as a template to search for and identify other beads within the digital images, comparing the digital images or pixels occupied by each of the other beads with the pixels of the bead used to generate the kernel (***claim 4***), assigning an initial pixel to the center of the particle as point (0,0) (***claim 5***), and assigning additional pixels immediately adjacent to the initial pixel (***claim 6***). Gelles teaches high precision measurement of molecular-scale movements of small objects in real time using a light microscope. Gelles teaches that the ability to do this has potential for providing insights into various biological processes (Fig. 1 and page 453, second from last paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have employed the Gelles method and system to accurately and precisely track the oligonucleotides disclosed by Brenner. The person of ordinary skill in the art at the time of the invention would have been motivated to combine the references because Gelles teaches that his method can provide insights into various biologic processes, such as the hybridization of the oligonucleotides disclosed in Brenner.

28. The proposed rejection of claims 1-2 under 35 U.S.C. 103(a) as being unpatentable over **Brenner in view of Gelles is not adopted for claim 1.**

As was set forth above, the proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted herein (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim

is anticipated by the reference, no question of obviousness is present. Because Brenner anticipates claim 1, there are no differences between patented claim 1 and Brenner, which would require modification by Gelles to meet the limitations of the claim.

29. **GROUND H10 (SNQ 17):**

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brenner in view of NIH.

The proposed rejection is ***adopted*** for claims 2-3 and is ***not adopted*** for claim 1.

This rejection of claims 1-3 was proposed by the third party requester (see pages 82-85 of the request and Exhibit CC-H-10) and **is adopted with respect to claims 2-3** for the reasons stated in the request and those reasons set forth below.

As was set forth *supra* in Ground A, which is incorporated herein by reference in its entirety, Brenner teaches a computer readable program of instructions designed to generate images of a planar array of microparticles and to define the positions of individual particles during a sequence of processing steps. Brenner teaches observing the movement of microparticles with a microscope which is connected to a computer for digitizing the images. Brenner teaches that digital computers and software for performing these functions are commercially available (page 26, lines 3-23). Brenner does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel.

NIH is a public domain image processing and analysis program which was available at the time of the invention (page 2, first full paragraph). NIH discloses digitization of images from

TV cameras, VCRs, or video disks and displaying the images as two dimensional arrays of pixels (paragraph bridging pages 3-4). NIH discloses that the apparatus can be used to measure the area, mean, centroid or center (***claim 2***), etc. of user defined regions of interest (page 2, second full paragraph). NIH teaches that spatial calibration is supported to provide real world measurement of path length and angles (page 2, paragraph 2). NIH also teaches that a selected object is viewed as a plurality of pixels (***claim 3***, page 6, third paragraph and page 9).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to have combined the NIH software with the method and apparatus disclosed by Brenner because Brenner suggests using commercially available software and NIH is an image processing and analysis program intended for tracking microscopic images, which was publicly available at the time the invention was made.

30. The proposed rejection of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over **Brenner in view of NIH is not adopted with respect to claim 1.**

As was set forth above, the proposed rejection of claim 1 under 102(b) as anticipated by Brenner has been adopted herein (see Ground A). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Brenner, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Brenner anticipates claim 1, there are no differences between patented claim 1 and Brenner, which would require modification by NIH to meet the limitations of the claim.

31. **GROUND I 1 (SNQ 18):**

Claims 1-6 are rejected under 103(a) as unpatentable over Gelles in view of Stern.

This rejection as proposed by Requester (see pages 86-90 of the Request and Exhibit CC-I-1) is **not adopted.**

As was set forth above, the proposed rejection of claims 1-6 under 102(b) as anticipated by Gelles has been adopted herein (see Ground B). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Gelles, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Gelles anticipates claims 1-6, there are no differences between the patented claims and Gelles which would require modification by Stern to meet the limitations of the claims.

32. **GROUND I 2 (SNQ 19):**

Claims 1-6 are rejected under 103(a) as unpatentable over Gelles in view of Douglass.

This rejection, as proposed by Requester (see pages 90-95 of the Request and Exhibit CC-I-2), is **not adopted.**

As was set forth above, the proposed rejection of claims 1-6 under 102(b) as anticipated by Gelles has been adopted herein (see Ground B). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Gelles, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Gelles anticipates

claims 1-6, there are no differences between the patented claims and Gelles which would require modification by Douglass in order to meet the limitations of the claims.

33. **GROUND I 3 (SNQ 20):**

Claims 1-6 are rejected under 103(a) as unpatentable over Gelles in view of Douglass and Stern.

This rejection, as proposed by Requester (see pages 95-101 of the Request and Exhibit CC-I-3), is **not adopted.**

As was set forth above, the proposed rejection of claims 1-6 under 102(b) as anticipated by Gelles has been adopted herein (see Ground B). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Gelles, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Gelles anticipates claims 1-6, there are no differences between the patented claims and Gelles which would require modification by Douglass and Stern to meet the limitations of the claims.

34. **GROUND I 4 (SNQ 21):**

Claims 1-6 are rejected under 103(a) as unpatentable over Gelles in view of King.

This rejection as proposed by Requester (see pages 101-105 of the Request and Exhibit CC-I-4) is **not adopted.**

As was set forth above, the proposed rejection of claims 1-6 under 102(b) as anticipated by Gelles has been adopted herein (see Ground B). Therefore, the proposed rejection of claims

1-6 under 103(a) over the same reference, Gelles, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Gelles anticipates claims 1-6, there are no differences between the patented claims and Gelles which would require modification by King to meet the limitations of the claims.

35. **GROUND I 5 (SNQ 22):**

Claims 1-6 are rejected under 103(a) as unpatentable over Gelles in view of Luck.

This rejection, as proposed by Requester (see pages 105-110 of the Request and Exhibit CC-I-5), is **not adopted.**

As was set forth above, the proposed rejection of claims 1-6 under 102(b) as anticipated by Gelles has been adopted herein (see Ground B). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Gelles, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Gelles anticipates claims 1-6, there are no differences between the patented claims and Gelles which would require modification by Luck to meet the limitations of the claims.

36. **GROUND I 6 (SNQ 23):**

Claims 1-6 are rejected under 103(a) as unpatentable over Gelles in view of Sizto.

This rejection, as proposed by Requester (see pages 110-115 of the Request and Exhibit CC-I-6), is **not adopted.**

As was set forth above, the proposed rejection of claims 1-6 under 102(b) as anticipated by Gelles has been adopted herein (see Ground B). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Gelles, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Gelles anticipates claims 1-6, there are no differences between the patented claims and Gelles which would require modification by Sizto to meet the limitations of the claims.

37. **GROUND I 7 (SNQ 24):**

Claims 1-6 are rejected under 103(a) as unpatentable over Gelles in view of DiMilla.

This rejection as proposed by Requester (see pages 115-119 of the Request and Exhibit CC-I-7) is **not adopted.**

As was set forth above, the proposed rejection of claims 1-6 under 102(b) as anticipated by Gelles has been adopted herein (see Ground B). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Gelles, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Gelles anticipates claims 1-6, there are no differences between the patented claims and Gelles which would require modification by DiMilla to meet the limitations of the claims.

38. **GROUND I 8 (SNQ 25):**

Claims 1-6 are rejected under 103(a) as unpatentable over Gelles in view of NIH.

This rejection as proposed by Requester (see pages 119-123 of the Request and Exhibit CC-I-8) is **not adopted.**

As was set forth above, the proposed rejection of claims 1-6 under 102(b) as anticipated by Gelles has been adopted herein (see Ground B). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Gelles, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Gelles anticipates claims 1-6, there are no differences between the patented claims and Gelles which would require modification by NIH in order to meet the limitations of the claims.

39. **GROUND J1 (SNQ 26):**

Claims 1-3 are rejected under 35 U.S.C. 103(a) as unpatentable over Lee in view of Brenner.

This rejection as proposed by Requester (see pages 124-128 of the Request and Exhibit CC-J-1) is **not adopted.**

As was set forth above, the proposed rejection of claims 1-3 under 102(e) as anticipated by Lee has been adopted herein (see Ground C). Therefore, the proposed rejection of claims 1-3 under 103(a) over the same reference, Lee, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between patented claims 1-3 and Lee which would require modification by Brenner to meet the limitations of the claims.

40. **GROUND J2 (SNQ 27):**

Claims 1-3 are rejected under 35 U.S.C. 103(a) as unpatentable over Lee in view of Stern.

This rejection as proposed by Requester (see pages 128-131 of the Request and Exhibit CC-J-2) is **not adopted.**

As was set forth above, the proposed rejection of claims 1-6 under 102(e) as anticipated by Lee has been adopted herein (see Ground C). Therefore, the proposed rejection of claims 1-3 under 103(a) over the same reference, Lee is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between patented claims 1-3 and Lee which would require modification by Stern to meet the limitations of the claims.

41. **Ground J3 (SNQ 28):**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as unpatentable over Lee in view of Douglass.

The proposed rejection is ***adopted*** for claims 4-6 and is ***not adopted*** for claims 1-3.

