UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ABS GLOBAL, INC.,

v.

Inguran, LLC
Patent Owner

Patent No. 8,198,092
Issued: June 12, 2012
Filed: May 17, 2011

Inventors: Gary Durack, Jeffrey D. Wallace, Gary P. Vandre, Lon A. Westfall, Jeremy T. Hatcher, and Niraj V. Nayak

Title: DIGITAL SAMPLING APPARATUS AND METHODS FOR SORTING PARTICLES

Inter Partes Review No. 2016-00927

PETITION FOR INTER PARTES REVIEW

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I. Compliance with Requirements of an *Inter Partes* Review Petition

A. Certification that the Patent May Be Contested via *Inter Partes* Review by the Petitioner

Petitioner certifies it is not barred or stopped from requesting *inter partes* review of U.S. Patent No. 8,198,092 ("'092 Patent") (Ex. 1001). Neither petitioner, nor any party in privity with Petitioner: (i) has filed a civil action challenging the validity of any claim of the '092 Patent; or (ii) has been served a complaint alleging infringement of the '092 Patent more than a year prior to the present date. Also, the '092 Patent has not been the subject of a prior *inter partes* review or a finally concluded district court litigation involving Petitioner.

B. Fee for Inter Partes Review (§ 42.15(a))

The director is authorized to charge the fee specified by 37 CFR § 42.15(a) to Deposit Account No. 50-1597.

C. Mandatory Notices (37 CFR § 42.8(b))

1. Real Party in Interest (§ 42.8(b)(1))

The real party in interest is ABS Global, Inc., located at 1525 River Rd., DeForest, WI 53532. Genus plc, located at Belvedere House, Basing View, Basingstoke, Hampshire RG21 4DZ, UK is the ultimate parent of ABS Global, Inc.

2. Other Proceedings (§ 42.8(b)(2))

The ’092 Patent is the subject of litigation in the United States District Court for the Western District of Wisconsin (Civil Action Case No. 14-cv-503), which names ABS Global, Inc. and Genus plc as counterclaim defendants.

3. Lead and Backup Lead Counsel (§ 42.8(b)(3))

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4. Service on Petitioner

Service on Petitioner may be made by mail or hand delivery to: Sidley Austin LLP, 1501 K Street, N.W., Washington, D.C. 20005. The fax number for Petitioner’s counsel is (202) 736-8711.

5. Proof of Service (§§ 42.6(e) and 42.105(a))

Proof of service of this petition is provided in Attachment A.

II. Identification of Claims Being Challenged (§ 42.10(b))

Claims 1-13, 16, 18-19, 21, 26-28, 32, 41-46, and 49 of the ’092 Patent are unpatentable as obvious in view of the prior art under 35 U.S.C. § 103. Specifically:

1. Ground 1: Claims 1-3, 5-9, 11-13, 16, 18-19, 21, 28, 32, 40-41, and 43-46 Are Unpatentable Over Godavarti 1996 in view of Leary 2002.

2. Ground 2: Claims 4, 26-27, 42 and 49 Are Unpatentable Over Godavarti 1996 in View of Leary 2002, and Further In View Of Johnson 1999.

3. Ground 3: Claim 10 is Unpatentable Over Godavarti 1996 in View of Leary 2002, and Further in Combination With Piper 1992.

Petitioner's proposed construction of the claims, the evidence relied upon, and the precise reasons why the claims are unpatentable are provided in § IV, below. A list of evidence relied upon in support of this petition is set forth in Attachment B.

III. Introduction

The '092 patent is directed to systems and methods of sorting particles in a flow cytometer that uses a digital signal processor to analyze and classify the particles and to provide a sorting signal. *See e.g., id.*, cl. 1. Flow cytometers using analog electronics for that purpose had been used to sort cells for decades prior to 2003. Ex. 1003 (Robinson Decl.) at ¶¶40-47. As digital signal processors became faster and more sophisticated, those skilled in the art increasingly applied them in the field of flow cytometry. *See, infra,* at IV.C.1-2. The purported invention of the '092 patent – use of a digital signal processor in place of analog circuitry that performs the same function – is quintessential *KSR* obviousness. *KSR*

International Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007) ("if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

The prior art demonstrates that others had recognized the benefits of using digital signal processors in flow cytometry instruments and had begun using them before the earliest effective filing date of the contested patent. The prior art also shows that those skilled in the art recognized that until digital signal processors became fast enough for use in real time cell sorting, their use in flow cytometers could be limited. But the prior art also shows those types of advancements in digital signal processors occurred well before 2002 – by that date, more powerful digital signal processers suitable for use with real time cell sorting in flow cytometers – processors with increased in speed and accessibility – had become commercially available. Indeed, to implement the putative invention, the '092 patent inventors simply purchased commercially available digital signal processors that were fast enough for use in cell sorting. Thus, all of the challenged '092 patent claims are unpatentable as obvious.

IV. Relevant Information Concerning the Contested Patent

A. Effective Filing Date of the '092 Patent

The application that led to the '092 Patent claims priority to two provisional applications that were filed on March 28, 2003. For the purposes of this proceeding, Petitioner will assume that the '092 Patent is entitled to the benefit of the earliest filing date in the chain of applications to which the '092 Patent claims priority (*i.e.*, March 28, 2003).

B. Person of Ordinary Skill in the Art

Solely for purposes of this Petition, Petitioner submits that a person of skill in the art would be someone who has a bachelors or a masters degree in the fields of biology, biochemistry, or engineering, at least five years of experience in designing and developing flow cytometers, and knowledge of sperm cell physiology. That definition of the person of ordinary skill was advanced by Patent Owner in related litigation.

C. Background Of The Technology

The '092 Patent describes the use of a well-known fluorescence-based flow cytometer in which cells are treated with a fluorescent dye that binds to the cells' DNA. Ex. 1003 at ¶¶67-72. The overall scheme for a fluorescence-based cell sorter is depicted, for example, in Figure 1.1 of Durack 2000, and would have been well known to a person of ordinary skill in the art:

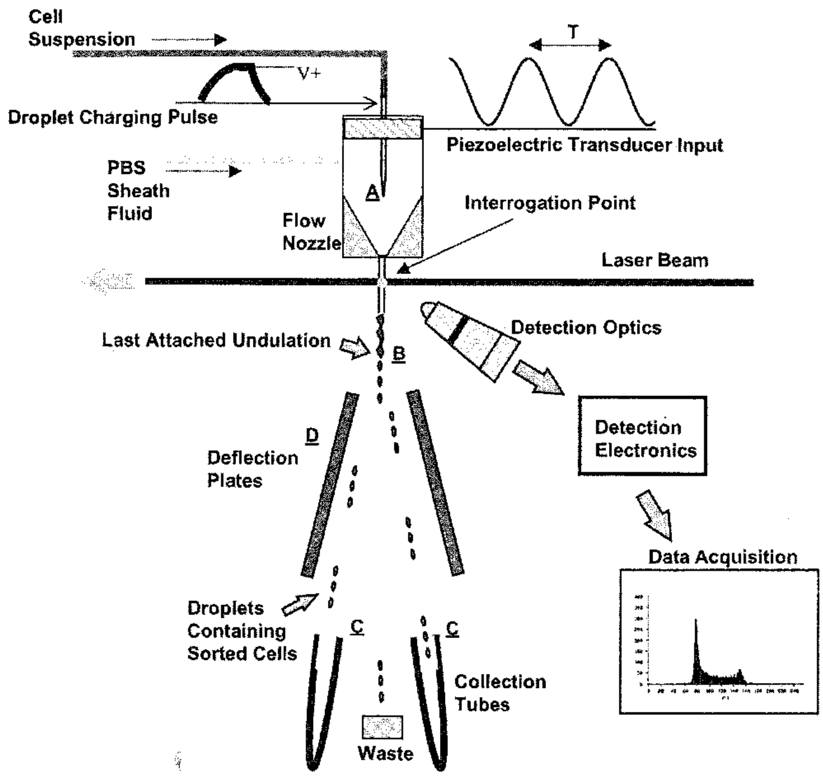

Fig. 1.1. A typical laser-based droplet cell sorter.

Ex. 1008 at 4; Ex. 1003 at ¶¶40, 71-72. As shown in the figure above, a sample liquid containing the cells to be sorted (which are typically pre-dyed with a fluorescent reagent) and sheath fluid are introduced into a nozzle. Ex. 1008 at 4-5; Ex. 1003 at ¶40. The liquid is pressurized and forms a stream in which the cells in the sample liquid (e.g., blood, semen, or the like) become enveloped by the sheath fluid. *Id.* A vibrator on the nozzle is used to convert the stream into droplets. Ex. 1008 at 4-5; Ex. 1003 at ¶40. Preferably, the droplets contain one cell from the sample liquid. *Id.* The droplets flow past a laser beam and the resulting fluorescence emitted from the cells is detected by a photodetector. Ex. 1008 at 13-14; Ex. 1003 at ¶40.