This rejection of claims 1-6 was proposed by the third party requester (see pages 131-135 of the request and Exhibit CC-J-3) and **is adopted for claims 4-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground C, which is incorporated herein by reference in its entirety, Lee teaches an apparatus for recording images of fluorescent microparticles seeded in a

planar array on the surface of a cell-culture dish. Lee teaches software (NIH Image) for digitizing and storing the images. Lee teaches determining the center of the microparticles to enable measurement of cell positions before and after stretch. The NIH system used by Lee assigns additional pixels around the center pixel of the image as part of the process of determining location of the cells. Lee does not specifically teach assigning an initial pixel to the center of the microparticle or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle, as in patented claims 4-6.

As was set forth *supra* in Ground G, also incorporated herein by reference in its entirety, Douglass teaches a device readable medium with a program of instructions applicable for generating digital images of cells. Douglass teaches computing the centroid or center of each cell and assigning pixel data to the centroid and the area centered about the centroid. Douglass teaches that the system can be used for detection of analytes. For example, Douglass teaches one application of the system for identifying cells in a blood sample via an antigen (analyte), which is reacted with an enzyme-labeled antibody (reagent) and which produces a colored precipitate in the presence of an enzyme reaction occurring at the location of the antigen (column 1, lines 32-45). Douglass also contemplates using the system for other analytical detection methods, such as *in situ* hybridization and RT-PCR (reverse transcriptase polymerase chain reaction), for example (column 4, line 66, through column 5, line 21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have combined the methods of Lee and Douglass in order to measure the

interactions of processing reagents and analytes on the surfaces of microparticles, as suggested by Douglass. The person of ordinary skill in the art at the time of the invention would had a reasonable expectation of success combining the references because Lee teaches precision measurement of cells via digital imaging and Douglass teaches monitoring antigen/antibody and nucleic acid hybridization reactions by digital image processing.

42. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over **Lee in view of Douglass is not adopted with respect to claims 1-3.**

As was set forth above, the proposed rejection of claims 1-3 under 102(e) as anticipated by Lee has been adopted herein (see Ground C). Therefore, the proposed rejection of claims 1-3 under 103(a) over the same reference, Lee, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between patented claims 1-3 and Lee which would require modification by Douglass to meet the limitations of the claims.

43. **GROUND J4 (SNQ 29):**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as unpatentable over Lee in view of Douglass and Stern.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over **Lee in view of Douglass and Stern is not adopted.**

As was set forth above, the proposed rejection of claims 1-3 under 102(e) as anticipated by Lee has been adopted herein (see Ground C). Therefore, the proposed rejection of claims 1-3 under 103(a) over the same reference, Lee, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between patented claims 1-3 and Lee which would require modification by Douglass and Stern to meet the limitations of the claims.

With respect to claims 4-6, the proposed rejection of claims 1-6 under 103(s) as unpatentable over Lee in view of Douglass has been adopted with respect to claims 4-6 (see Ground J3). Here again, for the additional obviousness rejection over Lee in view of Douglass and Stern, the combination of Lee and Douglass must be modified in order to meet the claim limitations. Requester has failed to point to any deficiencies in the combination of Brenner and Douglass which would necessitate the addition of Stern in order to meet the claims.

44. **GROUND J5 (SNQ 30):**

Claims 1-3 are rejected under 35 U.S.C. 103(a) as unpatentable over Lee in view of King.

The proposed rejection (see the request at pages 140-143 and Exhibit CC-J-5) of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over **Lee in view of King is not adopted.**

As was set forth above, the proposed rejection of claims 1-3 under 102(e) as anticipated by Lee has been adopted herein (see Ground C). Therefore, the proposed rejection of claims 1-3 under 103(a) over the same reference, Lee, is improper. In a rejection based on 35 U.S.C. 103,

the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between patented claims 1-3 and Lee which would require modification by King to meet the limitations of the claims.

45. **Ground 17 (SNQ 31):**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as unpatentable over Lee in view of Gelles.

The proposed rejection is ***adopted*** for claims 4-6 and is ***not adopted*** for claims 1-3.

This rejection of claims 1-6 was proposed by the third party requester (see pages 143-147 of the request and Exhibit CC-J-6) and **is adopted with respect to claims 4-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground C, which is incorporated herein by reference in its entirety, Lee teaches apparatus for recording images of fluorescent microparticles seeded in a planar array on the surface of a cell-culture dish. Lee teaches software (NIH Image) for digitizing and storing the images. Lee teaches determining the center of the microparticles to enable measurement of cell positions before and after stretch. The NIH system used by Lee assigns additional pixels around the center pixel of the image as part of the process of determining location of the cells. Lee does not specifically teach assigning an initial pixel to the center of the microparticle or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the

geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle, as in patented claims 4-6.

As was set forth supra in Ground B, which is incorporated by reference herein in its entirety, Gelles teaches a system for recording, analyzing, and determining precise positional information of microparticles as they attach to and move along microtubules *in vitro*. Gelles teaches determining the approximate center of each microparticle, assigning a plurality of pixels to each microparticle by analyzing a kernel, using cross-correlation analysis as a template to search for and identify other beads within the digital images, comparing the digital images or pixels occupied by each of the other beads with the pixels of the bead used to generate the kernel (***claim 4***), assigning an initial pixel to the center of the particle as point (0,0) (***claim 5***), and assigning additional pixels immediately adjacent to the initial pixel (***claim 6***). Gelles teaches high precision measurement of molecular-scale movements of small objects in real time using a light microscope. Gelles teaches that the ability to do this has potential for providing insights into various biological processes (Fig. 1 and page 453, second from last paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have employed the Gelles method and system to accurately and precisely measure the effects of stretch on cellular functions in the cells disclosed by Lee. The person of ordinary skill in the art at the time of the invention would have been motivated to combine the references because Gelles teaches that his method can provide insights into various biologic processes, such as the cellular stretch experiments described in Lee.

46. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over **Lee in view of Gelles is not adopted with respect to claims 1-3.**

As was set forth above, the proposed rejection of claims 1-3 under 102(e) as anticipated by Lee has been adopted herein (see Ground C). Therefore, the proposed rejection of claims 1-3 under 103(a) over the same reference, Lee, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between patented claims 1-3 and Lee which would require modification by Gelles in order to meet the limitations of the claims.

47. **Ground J7 (SNQ 32):**

Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over Lee in view of Luck.

The proposed rejection is ***adopted*** for claims 4-6 and is ***not adopted*** for claims 1-3.

This rejection of claims 1-6 was proposed by the third party requester (see pages 148-151 of the request and Exhibit CC-J-7) and **is adopted with respect to claims 4-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground C, which is incorporated herein by reference in its entirety, Lee teaches an apparatus for recording images of fluorescent microparticles seeded in a planar array on the surface of a cell-culture dish. Lee teaches software (NIH Image) for digitizing and storing the images. Lee teaches determining the center of the microparticles to enable measurement of cell positions before and after stretch. The NIH system used by Lee

assigns additional pixels around the center pixel of the image as part of the process of determining location of the cells. Lee does not specifically teach assigning an initial pixel to the center of the microparticle or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle, as in patented claims 4-6.

Luck teaches a system for classification of biological cells comprising a computer readable program of instructions for generating images of the cells in a planar array on a microscopic slide (a "PAP smear") for classification of the cells as benign, premalignant or malignant (see the abstract). The system disclosed by Luck comprises an automated microscope, a computer, a camera for capturing images of the cells, an image processor, and a digitizer (column 4, line 6-58, and column 5, line 25, through column 6, line 22). The system disclosed by Luck utilizes software to perform the functions (column 6, lines 23-32). Thus, Luck teaches a device-readable medium having a program of instructions for generating images of a planar array of cells. Absent a limiting definition in the '505 patent disclosure, "microparticles" is interpreted for prior art purposes as encompassing the cells described by Luck.

Regarding ***claim 5***, Luck teaches that the processing system performs a primary classification of the image and determines the centroids of biological objects in the image having attributes of the cell class for which screening is being performed (column 4, lines 11-26, and column 8, lines 58-62).

Regarding ***claim 6***, Luck teaches an array of pixels surrounding the centroid called a net image. Thus, Luck teaches that additional pixels are assigned immediately adjacent to the

centroid. The net image is used to determine characteristics of a premalignant or malignant cell based on the gray scale density (*i.e.,* determines at least one property of the optical signals generated at each microparticle) (see column 7, lines 49-59).

With respect to ***claim 4***, Luck teaches that the assigned array of pixels corresponds to a one micron per pixel resolution during the high resolution rescan pass (column 6, lines 44-53). Luck also teaches that the system initially classifies cells by size based on the pixels recorded (column 8, lines 42-62). Thus, Luck teaches that the number of pixels assigned to each cell corresponds to the size of the cell (microparticle).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used Luck's image processing system with the device-readable medium and program disclosed by Lee in order to more efficiently track the cellular processes of the cells undergoing stretch. The person of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success because both Lee and Luck disclose automated systems for visualizing microparticles within a planar array by digitizing optical signals and analyzing the digitized signals using a computer with software embodying a program of instructions for doing so.

48. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over **Lee in view of Luck is not adopted with respect to claims 1-3.**

As has been set forth previously herein, the proposed rejection of claims 1-3 under 102(e) as anticipated by Lee has been adopted (see Ground C). Therefore, the proposed rejection of claims 1-3 under 103(a) over the same reference, Lee, is improper. In a rejection based on 35

U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between the patented claims and Lee which would require modification by Luck to meet the limitations of the claims.

49. **Ground J8 (SNQ 33):**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as unpatentable over Lee in view of Sizto.

The proposed rejection is ***adopted*** for claims 4-6 and is ***not adopted*** for claims 1-3.

This rejection of claims 1-6 was proposed by the third party requester (see pages 152-155 of the request and Exhibit CC-J-8) and **is adopted with respect to claims 4-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground 3, which is incorporated herein by reference in its entirety, Lee teaches apparatus for recording images of fluorescent microparticles seeded in a planar array on the surface of a cell-culture dish. Lee teaches software (NIH Image) for digitizing and storing the images. Lee teaches determining the center of the microparticles to enable measurement of cell positions and functions before and after stretch. The NIH system used by Lee assigns additional pixels around the center pixel of the image as part of the process of determining location of the cells. Lee does not specifically teach assigning an initial pixel to the center of the microparticle or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from

the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle, as in patented claims 4-6.

Sizto teaches a computerized method with software to analyze cells within a cellular sample, such as a blood sample, by generating a plurality of digital images of the cells and processing the images by correlating optical signals generated at the site of each of the cells with its corresponding image in a plurality of digital images (see the abstract and column 2, lines 42-67).

Regarding ***claim 5***, Sizto teaches detecting a cell or cell constituent using an algorithm based on the average of two images. A 5 x 5 pixel map surrounding each pixel is defined in sequence, the center pixel is then determined, and the *x* and *y* coordinates for the center pixel are saved (see column 14, lines 35-58). As has been set forth previously herein, the "microparticles" of the patent claims are determined to encompass the cells disclosed by Sizto for prior art purposes, absent a limiting definition to the contrary in the '505 patent disclosure. Thus, Sizto teaches determining the approximate center of each of the cells or microparticles and assigning an initial pixel which encloses the center of particle.

With respect to ***claim 6,*** once the *x* and *y* coordinates for the center pixel are saved, a 7 x 7 pixel map, or neighborhood, surrounding the center pixel is saved. Thus, Sizto teaches assigning a plurality of pixels to each microparticle, wherein the additional pixels are immediately adjacent to the initial center pixel. Sizto teaches that the system is used to generate information relevant to detectable characteristics of the cells or cellular constituents (column 2, lines 53-57).

Regarding ***claim 4***, a neighborhood of pixels is defined for each of a plurality of identified segments in the scanned images, which is larger than the expected size of a target cell. The perimeter of the neighborhood is determined based on the expected shape of the target cell or cellular constituents within the neighborhood (column 3, lines 14-37). This is equivalent to assigning the number of pixels to a given microparticle based on the size and uniformity of the diameter and shape of the cell or microparticle.

Sizto teaches that this system processes scanned data which is very robust and accurate and allows for continuous scans of large volumes of data. Sizto further teaches that it allows for concurrent data collection and analysis, as well as analysis of data after collection. Lastly, Sizto also teaches that the system allows for completion of data analysis very rapidly (column 15, lines 44-58).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have employed the system described by Sizto to more efficiently study cellular functions in the cells disclosed by Lee before and after stretch and also to expand the number of cells studied. The person of ordinary skill in the art at the time of the invention would have been motivated to combine the references because Sizto teaches that his system is able to process large volumes of data rapidly and accurately.

50. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over **Lee in view of Sizto is not adopted with respect to claims 1-3.**

As has been set forth previously herein, the proposed rejection of claims 1-3 under 102(e) as anticipated by Lee has been adopted (see Ground C). Therefore, the proposed rejection of

claims 1-3 under 103(a) over the same reference, Lee, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between the patented claims and Lee which would require modification by Sizto in order to meet the limitations of the claims.

51. **GROUND J9 (SNQ 34):**

Claims 1-3 are rejected under 3 U.S.C. 103(a) as being unpatentable over Lee in view of DiMilla.

The proposed rejection of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over Lee in view of DiMilla (see the Request at pages 155-158 and Exhibit CC-J-9) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-3 under 102(e) as anticipated by Lee has been adopted (see Ground C). Therefore, the proposed rejection of claims 1-3 under 103(a) over the same reference, Lee, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between the patented claims and Lee which would require modification by DiMilla in order to meet the limitations of the claims.

52. **GROUND J10 (SNQ 35):**

Claims 1-3 are rejected under 3 U.S.C. 103(a) as being unpatentable over Lee in view of NIH.

The proposed rejection of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over Lee in view of NIH (see the Request at pages 158-161 and Exhibit CC-J-10) **is not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-3 under 102(e) as anticipated by Lee has been adopted (see Ground C). Therefore, the proposed rejection of claims 1-3 under 103(a) over the same reference, Lee, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Lee anticipates claims 1-3, there are no differences between the patented claims and Lee which would require modification by NIH in order to meet the limitations of the claims.

53. **GROUND K1 (SNQ 36):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of Brenner.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of Brenner (see the request at pages 161-166 and Exhibit CC-K-1) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims

and Schmidt which would require modification by Brenner in order to meet the limitations of the claims.

54. **GROUND K2 (SNQ 37):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of Dow

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of Dow (see the request at pages 166-171 and Exhibit CC-K-2) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims and Schmidt which would require modification by Dow to meet the limitations of the claims.

55. **GROUND K3 (SNQ 38):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of Stern

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of Stern (see the request at pages 171-175 and Exhibit CC-K-3) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims and Schmidt which would require modification by Stern to meet the limitations of the claims.

56. **GROUND K4 (SNQ 39):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of Douglass.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of Douglass (see the request at pages 175-180 and Exhibit CC-K-4) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims and Schmidt which would require modification by Douglass to meet the limitations of the claims.

57. **GROUND K5 (SNQ 40):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of Douglass and Stern

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of Douglass and Stern (see the request at pages 180-186 and Exhibit CC-K-5) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims and Schmidt which would require modification by Douglass and Stern to meet the limitations of the claims.

58. **GROUND K6 (SNQ 41):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of King.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of King (see the request at pages 186-190 and Exhibit CC-K-6)is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection

of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims and Schmidt which would require modification by King in order to meet the limitations of the claims.

59. **GROUND K7 (SNQ 42):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of Gelles/

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of Gelles (see the request at pages 190-195 and Exhibit CC-K-7) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims and Schmidt which would require modification by Gelles in order to meet the limitations of the claims.

60. **GROUND K8 (SNQ 43):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of Sizto.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of Sizto (see the request at pages 195-200 and Exhibit CC-K-8) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims and Schmidt which would require modification by Sizto in order to meet the limitations of the claims.

61. **GROUND K9 (SNQ 44):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of DiMilla.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of DiMilla (see the request at pages 200-203 and Exhibit CC-K-9) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection

of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims and Schmidt which would require modification by DiMilla in order to meet the limitations of the claims.

62. **GROUND K10 (SNQ 45):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as unpatentable over Schmidt in view of NIH.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Schmidt in view of NIH (see the request at pages 204-207 and Exhibit CC-K-10) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(b) as anticipated by Schmidt has been adopted (see Ground D). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Schmidt, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Schmidt anticipates claims 1-3, there are no differences between the patented claims and Schmidt which would require modification by NIH in order to meet the limitations of the claims.

63. **GROUND L1 (SNQ 46):**

Claim 1 is rejected under 3 U.S.C. 103(a) as being unpatentable over Wilson in view of Brenner.

The proposed rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Wilson in view of Brenner (see the request at pages 208-211 and Exhibit CC-L-1) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Wilson has been adopted (see Ground E). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Wilson, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Wilson anticipates claim 1, there are no differences between the patented claims and Wilson which would require modification by Brenner in order the meet the limitation of the claim.

64. **GROUND L2 (SNQ 47):**

Claim 1 is rejected under 3 U.S.C. 103(a) as being unpatentable over Wilson in view of Stern.

The proposed rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Wilson in view of Stern (see the request at pages 211-214 and Exhibit CC-L-2) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Wilson has been adopted (see Ground E). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Wilson, is improper. In a rejection based on 35

U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Wilson anticipates claim 1, there are no differences between the patented claims and Wilson which would require modification by Stern.

65. **Ground L3 (SNQ 48). Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over Wilson in view of Douglass.**

The proposed rejection is ***adopted*** for claims 2-6 and is ***not adopted*** for claim 1.

This rejection of claims 1-6 was proposed by the third party requester (see pages 214-218 of the request and Exhibit CC-L-3) and **is adopted with respect to claims 2-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground 5, which is incorporated herein by reference in its entirety, Wilson teaches a system with software for sequentially imaging fluorescent or colloidal gold microparticles conjugated to monoclonal antibody and attached to cells at the site of cell surface MHC molecules by single particle tracking. Wilson teaches that single particle tracking provides a powerful approach to observing receptor movement at high spatial resolution (see page 2101, column 2, last partial paragraph). Wilson does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle.