The fluorescence emitted from the cells is in the form of a continuous wave, known as an analog signal or a waveform. *Id.* Examples of these analog signals are shown in the following diagram:

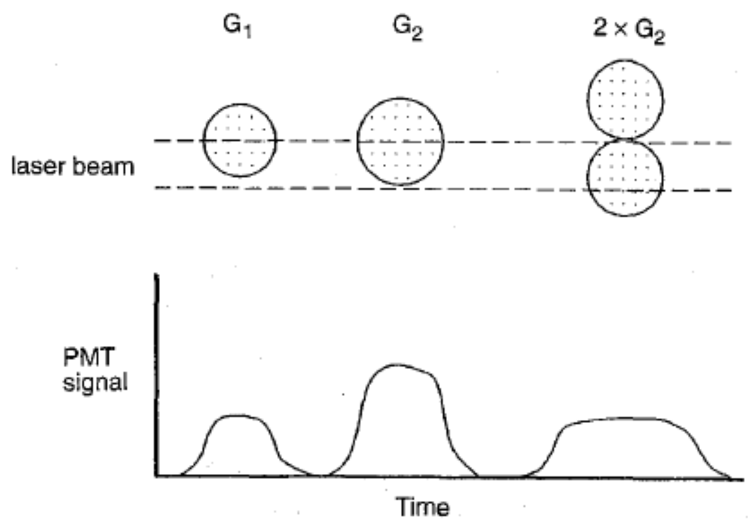

Figure 2 The signals generated when a cell in G_1, a cell in G_2, or two cells in G_1 of the cell cycle cross the laser beam.

Ex. 1009 (Ormerod 2000) at 86. As shown in the diagram, cells with different physical characteristics (i.e. G_1 and G_2) will generate different pulses. *Id.* In the traditional application, the cell sorter analyzes the analog signal and the properties of the corresponding cells. Ex. 1008 at 12; Ex. 1003 at ¶44. Based on the properties of the cells, the cell sorter electronics applies a positive or negative charge to the cells (or no charge at all) depending on the characteristics of each cell. *Id.* at 6. The cells next pass electrostatic deflecting plates and the falling droplets are directed into different directions depending on their charge. *Id.* The charged droplets are collected into different containers. *Id.* Uncharged droplets fall straight down and can be collected or discarded. *Id*. This type of fluorescence-based flow cytometer has been known for decades. Ex. 1003 at ¶¶44-46.

The purported invention of the ’092 patent is the use of a digital signal processor in place of traditional analog processors to perform the same function as that older analog processor; namely to analyze and classify cells and generate sorting signals. Thus, the ’092 Patent proposes the use of an analog-to-digital converter (“ADC”) to convert the analog waveform pulses that are output from the photodetector into a digital signal (Ex. 1001at col. 54:16-54), and processing of that digital information using digital signal processors (“DSP”) (*id*. at col. 54:56-58). However, the concept of digitizing the analog output of a photomultiplier tube and using a DSP in place of the older analog circuitry to analyze, classify, and sort particles in flow cytometers was known long before the ’092 Patent was filed.

1. The Benefits of Digital Processing In Flow Cytometry Were Well Known By 2003

The benefits of using digital processing in cell sorting were readily apparent to the skilled person and had been described in several publications before 2003. *See* Ex. 1003 at ¶¶51-62. Indeed, by at least early 2001, the advantages of digital signal processing over traditional analog flow cytometers were widely recognized by those of ordinary skill. Among other benefits, it was recognized that digital processing could improve upon inaccuracies resulting from analog logarithm conversions (*see, e.g.,* Ex. 1010 (Feb. 27, 2001 Roederer post))[1] and that digital data could be manipulated and analyzed using a wide range of algorithms. It was also recognized digital processing allowed one to obtain detailed information on the shapes of pulses as well as the more conventional measures of pulse height, width, and area. *See* Ex. 1011 Shapiro 2001 at 161. In fact, at least one prominent commentator in the flow cytometry community remarked in May 2001 that "There is NO DOUBT that digital electronics, whether it be Coulter, Cytomation, or BD is the wave of the future--for the good reason that the data we will get will be far superior." Ex. 1012 (May 17, 2001 Roederer post). *See* Ex. 1003 at ¶51.

In the 1990s, the primary potential obstacle to achieving the well-known advantages of digital processing was speed—the signal acquisition, digitization, and processing had to occur fast enough to permit a sort decision to be made and then carried out between the time the particle was detected and the time it

[1] Exs. 1010, 1012-1016, 1018, 1033 and 1038 are excerpts from a publicly accessible internet message board that was coordinated and hosted by Petitioner's expert, Professor J. Paul Robinson. Ex. 1003 at ¶51, n.9. As Dr. Robinson explains, this message board was widely used by those in the field of flow cytometry, including the first-named inventor of the '092 patent. It was publicly accessible on the Internet and indexed by topic. *Id*. Thus, Exs. 1010, 1012-1016, 1018, 1033 and 1038 qualify as printed publications under 35 U.S.C. § 102(b).

encountered the machine's sorting mechanism. *See* Ex. 1003 at ¶¶55-58. However, by the time the '092 patent was filed, that perceived obstacle no longer existed; DSPs and related electronics had become fast enough for this application. *Id*. Indeed, the '092 Patent reported that commercially available, off the shelf DSPs and ADCs were used. *See, e.g.,* Ex. 1001 at 54:56-57 ("Pulse processing takes place in four (4) TigerSharc DSP processors"); *id*. at 55:27-28 (noting the use of a "Bitware Corp. 105 MHz/2-channel, 14 bit capable of 105 MHz" ADC). Thus, because digital signal processors having the requisite speed and power had become widely available before March of 2003, no obstacles existed to integration of them into flow cytometers, a result predicted in the prior art. In other words, by March of 2003, there was nothing inventive about moving from analog to digital processing in flow cytomers to obtain the well understood benefits of digital signal processing.

2. There Are Numerous Examples Of The Application Of Digital Electronics To Flow Cytometry Before 2003

a. Godavarti 1996

Godavarti 1996[2] is entitled "Automated Particle Classification Based on Digital Acquisition and Analysis of Flow Cytometric Pulse Waveforms," and was

[2] Godavarti, M. et al., "Automated Particle Classification Based on Digital Acquisition and Analysis of Flow Cytometric Pulse Waveforms." *Cytometry* 24

not before the PTO during prosecution of the application resulting in the '092 patent.

Godavarti 1996 taught a digital data acquisition system that is used with a conventional flow cytometer. Ex. 1005 (Godavarti 1996) at 331. Godavarti 1996 stated that the data acquisition system of traditional flow cytometry systems was "front-end analog circuits to provide feature values that characterize the shapes of the individual pulse waveforms . . . ." *Id.* It recognized that using "analog circuits limits the features that can be extracted from the pulse shape to pulse height, area, and width." *Id.* Thus, Godavarti described "[a]n alternative to analog pulse processing [that] involves the use of digital sampling, in which the complete pulse waveforms are digitized at the point of detection." *Id.* Godavarti 1996 also noted the obvious benefits of digital signal processing, which could be used to "extract a wide variety of feature values" that could "be used to discriminate between pulse waveforms that cannot be classified using the pulse height, pulse integral, and pulse width feature values produced by analog hardware." *Id.*

Godavarti 1996 described a "first-generation digital data acquisition system," where the design permitted "the capture of only a subset of the pulses generated by the flow cytometer," and where the issues of "real-time

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(1996): 330-339 ("Godavarti 1996"). Godavarti 1996 is discussed in more detail below and in Ex. 1003 at ¶¶151-166.

classification" were not addressed. *Id*. at 339. Godavarti 1996 explained that classification using DSPs was limited by the speed of then-available electronics and expressly contemplated real-time cell sorting using DSPs in the future:

> [C]lassification [was] implemented in software by using the C programming language. For the purposes of this comparative analysis, the algorithms were run on a Sun Microsystems computer work station to take advantage of the convenient sohare-development environment. However, for real-time applications, the software would be compiled to run on the DSP chip in the digital analysis system.