As was set forth *supra* in Ground 7, which is incorporated herein by reference in its entirety, Douglass teaches a system for generating digitized images of biological cells on a microscope slide (*i.e.*, a planar array) for tracking and selecting candidate cells which exhibit a particular marker of interest (*e.g.*, a tumor marker) for further analysis (see the abstract and column 6, line 65, through column 7, line 3).

Regarding ***claim 2***, Douglass teaches computing the centroid, or approximate center, of each cell and storing the data for evaluation of marker-identifying precipitate (column 7, lines 8-10 and 26-31).

Regarding ***claim 3***, Douglass teaches assigning pixel data to the area centered about the centroid for determining the amount of marker identifying precipitate (column 7, lines 3-26).

With respect to ***claim 4***, Douglass teaches that two colors of pixels are assigned and the system computes a ratio of two color components for the pixels in a regularly shaped area around the identified centroid (column 7, lines 11-51).

Regarding ***claim 5,*** Douglass discloses assigning the pixels to the area surrounding the centroid after assigning a pixel to the centroid (column 4, lines 11-51, and column 7, lines 4-26).

With respect to ***claim 6***, Douglass teaches assigning additional pixels to each microparticle in an area centered around the centroid (column 4, lines 11-32, and column 7, lines 4-26).

Douglass teaches that his system offers advantages over other systems which may be used to track cells or microparticles in that it identifies individual cells within a specimen even when the cells overlap, uses a regularly shaped area to effectively identify only those pixels representing the areas of interest in the cells without the necessity to locate and traverse the

perimeter of the object of interest, and reduces electronic noise for improved accuracy (column 3, lines 55-58, column 4, line 66, through column 5, line 40).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to have used the methods described by Douglass to determine the approximate center of each microparticle, assign an initial pixel to the center, and assign additional pixels adjacent to the initial pixel in the Wilson system for sequentially imaging fluorescent or colloidal gold microparticles conjugated to monoclonal antibody and attached to cells at the site of cell surface MHC molecules. The person of ordinary skill in the art at the time of the invention would have been motivated to combine the Wilson and Douglass references in order to improve precision and accuracy in the system disclosed by Wilson, as is suggested by Douglass.

66. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Wilson in view of Douglass is **not adopted for claim 1.**

As has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Wilson has been adopted (see Ground E). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Wilson, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Wilson anticipates claim 1, there are no differences between the patented claims and Wilson which would require modification by Douglass in order to meet the limitation of the claim.

67. **GROUND L4 (SNQ 49).**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as being unpatentable over Wilson in view of Douglass and Stern.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Wilson in view of Douglass and Stern is **not adopted.**

As has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Wilson has been adopted (see Ground E). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Wilson, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Wilson anticipates claim 1, there are no differences between the patented claims and Wilson which would require modification by Douglass and Stern to meet the limitations of the claim.

With respect to claims 2-6, the proposed rejection of claims 1-6 under 103(s) as unpatentable over Wilson in view of Douglass has been adopted (see Ground L3). Once again, for the additional obviousness rejection over Wilson in view of Douglass and Stern, the combination of Wilson and Douglass must be modified in order to meet the claims. Requester has not pointed out any deficiencies in the combination of Wilson and Douglass which would necessitate the addition of Stern.

68. **Ground L5 (SNQ 50).**

Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over Wilson in view of Gelles.

The proposed rejection is ***adopted*** for claims 2-6 and is ***not adopted*** for claim 1.

This rejection was proposed by the third party requester (see pages 223-227 of the request and Exhibit CC-L-5) and **is adopted with respect to claims 2-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground E which is incorporated herein by reference in its entirety, Wilson teaches a system with software for sequentially imaging fluorescent or colloidal gold microparticles conjugated to monoclonal antibody and attached to cells at the site of cell surface MHC molecules by single particle tracking. Wilson teaches that single particle tracking provides a powerful approach to observing receptor movement at high spatial resolution (see page 2101, column 2, last partial paragraph). Wilson does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle.

As was set forth *supra* in Ground 2, which is incorporated by reference herein in its entirety, Gelles teaches a system for recording, analyzing, and determining precise positional information of microparticles as they attach to and move along microtubules *in vitro*. Gelles teaches determining the approximate center of each microparticle (***claim 2***), assigning a plurality of pixels to each microparticle (***claim 3***) by analyzing a kernel, using cross-correlation analysis as a template to search for and identify other beads within the digital images, comparing the digital images or pixels occupied by each of the other beads with the pixels of the bead used to generate the kernel (***claim 4***), assigning an initial pixel to the center of the particle as point (0,0)

(***claim 5***), and assigning additional pixels immediately adjacent to the initial pixel (***claim 6***). Gelles teaches high precision measurement of molecular-scale movements of small objects in real time using a light microscope. Gelles teaches that the ability to do this has potential for providing insights into various biological processes (Fig. 1 and page 453, second from last paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have employed the Gelles method and system in order to accurately and precisely track HLA-DR molecules in the method of Wilson. The person of ordinary skill in the art at the time of the invention would have been motivated to combine the references because Gelles teaches that his method can provide insights into various biologic processes, such as the receptor tracking experiments described in Wilson.

69. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Wilson in view of Gelles is **not adopted with respect to claim 1.**

As has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Wilson has been adopted (see Ground E). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Wilson, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Wilson anticipates claim 1, there are no differences between the patented claims and Wilson which would require modification by Gelles in order to meet the limitation of the claim.

70. **Ground L6 (SNQ 51):**

Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over Wilson in view of Sizto.

The proposed rejection is ***adopted*** for claims 2-6 and is ***not adopted*** for claim 1.

This rejection proposed by the third party requester (see pages 227-230 of the request and Exhibit CC-L-6) and **is adopted with respect to claims 2-6** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground E, which is incorporated herein by reference in its entirety, Wilson teaches a system with software for sequentially imaging fluorescent or colloidal gold microparticles conjugated to monoclonal antibody and attached to cells at the site of cell surface MHC molecules by single particle tracking. Wilson teaches that single particle tracking provides a powerful approach to observing receptor movement at high spatial resolution (see page 2101, column 2, last partial paragraph). Wilson does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle.

Sizto teaches a computerized method with software to analyze cells within a cellular sample, such as a blood sample, by generating a plurality of digital images of the cells and processing the images by correlating optical signals generated at the site of each of the cells with its corresponding image in a plurality of digital images (see the abstract and column 2, lines 42-67).

Regarding ***claims 2 and 5***, Sizto teaches detecting a cell or cell constituent using an algorithm based on the average of two images. A 5 x 5 pixel map surrounding each pixel is defined in sequence, the center pixel is then determined, and the *x* and *y* coordinates for the center pixel are saved (see column 14, lines 35-58). As has been set forth previously herein, the "microparticles" of the patent claims are determined to encompass the cells disclosed by Sizto for prior art purposes, absent a limiting definition to the contrary in the '505 patent disclosure. Thus, Sizto teaches determining the approximate center of each of the cells or microparticles and assigning an initial pixel which encloses the center of particle.

With respect to ***claims 3 and 6,*** once the *x* and *y* coordinates for the center pixel are saved, a 7 x 7 pixel map, or neighborhood, surrounding the center pixel is saved. Thus, Sizto teaches assigning a plurality of pixels to each microparticle, wherein the additional pixels are immediately adjacent to the initial center pixel. Sizto teaches that the system is used to generate information relevant to detectable characteristics of the cells or cellular constituents (column 2, lines 53-57)

Regarding ***claim 4***, a neighborhood of pixels is defined for each of a plurality of identified segments in the scanned images, which is larger than the expected size of a target cell. The perimeter of the neighborhood is determined based on the expected shape of the target cell or cellular constituents within the neighborhood (column 3, lines 14-37). This is equivalent to assigning the number of pixels to a given microparticle based on the size and uniformity of the diameter and shape of the cell or microparticle.

Sizto teaches that this system processes scanned data which is very robust and accurate and allows for continuous scans of large volumes of data. Sizto further teaches that it allows for

concurrent data collection and analysis, as well as analysis of data after collection. Lastly, Sizto also teaches that the system allows for completion of data analysis very rapidly (column 15, lines 44-58).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have employed the system described by Sizto to more efficiently study the cellular receptors disclosed by Wilson and also to expand the number of cells studied. The person of ordinary skill in the art at the time of the invention would have been motivated to combine the references because Sizto teaches that his system is able to process large volumes of data rapidly and accurately.

71. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Wilson in view of Sizto is **not adopted with respect to claim 1.**

As has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Wilson has been adopted (see Ground E). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Wilson, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Wilson anticipates claim 1, there are no differences between the patented claims and Wilson which would require modification by Sizto to meet the limitation of the claim.

72. **Ground L7 (SNQ 52).**

Claims 1-2 are rejected Under 35 U.S.C. 103(a) as being unpatentable over Wilson in view of DiMilla.