Id. at 333. Recognizing that DSPs were becoming faster and easier to use, Godavarti 1996 stated that "in the next-generation digital data acquisition system, our design calls for real-time performance." *Id*. at 339.

b. Leary 2002

Another example of a flow cytometry-based cell sorter using digital electronics is Leary 2002, entitled "Advanced 'Real-Time' Classification Methods for Flow Cytometry Data Analysis and Cell Sorting."[3] The cell sorting system in Leary 2002 is shown in Figure 2, reproduced below:

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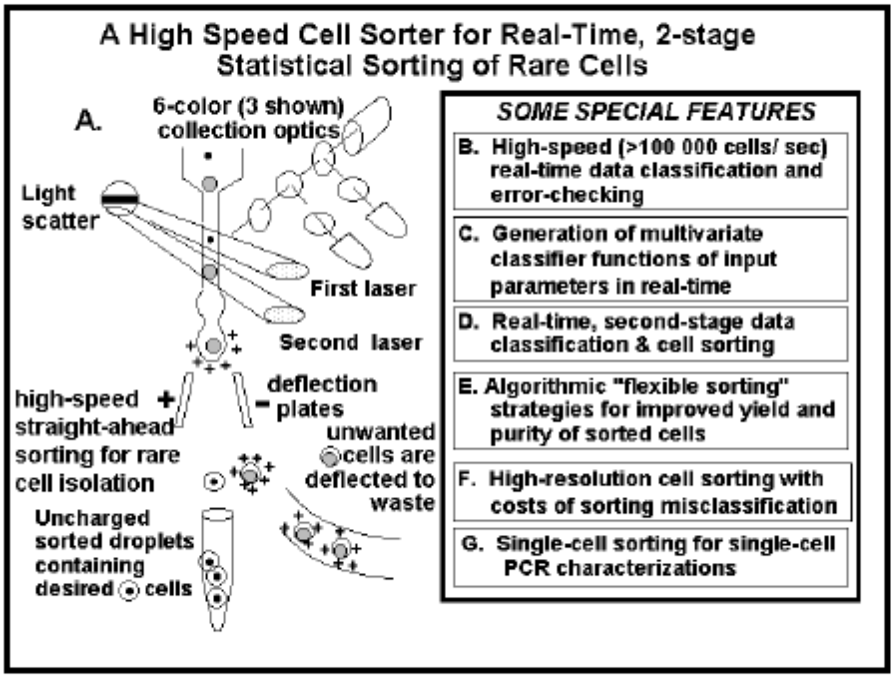
[3] Leary, J.F., et al. "Advanced real-time classification methods for flow cytometry data analysis and cell sorting." *Proc. SPIE* 4622, Optical Diagnostics of Living Cells V, 204 (May 28, 2002). It was received by a library at least as early as June



Ex. 1006 at 205.

Leary 2002 employed an optical system as in a typical flow cytometer. The "Real-time, second-stage data classification & cell sorting" processing in step "D" in the figure above was carried out by a digital signal processing board. *Id*. at 204-205; Ex. 1003 at ¶¶167-191.

Leary 2002 recognized that employing more sophisticated algorithms when sorting cells was desirable, and that the use of digital signal processors enabled them to be implemented. Ex. 1006 at 209 ("For many applications sorting decisions should and can be made on the basis of more sophisticated multivariate statistical methods that look at the full dimensionality of the data. These methods

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24, 2002, prior to the earliest possible effective filing date of the '092 patent. Ex. 1006 (Leary 2002) at p. 2.

can now be practically implemented."). One of the problems had been the difficulty of making digital electronics work at a fast enough speed. *Id*. at 204 (a "fundamental problem" in prior cell sorting systems was "that the data analysis techniques have been performed using relatively slow computational methods that take far more time than is allowed by the sort decision on a cell sorter (typically less than a millisecond).")

Leary 2002 explained that the switch to digital signal processing was driven by the practical availability of components and software tools at reasonable prices:

> Now that digital signal processing boards are at a reasonable price and programming software is easier to use, previous constraints such as what we encountered when we built these signal processing electronics for our home-built cell sorter are no longer an engineering or financial barrier. While the original system was built some time ago before DSP boards and the software to program them were commonplace and inexpensive, we are now in the process of implementing the features of the original system using DSP boards, MatLab™ to program the DSP boards, and LabView™ programming for the main data acquisition interface with special features to be added in C/C++.