The proposed rejection is ***adopted*** for claim 2 and is ***not adopted*** for claim 1.

This rejection of claims 1-2 was proposed by the third party requester (see pages 231-233 of the request and Exhibit CC-L-7) and **is adopted with respect to claim 2** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground E, which is incorporated herein by reference in its entirety, Wilson teaches a system with software for sequentially imaging fluorescent or colloidal gold microparticles conjugated to monoclonal antibody and attached to cells at the site of cell surface MHC molecules by single particle tracking. Wilson teaches that single particle tracking provides a powerful approach to observing receptor movement at high spatial resolution (see page 2101, column 2, last partial paragraph). Wilson does not teach determining the center of the particles.

DiMilla teaches a method of tracking individual cells in a planar array on the bottom of a 35 mm diameter cell culture dish using time-lapse videomicroscopy and digital image analysis. DiMilla teaches determining the centroids of individual cells and tracking the centroids at intervals of 15 minutes for up to 36 hours using a semiautomated algorithm, in which a single field is analyzed at a time. DiMilla teaches determining pixel coordinates as a function of elapsed tracking time for each cell tracked. DiMilla teaches converting the pixel coordinates to real physical displacements for a qualitative description of the path traveled by each individual cell (page 731, column 2, third, fourth and fifth full paragraphs).

The person of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to have used the DiMilla method and system encompassing centroid determination for accurate tracking of individual migration of a target object as a convenient and accurate means of tracking the cellular receptors disclosed by Wilson.

73. The proposed rejection of claims 1-2 under 35 U.S.C. 103(a) as being unpatentable over Wilson in view of DiMilla is **not adopted for claim 1.**

As has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Wilson has been adopted (see Ground E). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Wilson, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Wilson anticipates claim 1, there are no differences between the patented claims and Wilson which would require modification by DiMilla in order to meet the limitations of the claims.

74. **Ground L8 (SNQ 53).**

Claims 1-3 are rejected Under 35 U.S.C. 103(a) as unpatentable over Wilson in view of NIH.

The proposed rejection is ***adopted*** for claims 2-3 and is ***not adopted*** for claim 1.

This rejection of claims 1-3 was proposed by the third party requester (see pages 233-236 of the request and Exhibit CC-L-8) and **is adopted with respect to claims 2-3** for the reasons stated in the request and for those reasons set forth below.

As was set forth *supra* in Ground E, which is incorporated herein by reference in its entirety, Wilson teaches a system with software for sequentially imaging fluorescent or colloidal gold microparticles conjugated to monoclonal antibody and attached to cells at the site of cell surface MHC molecules by single particle tracking. Wilson teaches that single particle tracking provides a powerful approach to observing receptor movement at high spatial resolution (see page 2101, column 2, last partial paragraph. Wilson does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel.

NIH is a public domain image processing and analysis program which was available at the time of the invention (page 2, first full paragraph). NIH discloses digitization of images from TV cameras, VCRs, or video disks and displaying the images as two dimensional arrays of pixels (paragraph bridging pages 3-4). NIH discloses that the apparatus can be used to measure area, mean, centroid or center (***claim 2***), etc. of user defined regions of interest (page 2, second full paragraph). NIH teaches that spatial calibration is supported to provide real world measurement of path length and angles (page 2, paragraph 2). NIH also teaches that a selected object is viewed as a plurality of pixels (***claim 3***, page 6, third paragraph and page 9).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to have used the NIH software in the method and with the apparatus disclosed by Wilson because NIH is an image processing and analysis program intended for tracking microscopic images, which was well-developed and publicly available at the time the invention was made.

75. The proposed rejection of claims 1-2 under 35 U.S.C. 103(a) as being unpatentable over Wilson in view of NIH is **not adopted with respect to claim 1.**

As has been set forth previously herein, the proposed rejection of claim 1 under 102(b) as anticipated by Wilson has been adopted (see Ground E). Therefore, the proposed rejection of claim 1 under 103(a) over the same reference, Wilson, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Wilson anticipates claim 1, there are no differences between the patented claims and Wilson which would require modification by NIH to meet the limitations of the claims.

76. **GROUND M1 (SNQ 54):**

Claims 1-4 are rejected under 3 U.S.C. 103(a) as being unpatentable over Dow in view of Brenner.

This proposed rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Dow in view of Brenner (see the Request at pages 236-240 and CC-M-1) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by Brenner in order to meet the limitations of the claims.

77. **GROUND M2 (SNQ 55).**

Claims 1-4 are rejected under 3 U.S.C. 103(a) as being unpatentable over Dow in view of Stern.

The proposed rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Dow in view of Stern (see the Request at pages 240-243 and Exhibit CC-M-2) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by Stern to meet the limitations of the claims.

78. **GROUND M3 (SNQ 56):**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as unpatentable over Dow in view of Douglass.

The rejection is ***adopted*** for claims 5-6 and is ***not adopted*** for claims 1-4.

This rejection of claims 1-6 was proposed by the third party requester (see pages 243-247 of the request and Exhibit CC-M-3) and **is adopted with respect to claims 5 and 6** for the reasons stated in the request and for those reasons set forth below.

As set forth *supra* in Ground F, which is incorporated herein by reference in its entirety, Dow teaches an image analysis package which digitizes images of moving cells in a focal plane

and stores the digitized data on a microcomputer. Dow teaches that the system can simultaneously track many moving cells in a planar array *in vitro*. Dow teaches finding the centroid or center of the cells and assigning pixels. Dow does not specifically teach assigning an initial pixel enclosing the center of the microparticles or assigning additional pixels immediately adjacent to the initial pixel.

As was set forth *supra* in Ground G, also incorporated herein by reference in its entirety, Douglass teaches a device readable medium with a program of instructions applicable for generating digital images of cells. Regarding ***claims 5 and 6,*** Douglass discloses assigning the pixels to the area surrounding the centroid, after an initial pixel is assigned to the centroid (column 4, lines 11-51, and column 7, lines 4-26).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have assigned an initial pixel to the centroid and additional pixels immediately adjacent to the centroid in the cells of Dow, according to the teachings of Douglass, as a means to better facilitate cell tracking.

79. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Dow in view of Douglass is **not adopted for claims 1-4.**

As has been set forth previously herein**,** the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow

anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by Douglass in order to meet the limitations of the claims.

80. **GROUND M4 (SNQ 57):**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dow in view of Douglass and Stern.

This rejection as proposed by Requester (see pages 247-252 of the request and Exhibit CC-M-4) is **not adopted**.

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by Douglass in order to meet the limitations of the claims.

With respect to claims 5-6, the proposed rejection of claims 5-6 under 103(s) as unpatentable over Dow in view of Douglass has been adopted (see Ground M3). Similarly, for the additional obviousness rejection over Dow in view of Douglass and Stern, the combination of Dow and Douglass must be modified in order to meet the claims. Requester has failed to point to any deficiencies in the combination of Dow with Douglass which would necessitate the addition of Stern.

81. **GROUND M5 (SNQ 58):**

Claims 1-4 are rejected under 35 U.S.C. 103(a) as unpatentable over Dow in view of King.

The proposed rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Dow in view of King (see the request at pages 252-255 and Exhibit CC-M-5) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by King in order to meet the limitations of the claims.

82. **GROUND M6 (SNQ 59):**

Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over Dow in view of Gelles.

The rejection is ***adopted*** for claims 5-6 and is ***not adopted*** for claims 1-4.

This rejection of claims 1-6 was proposed by the third party requester (see pages 255-259 of the request and Exhibit CC-M-6) and **is adopted with respect to claims 5-6** for the reasons stated in the request and for those reasons set forth below.

As set forth *supra* in Ground F, which is incorporated herein by reference in its entirety, Dow teaches an image analysis package based on a microcomputer, which can simultaneously

track many moving cells in a planar array *in vitro*. Dow teaches finding the centroid and assigning pixels to the cells according to the size and shape of cells. Dow does not specifically teach assigning an initial pixel to the centroid or adjacent pixels immediately adjacent to the initial pixel.

As was set forth supra in Ground B, which is also incorporated by reference herein in its entirety, Gelles teaches a system for recording, analyzing, and determining precise positional information of microparticles as they attach to and move along microtubules *in vitro*. Gelles teaches high precision measurement of molecular-scale movements of small objects in real time. Gelles teaches that the ability to do this has potential for providing insights into various biological processes (Fig. 1 and page 453, second from last paragraph).

Regarding ***claim 5***, Gelles teaches assigning an initial pixel to the center of the particle by teaching assigning the center of the bead to be the point (0,0) (Fig. 1).

With respect to ***claim 6***, Gelles teaches that the kernel comprises pixels immediately adjacent to the centroid by teaching that positional information is derived from the entire bead image rather than from an individual point or edge in order to maximize precision. Thus, Gelles teaches additional pixels immediately adjacent to the initial pixel (Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have assigned an initial pixel to the centroid and additional pixels immediately adjacent to the centroid in the cells of Dow, according to the teachings of Gelles, in order to better facilitate cell tracking.

83. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Dow in view of Gelles is **not adopted for claims 1-4.**

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by Gelles in order to meet the limitations of the claims.

84. **Ground M7 (SNQ 60):**

Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over Dow in view of Luck.

The proposed rejection is ***adopted*** for claims 5-6 and is ***not adopted*** for claims 1-4.

This rejection of claims 1-6 was proposed by the third party requester (see pages 259-263 of the request and Exhibit CC-M-7) and **is adopted** with respect to claims 5-6 for the reasons stated in the request and for those reasons set forth below.

As set forth *supra* in Ground F, which is incorporated herein by reference in its entirety, Dow teaches an image analysis package based on a microcomputer, which can simultaneously track many moving cells in a planar array *in vitro*. Dow teaches finding the centroid and assigning pixels to the cells according to the size and shape of cells. Dow does not specifically

teach assigning an initial pixel to the centroid or adjacent pixels immediately adjacent to the initial pixel.

As was set forth *supra* in Ground 9, also incorporated herein by reference in it's entirety, Luck teaches a system for classification of biological cells comprising a computer readable program of instructions for generating images of cells in a planar array on a microscopic slide (a "PAP smear") for classification of the cells as benign, premalignant or malignant.

Regarding ***claim 5***, Luck teaches that the processing system performs a primary classification of the image and assigns pixels to the centroids of biological objects in the image having attributes of the cell class for which screening is being performed (column 4, lines 11-26, and column 8, lines 58-62).

Regarding ***claim 6***, Luck teaches an array of pixels immediately surrounding the centroid called a net image. Thus, Luck teaches that additional pixels are assigned immediately adjacent to the centroid.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have assigned an initial pixel to the centroid and additional pixels immediately adjacent to the centroid in the cells of Dow, according to the teachings of Luck, in order to better facilitate cell tracking.

85. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Dow in view of Luck is **not adopted for claims 1-4.**

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of

claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by Luck to meet the limitations of the claims.

86. **Ground M8 (SNQ 61):**

Claims 1-6 are rejected under 35 U.S.C. 103(a) as unpatentable over Dow in view of Sizto.

The proposed rejection is ***adopted*** for claims 5-6 and is ***not adopted*** for claims 1-4.

This rejection of claims 1-6 was proposed by the third party requester (see pages 263-266 of the request and Exhibit CC-M-8) and **is adopted** with respect to claims 5-6 for the reasons stated in the request and for those reasons set forth below.

As set forth *supra* in Ground F, which is incorporated herein by reference in its entirety, Dow teaches an image analysis package based on a microcomputer, which can simultaneously track many moving cells in a planar array *in vitro*. Dow teaches finding the centroid and assigning pixels to the cells according to the size and shape of cells . Dow does not specifically teach assigning an initial pixel to the centroid or adjacent pixels immediately adjacent to the initial pixel.

As set forth *supra,* Sizto teaches a computerized method with software to analyze cells within a cellular sample, such as a blood sample.

Regarding ***claim 5***, Sizto teaches detecting a cell or cell constituent using an algorithm based on the average of two images. A 5 x 5 pixel map surrounding each pixel is defined in sequence, the center pixel is then determined, and the *x* and *y* coordinates for the center pixel are saved (see column 14, lines 35-58). Thus, Sizto teaches determining the approximate center of each of the cells or microparticles and assigning an initial pixel which encloses the center of particle.

With respect to ***claim 6,*** once the *x* and *y* coordinates for the center pixel are saved, a 7 x 7 pixel map, or neighborhood, surrounding the center pixel is saved. Thus, Sizto teaches assigning a plurality of pixels to each microparticle, wherein the additional pixels are immediately adjacent to the initial center pixel. Sizto teaches that the system is used to generate information relevant to detectable characteristics of the cells or cellular constituents (column 2, lines 53-57).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have assigned an initial pixel to the centroid and additional pixels immediately adjacent to the centroid in the cells of Dow, according to the teachings of Sizto, in order to better facilitate cell tracking.

87. The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Dow in view of Sizto is **not adopted for claims 1-4.**

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35

U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by Sizto in order to meet the limitations of the claims.

88. **GROUND M9 (SNQ 62).**

Claims 1-4 are rejected under 3 U.S.C. 103(a) as being unpatentable over Dow in view of DiMilla.

The proposed rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Dow in view of DiMilla (see the Request at pages 266-269 and Exhibit CC-M-9) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by DiMilla in order to meet the limitations of the claims.

89. **GROUND M10 (SNQ 63).**

Claims 1-4 are rejected under 3 U.S.C. 103(a) as being unpatentable over Dow in view of NIH.

The proposed rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Dow in view of NIH (see the request at pages 269-272 and Exhibit CC-M-10) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by NIH in order to meet the limitations of the claims.

90. **Ground N1 (SNQ 64).**

Claims 1-3 are rejected Under 35 U.S.C. 103(a) as unpatentable over NIH in view of Stern.

This rejection of claims 1-3 was proposed by the third party requester (see pages 272-275 of the request and Exhibit CC-N-1) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Regarding ***claim 1***, NIH is a public domain image processing and analysis program for a computer which can be used to measure area and centroid (as in patented ***claim 2***; see page 2, first and second paragraphs), among other parameters, of regions of interest. NIH uses a frame grabber card to digitize images from TV cameras, VCRs or video disks (page 5, last paragraph). NIH manipulates, displays and analyses images as two dimensional arrays of pixels (as in patented ***claim 3***; see page 2, first and second paragraphs and the paragraph bridging pages 3-4).

Because it was developed at the National Institutes of Health, one of ordinary skill in the art at the time of the invention would have immediately envisioned NIH Image as applicable for analysis of biological material. See also the biological image depicted at page 3. NIH Image does not teach tracking microparticles during a series of processing steps.

Stern teaches a scanning system and methods for high speed imaging of arrays of oligonucleotide arrays (page 1, last full paragraph). Stern teaches that confocal scanning microscopes of the system combine the high scan rate of galvanometer based scanning microscopes with a sufficiently high resolution, sensitivity, and large enough field of view for imaging high density arrays of materials, such as those found in the fields of combinatorial chemistry and genetic (polynucleotide) analysis (page 3, lines 10-21). Stern teaches that the system comprises a computer which receives, compiles, and stores input from a fluorescent detector or photomultiplier tube to produce an output of a fluorescent signal as an indication of particle position in an array.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the NIH Image software in the method and system of Stern because NIH teaches that it was in the public domain and readily available.

91. **Ground N2 (SNQ 66).**

Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over NIH in view of Luck.

This rejection of claims 1-6 was proposed by the third party requester (see pages 279-282 of the request and Exhibit CC-N-3) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Regarding ***claim 1***, NIH is a public domain image processing and analysis program for a computer which can be used to measure area and centroid (as in patented ***claim 2***; see page 2, first and second paragraphs), among other parameters, of regions of interest. NIH uses a frame grabber card to digitize images from TV cameras, VCRs or video disks (page 5, last paragraph). NIH manipulates, displays and analyses images as two dimensional arrays of pixels (as in patented ***claim 3***; see page 2, first and second paragraphs and the paragraph bridging pages 3-4). Because it was developed at the National Institutes of Health, one of ordinary skill in the art at the time of the invention would have immediately envisioned NIH Image as applicable for analysis of biological material. See also the biological image depicted at page 3. NIH Image does not teach tracking microparticles during a series of processing steps.

Luck teaches a system for classification of biological cells comprising a computer readable program of instructions for generating images of the cells in a planar array on a microscopic slide (a "PAP smear") for classification of the cells as benign, premalignant or malignant (see the abstract). The system disclosed by Luck comprises an automated microscope, a computer, a camera for capturing images of the cells, an image processor, and a digitizer (column 4, line 6-58, and column 5, line 25, through column 6, line 22). The system disclosed by Luck utilizes software to perform the functions (column 6, lines 23-32). Thus, regarding ***claim 1***, Luck teaches a device-readable medium having a program of instructions for generating images of a planar array of cells. Absent a limiting definition in the '505 patent disclosure,

"microparticles" is interpreted for prior art purposes as encompassing the cells described by Luck.

Regarding ***claims 2 and 5***, Luck teaches that the processing system performs a primary classification of the image and determines the centroids of biological objects in the image having attributes of the cell class for which screening is being performed (column 4, lines 11-26, and column 8, lines 58-62).

Regarding ***claim 3 and 6***, Luck teaches an array of pixels surrounding the centroid called a net image. Thus, Luck teaches that additional pixels are assigned immediately adjacent to the centroid. The net image is used to determine characteristics of a premalignant or malignant cell based on the gray scale density (*i.e.*, determines at least one property of the optical signals generated at each microparticle) (see column 7, lines 49-59).

With respect to ***claim 4***, Luck teaches that the assigned array of pixels corresponds to a one micron per pixel resolution during the high resolution rescan pass (column 6, lines 44-53). Luck also teaches that the system initially classifies cells by size based on the pixels recorded (column 8, lines 42-62). Thus, Luck teaches that the number of pixels assigned to each cell corresponds to the size of the cell (microparticle).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used NIH Image as the computer readable program of instructions for generating images of the cells in Luck's image processing system because the NIH software was well-developed and publicly available.

92. **Ground N3 (SNQ 66).**

Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over NIH in view of Luck.

This rejection of claims 1-6 was proposed by the third party requester (see pages 279-282 of the request and Exhibit CC-N-3) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Regarding ***claim 1***, NIH is a public domain image processing and analysis program for a computer which can be used to measure area and centroid (as in patented ***claim 2***; see page 2, first and second paragraphs), among other parameters, of regions of interest. NIH uses a frame grabber card to digitize images from TV cameras, VCRs or video disks (page 5, last paragraph). NIH manipulates, displays and analyses images as two dimensional arrays of pixels (as in patented ***claim 3***; see page 2, first and second paragraphs and the paragraph bridging pages 3-4). Because it was developed at the National Institutes of Health, one of ordinary skill in the art at the time of the invention would have immediately envisioned NIH Image as applicable for analysis of biological material. See also the biological image depicted at page 3. NIH Image does not teach tracking microparticles during a series of processing steps.

Luck teaches a system for classification of biological cells comprising a computer readable program of instructions for generating images of the cells in a planar array on a microscopic slide (a "PAP smear") for classification of the cells as benign, premalignant or malignant (see the abstract). The system disclosed by Luck comprises an automated microscope, a computer, a camera for capturing images of the cells, an image processor, and a digitizer (column 4, line 6-58, and column 5, line 25, through column 6, line 22). The system disclosed

by Luck utilizes software to perform the functions (column 6, lines 23-32). Absent a limiting definition in the '505 patent disclosure, "microparticles" is interpreted for prior art purposes as encompassing the cells described by Luck.

Regarding ***claims 2 and 5***, Luck teaches that the processing system performs a primary classification of the image and determines the centroids of biological objects in the image having attributes of the cell class for which screening is being performed (column 4, lines 11-26, and column 8, lines 58-62).

Regarding ***claim 3 and 6***, Luck teaches an array of pixels surrounding the centroid called a net image. Thus, Luck teaches that additional pixels are assigned immediately adjacent to the centroid. The net image is used to determine characteristics of a premalignant or malignant cell based on the gray scale density (*i.e.,* determines at least one property of the optical signals generated at each microparticle) (see column 7, lines 49-59).

With respect to ***claim 4***, Luck teaches that the assigned array of pixels corresponds to a one micron per pixel resolution during the high resolution rescan pass (column 6, lines 44-53). Luck also teaches that the system initially classifies cells by size based on the pixels recorded (column 8, lines 42-62). Thus, Luck teaches that the number of pixels assigned to each cell corresponds to the size of the cell (microparticle).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used NIH Image as the computer readable program of instructions for generating images of the cells in Luck's image processing system because the NIH Image software was well-eveloped and publicly available at the time the invention was made.

93. **Ground N4 (SNQ 67).**

Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over NIH in view of Sizto.

This rejection of claims 1-6 was proposed by the third party requester (see pages 283-286 of the request and Exhibit CC-N-4) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Regarding ***claim 1***, NIH is a public domain image processing and analysis program for a computer which can be used to measure area and centroid (as in patented ***claim 2***; see page 2, first and second paragraphs), among other parameters, of regions of interest. NIH uses a frame grabber card to digitize images from TV cameras, VCRs or video disks (page 5, last paragraph). NIH manipulates, displays and analyses images as two dimensional arrays of pixels (as in patented ***claim 3***; see page 2, first and second paragraphs and the paragraph bridging pages 3-4). Because it was developed at the National Institutes of Health, one of ordinary skill in the art at the time of the invention would have immediately envisioned NIH Image as applicable for analysis of biological material. See also the biological image depicted at page 3. NIH Image does not teach tracking microparticles during a series of processing steps.

Sizto teaches a computerized method with software to analyze cells within a cellular sample, such as a blood sample, by generating a plurality of digital images of the cells and processing the images by correlating optical signals generated at the site of each of the cells with its corresponding image in a plurality of digital images (see the abstract and column 2, lines 42-67).

Regarding ***claims 2 and 5***, Sizto teaches detecting a cell or cell constituent using an algorithm based on the average of two images. A 5 x 5 pixel map surrounding each pixel is defined in sequence, the center pixel is then determined, and the *x* and *y* coordinates for the center pixel are saved (see column 14, lines 35-58). As has been set forth previously herein, the "microparticles" of the patent claims are determined to encompass the cells disclosed by Sizto for prior art purposes, absent a limiting definition to the contrary in the '505 patent disclosure. Thus, Sizto teaches determining the approximate center of each of the cells or microparticles and assigning an initial pixel which encloses the center of particle.

With respect to ***claims 3 and 6,*** once the *x* and *y* coordinates for the center pixel are saved, a 7 x 7 pixel map, or neighborhood, surrounding the center pixel is saved. Thus, Sizto teaches assigning a plurality of pixels to each microparticle, wherein the additional pixels are immediately adjacent to the initial center pixel. Sizto teaches that the system is used to generate information relevant to detectable characteristics of the cells or cellular constituents (column 2, lines 53-57)

Regarding ***claim 4***, a neighborhood of pixels is defined for each of a plurality of identified segments in the scanned images, which is larger than the expected size of a target cell. The perimeter of the neighborhood is determined based on the expected shape of the target cell or cellular constituents within the neighborhood (column 3, lines 14-37). This is equivalent to assigning the number of pixels to a given microparticle based on the size and uniformity of the diameter and shape of the cell or microparticle.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used NIH Image as the computer readable program of instructions for

generating images of the cells in Sizto's image processing system because the NIH Image software was well-developed and publicly available at the time the invention was made.

94. **GROUND O1 (SNQ 68).**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as being unpatentable over Douglass in view of Zaun.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Douglass in view of Zaun (see the request at pages 286-290 and Exhibit CC-O-1) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(e) as anticipated by Douglass has been adopted (see Ground G). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Douglass, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-6, there are no differences between patented claims 1-6 and Douglass which would require modification by Zaun in order to meet the limitations of the claims.

95. **GROUND O2 (SNQ 69).**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as being unpatentable over Douglass in view of Stern.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Douglass in view of Stern (see the request at pages 290-293 and Exhibit CC-O-2) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(e) as anticipated by Douglass has been adopted (see Ground G). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Douglass, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-6, there are no differences between patented claims 1-6 and Douglass which would require modification by Stern in order to meet the limitations of the claims.

96. **GROUND O3 (SNQ 70).**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as being unpatentable over Douglass in view of DiMilla

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Douglass in view of DiMilla (see the request at pages 293-297 and Exhibit CC-O-3) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(e) as anticipated by Douglass has been adopted (see Ground G). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Douglass, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the

claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-6, there are no differences between patented claims 1-6 and Douglass which would require modification by DiMilla inorder to meet the limitations of the claims.

97. **GROUND O4 (SNQ 71).**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as being unpatentable over Douglass in view of Luck.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Douglass in view of Luck (see the request at pages 297-301 and Exhibit CC-O-4) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-6 under 102(e) as anticipated by Douglass has been adopted (see Ground G). Therefore, the proposed rejection of claims 1-6 under 103(a) over the same reference, Douglass, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-6, there are no differences between patented claims 1-6 and Douglass which would require modification by Luck in order to meet the limitations of the claims.

98. **GROUND O5 (SNQ 72):**

Claims 1-6 are rejected under 3 U.S.C. 103(a) as being unpatentable over Douglass in view of Sizto.

The proposed rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Douglass in view of Sizto (see the request at pages 301-305 and Exhibit CC-O-5) is **not adopted.**

As has been set forth previously herein, the proposed rejection of claims 1-4 under 102(b) as anticipated by Dow has been adopted (see Ground F). Therefore, the proposed rejection of claims 1-4 under 103(a) over the same reference, Dow, is improper. In a rejection based on 35 U.S.C. 103, the reference teachings must somehow be modified in order to meet the claims. If the claim is anticipated by the reference, no question of obviousness is present. Because Dow anticipates claims 1-4, there are no differences between patented claims 1-4 and Dow which would require modification by Sizto, in order to meet the limitations of the claims.

99. **Ground P1 (SNQ 73).**

Claims 1-4 are rejected Under 35 U.S.C. 103(a) as unpatentable over Stern in view of Zaun.

This rejection of claims 1-4 was proposed by the third party requester (see pages 305-308 of the request and Exhibit CC-P-1) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Stern teaches a system for detecting marked regions on a substrate surface to obtain images with high sensitivity and resolution at a high speed. Stern teaches that confocal scanning

microscopes of the system combine the high scan rate of galvanometer based scanning microscopes with a sufficiently high resolution, sensitivity, and large enough field of view for imaging high density arrays of materials, such as those found in the fields of combinatorial chemistry and genetic (polynucleotide) analysis (page 3, lines 10-21). Stern teaches that the system comprises a computer which receives, compiles, and stores input from a fluorescent detector or photomultiplier tube to produce an output of a fluorescent signal as an indication of particle position in an array. Stern does not specifically teach a planar array of microparticles, does not teach determining the approximate center of each microparticle, and does not teach assigning a plurality of pixels to the microparticles based on the degree to which the approximate center is likely to deviate from the geometric center, the size of the microparticle, or the uniformity of diameter and shape.