Id. at 205.

c. Becton Dickinson – BD FACSDiVa

By at least 2000, commercial manufacturers were developing digital flow cytometers. For example, in May 2000, Becton Dickinson ("BD") demonstrated a digital flow cytometry platform called "HiPer-FACS." Ex. 1013 (Feb. 27, 2001 HiPerFACS posts); Ex. 1003 at ¶60. By 2001, BD was shipping a more advanced digital system known as the "BD FACSDiVa" for certain BD flow cytometers, including the BD FACSVantage flow cytometer. *See* Ex. 1014 (Jan. 23, 2002 Roederer post); Ex. 1015 (Jan. 24, 2002 Schell post); Ex. 1016 (Oct. 16, 2001 Schmitz post); Ex. 1003 at ¶60. FACS refers to "fluorescence activated cell sorting" and "DiVa" refers to "digital vantage." Ex. 1014 ("we have had a BD Digital Vantage (DiVa) for nearly one year"); Ex. 1003 at ¶60.

BD published a white paper detailing the technical operation of its FACSDiVa system, which bears a date of "03/02." Ex. 1017 (BD White Paper); Ex. 1003 at ¶61. The BD system was a fully digital fluorescence-based flow cytometry droplet cell sorting system that was capable of four-way sorting. Ex. 1003 at ¶61. In the BD system, the analog output of the photodetector was continuously sampled by an ADC and fed into a series of DSPs, which analyzed, classified, and made sort decisions about the particles. *Id*. FACSDiVa systems were available to those of skill in the art prior to March 28, 2002. For example, FACSDiVa Systems had been ordered or were in use by at least the following individuals prior to March 28, 2002: Mario Roederer at NIH (Ex. 1014); Kathy Schell at University of Wisconsin (Ex. 1015); Marty Bigos at UC San Francisco (*see* Ex. 1018 (May 2, 2001 Bigos post); and Joern Schmitz at Harvard (Ex. 1016).[4]

D. Construction of Terms Used in the Claims

In an IPR, claims must be given their broadest reasonable construction in light of the specification. *See* 37 CFR 42.100(b); M.P.E.P § 2111.01.

1. "sampling" (all contested claims)

Each challenged claim requires that an ADC "sample" the analog output of the photodetector. Ex. 1001 (element (f) of claims 1, 16, 18, 19, 21, 26, 28 and 32; element (c) of claim 40). Petitioner does not contend that "sampling" requires construction, but instead contends that the ordinary meaning should be applied

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[4] Regardless of whether the BD FACSDiVa system qualifies as a prior art printed publication, it is useful evidence confirming that those skilled in the art were transitioning to digital electronics as sufficiently fast digital became available. Such evidence is relevant to an obviousness inquiry as, at a minimum, evidence of near simultaneous invention. *See e.g.*, *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000) (discussing "near simultaneous invention" as a secondary consideration, and noting the Supreme Court's observation that "[t]he fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art.") (citation omitted).

under the broadest reasonable construction standard. Patent Owner has argued in related litigation that the term "sampling" requires a sampling rate between about 25 MHz and 200 MHz based on a sentence in the specification that states: "[t]he sampling rate may be varied between about 25 and 200 MHz without departing from the scope of the present invention." *Id.* at 54:53-54.

However, the challenged claims do not recite this range, and the *broadest reasonable interpretation* of the term "sampling" is not one limited to a certain, specific scope. Ex. 1003 at ¶133. In fact, while most claims are silent as to the required sampling rate, claim 21 specifically requires a sampling rate that "is about 105 MHz or higher." Ex. 1001 at claim 21. Given that the inventors chose to claim a specific sampling rate range in one claim, claims lacking a specific range should not be limited to a particular sampling rate range under the broadest reasonable interpretation standard.

2. "detecting waveform pulses" (claims 1 and 40)

Claim 1 requires that the digital signal processor include "instructions for *detecting the waveform pulses* corresponding to the digital information." Ex. 1001, claim 1(g). Claim 40 requires a step of "*detecting waveform pulses* represented by the digital information." *Id.*, claim 40(d).

Petitioner does not contend that "detecting waveform pulses" requires construction, but instead contends that the ordinary meaning should be applied.

Patent Owner has argued in related litigation that "detecting waveform pulses" requires "applying logic to distinguish waveform pulses that represent live cells from waveforms that represent noise, debris, or dead cells."