Regarding ***claim 1***, Zaun teaches a system of generating images of and tracking a planar array of amplified nucleic acids Imicroparticles) using a fluorescence detection system that includes capturing images with a video camera, digitizing them with a computer, and processing them with NIH Image (see column 7, lines 19-26, column 14, lines 42-49, and column 39, lines 52-59). The NIH Image software digitizes images from TV cameras, VCRs, or video disks and displaying the images as two dimensional arrays of pixels (paragraph bridging pages 3-4). NIH discloses that the apparatus can be used to measure the area, mean, centroid or center (***claim 2***), etc. of user defined regions of interest (page 2, second full paragraph). NIH teaches that spatial calibration is supported to provide real world measurement of path length and angles (page 2, paragraph 2). NIH also teaches that a selected object is viewed as a plurality of pixels (***claims 3 and 4***, page 6, third paragraph and page 9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the NIH Image software disclosed by Zaun in the system of Stern as a convenient and ready-made software program, which was publicly available at the time of the invention.

100. **Ground P2 (SNQ 74):**

Claims 1-2 are rejected Under 35 U.S.C. 103(a) as unpatentable over Stern in view of DiMilla.

This rejection of claims 1-2 was proposed by the third party requester (see pages 308-310 of the request and Exhibit CC-P-2) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Stern teaches a system for detecting marked regions on a substrate surface to obtain images with high sensitivity and resolution at a high speed. Stern teaches that confocal scanning microscopes of the system combine the high scan rate of galvanometer based scanning microscopes with a sufficiently high resolution, sensitivity, and large enough field of view for imaging high density arrays of materials, such as those found in the fields of combinatorial chemistry and genetic (polynucleotide) analysis (page 3, lines 10-21). Stern teaches that the system comprises a computer which receives, compiles, and stores input from a fluorescent detector or photomultiplier tube to produce an output of a fluorescent signal as an indication of position in an array. Stern does not specifically teach a planar array of microparticles and does not teach determining the approximate center of each microparticle.

Regarding ***claim 1***, DiMilla teaches a method of tracking individual cells in a planar array on the bottom of a 35 mm diameter cell culture dish using time-lapse videomicroscopy and digital image analysis. Absent a limiting definition in the '505 patent specification and for prior art purposes, the microparticles of the patented claims are determined to encompass the cells disclosed by DiMilla. Regarding ***claim 2***, DiMilla teaches determining the centroids of individual cells and tracking the centroids at intervals of 15 minutes for up to 36 hours using a semiautomated algorithm, in which a single field is analyzed at a time. DiMilla teaches determining pixel coordinates as a function of elapsed tracking time for each cell tracked. DiMilla teaches converting the pixel coordinates to real physical displacements for a qualitative description of the path traveled by each individual cell (page 731, column 2, third, fourth and fifth full paragraphs).

The person of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to have used the DiMilla method and system encompassing microparticles and centroid determination of the microparticles as a convenient and accurate means of tracking individual particle positions in an array, as suggested by Stern.

101. **Ground P3 (SNQ 75). Claims 1-6 are rejected Under 35 U.S.C. 103(a) as unpatentable over Stern in view of Luck.**

This rejection of claims 1-6 was proposed by the third party requester (see pages 310-313 of the request) and **is adopted** for the reasons stated in the request and for those reasons set forth below.

Stern teaches a system for detecting marked regions on a substrate surface to obtain images with high sensitivity and resolution at a high speed. Stern teaches that confocal scanning microscopes of the system combine the high scan rate of galvanometer based scanning microscopes with a sufficiently high resolution, sensitivity, and large enough field of view for imaging high density arrays of materials, such as those found in the fields of combinatorial chemistry and genetic (polynucleotide) analysis (page 3, lines 10-21). Stern teaches that the system comprises a computer which receives, compiles, and stores input from a fluorescent detector or photomultiplier tube to produce an output of a fluorescent signal as an indication of particle position in an array. Stern does not specifically teach microparticles, does not teach determining the approximate center of each microparticle, assigning an initial pixel to the center, or assigning additional pixels adjacent to the initial pixel, wherein the number of additional pixels is determined based on deviation of the approximate center from the geometric center, the size of the microparticle, or the uniformity of diameter and shape of the particle.

Regarding ***claim 1***, Luck teaches a system for classification of biological cells comprising a computer readable program of instructions for generating images of the cells in a planar array on a microscopic slide (a "PAP smear") for classification of the cells as benign, premalignant or malignant (see the abstract). The system disclosed by Luck comprises an automated microscope, a computer, a camera for capturing images of the cells, an image processor, and a digitizer (column 4, line 6-58, and column 5, line 25, through column 6, line 22). The system disclosed by Luck utilizes software to perform the functions (column 6, lines 23-32). Thus, regarding Luck teaches a device-readable medium having a program of instructions for generating images of a planar array of cells. Absent a limiting definition in the

'505 patent disclosure, "microparticles" is interpreted for prior art purposes as encompassing the cells described by Luck.

Regarding ***claims 2 and 5***, Luck teaches that the processing system performs a primary classification of the image and determines the centroids of biological objects in the image having attributes of the cell class for which screening is being performed (column 4, lines 11-26, and column 8, lines 58-62).

Regarding ***claim 3 and 6***, Luck teaches an array of pixels surrounding the centroid called a net image. Thus, Luck teaches that additional pixels are assigned immediately adjacent to the centroid. The net image is used to determine characteristics of a premalignant or malignant cell based on the gray scale density (*i e.,* determines at least one property of the optical signals generated at each microparticle) (see column 7, lines 49-59).

With respect to ***claim 4***, Luck teaches that the assigned array of pixels corresponds to a one micron per pixel resolution during the high resolution rescan pass (column 6, lines 44-53). Luck also teaches that the system initially classifies cells by size based on the pixels recorded (column 8, lines 42-62). Thus, Luck teaches that the number of pixels assigned to each cell corresponds to the size of the cell (microparticle).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used Stern's rapid image processing system to analyze the cells in the PAP smear contemplated by Luck. The person of ordinary skill I the art at the time of the invention would have been motivated to do so in order to facilitate the scanning of high numbers of cells, while ensuring optimal accuracy and diagnostic sensitivity.

Conclusion

Claims 1-6 are rejected.

In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, which is intended to be an Action Closing Prosecution (ACP), will be governed by 37 CFR 1.116(b) and (d), which will be strictly enforced.

Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.985 to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,654,505 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this Inter Partes Reexamination proceeding should be directed to:

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DEBORAH D. JONES
CRU SPE-AU 3991

PADMASHRI PONNALURI
PRIMARY EXAMINER

EXHIBIT 24

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re U.S. Patent of:		§	
		§	
	Stephen C. Macevicz	§	Examiner: Unknown
		§	
Patent No.:	7,598,035 B2	§	Group Art Unit: Unknown
		§	
Issued:	October 6, 2009	§	Appl. No. Unknown
		§	
For:	METHOD AND COMPOSITION FOR ORDERING RESTRICTION FRAGMENTS	§	Atty Docket No.: INV850/36024/4-047REUS
		§	
		§	

MAIL STOP *INTER PARTES* REEXAM
ATTN: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR *INTER PARTES* REEXAMINATION OF U.S. PATENT NO. 7,598,035 B2.

Dear Sir:

Pursuant to 37 C.F.R. § 1.915(b)(8), the Real Party in Interest, Life Technologies Corporation ("Requester"), hereby respectfully requests reexamination pursuant to 35 U.S.C. §§ 311 *et seq.* and 37 C.F.R. §§ 1.902 *et seq.*, of Claims 1-5 of U.S. Patent No. 7,598,035 ("the '035 patent") (Exhibit PAT-A) filed October 8, 2004 and issued October 6, 2009 to Stephen C. Macevicz. The '035 patent was originally examined by examiner Frank W. Lu.

Requester informs the Examiner that the '035 patent is involved in litigation in the United States District Court for the District of Delaware, No. 1:09-cv-00706-RK.

In accordance with 37 C.F.R. § 1.915(a) and pursuant to 37 C.F.R. § 1.20(c)(2), the Commissioner is authorized to deduct a fee of $8,800 from VINSON & ELKINS L.L.P. Deposit Account Number 22-0365/INV850-36024. If additional fees are due or if an overpayment has been made, the Commissioner is authorized to deduct or credit the proper amount to VINSON & ELKINS L.L.P. Deposit Account Number 22-0365/INV850-36024.

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In view of the foregoing, it is respectfully submitted that a substantial new question of patentability of Claims 1-5 of U.S. Patent No. 7,598,035 has been raised by this Request. Accordingly, the Office is requested to grant this request and to initiate reexamination with special dispatch.

As an aid to the application to the presented prior art to the claims of the '035 patent, corresponding claim charts are provided at Exhibits CC-A through CC-N-9 attached hereto.

Date: January 13, 2010

Respectfully submitted,

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