"Detecting waveform pulses" does not require distinguishing between (1) live cells on the one hand, and (2) noise, debris, or dead cells on the other. *See* Ex. 1003 at ¶¶135-136. The specification teaches that "waveform pulses" are pulses in waveforms that are present in the time-varying analog output of the photodetector. For example, the '092 Patent states:

> The electrical signals output from the photodetector 117 of the epi-illumination system 415 are time-varying analog voltage signals indicative of the amplitude of the emitted fluorescence at any instant in time generated by each cell as it is illuminated by the laser beam 25. Thus, the analog signals (also referred to as analog output) are in the shape of time varying waveform pulses 497 as illustrated schematically in FIGS. 52 and 53. *In general a waveform pulse 497 is defined as a waveform or a portion of a waveform containing one or more pulses or some portion of a pulse.*

Ex. 1001 at 52:59-53:1 (emphasis added). Thus, a waveform pulse is simply a pulse in a waveform that is contained in the analog output of the photodetector. The pulse may or may not be caused by a live cell, and may or may not be caused by noise, debris or a dead cell.

The claims themselves make clear that "waveform pulses" are not limited to representations of live cells. For example, claim 1 provides that the waveform pulses are "indicative of characteristic A or characteristic B." *Id*. at Cl. 1(f). Claim 4, in turn, requires that "characteristic A is indicative of a live X sperm cell and characteristic B is indicative of other than a live X cell (˜X)." *Id*. at claim 4. Thus, dead X cells are within characteristic B. This is consistent with the specification's discussion of waveform pulses. *Id*.at 53:1-17 ("In general, as used herein, X cells refers to live X cells, Y cells refers to live Y cells and ~X cells refers to the combination of live Y cells and cells which otherwise produce a detectable fluorescence emission 31 but which cannot be identified with a reasonable probability as being live X cells."). Thus, pulses can represent live cells or dead cells (or noise or debris) and the "detecting" step does not require distinguishing between live cells and dead cells. *See* Ex. 1003 at ¶136. On the contrary, the processes of distinguishing cells are separately recited elements. For example, in addition to "detecting waveform pulses," claim 1 requires "extracting features in the detected waveform pulses, and instructions for discriminating the detected waveform pulses as a function of their extracted features." Ex. 1001, claim 1(g). In other words, the extracted features of the waveform pulses are used to discriminate between cells that have characteristic A and characteristic B—not in the detection of the waveform pulses themselves.

3. "sort processor" (claims 8, 9)

A person of ordinary skill in the art would understand the broadest reasonable construction of the term "sort processor" to mean "hardware that generates sorting instructions." Ex. 1003 at ¶¶138-139. A person of ordinary skill would understand that there are a variety of electronics that can be used to make sort decisions. The specification of the '092 patent describes a system employing four processors: (1) data mgmt processor, (2) pulse detection processor, (3) feature extraction/discrimination processor, and (4) sort processor. Ex. 1001 at FIG. 39. It explains that the "processor 863, 865, 867, 873 labels as used above and this application are used for convenience only and are not intended to be limiting in any way." *Id*. at col. 55:13-15. Thus, a "sort processor," under the broadest reasonable construction, should not be limited to a processor that exclusively makes sort decisions.

4. "enumerates the number of classified particles having characteristic A or having characteristic B" (claim 9)

A person of ordinary skill would understand the broadest reasonable construction of the term "enumerates the number of classified particles having characteristic A or having characteristic B" to mean "keep track of or count the number of cells classified as having characteristic A and characteristic B." Ex. 1003 at ¶¶141-143.

The '092 patent explains that "[s]ince the microprocessor 131 knows the droplet formation rate and identifies the cells within a droplet as X or ~X, the microprocessor 131 knows the cell content of each droplet 33 and keeps track of (or enumerates) the number of cells in each population 123, 125." Ex. 1001 at col. 53:29-34. Thus, the processor "enumerates the number of classified particles having characteristic A or having characteristic B" by keeping track of the number of cells it classified in each population.

5. "continuous sampling rate" (claims 18, 19, 21)

A person of ordinary skill would understand the broadest reasonable construction of "continuous sampling rate" to mean "sampling to produce digital information corresponding to the analog output." Ex. 1003 at ¶145. The '092 Patent provides this definition:

> Synchronously sampling means sampling to produce digital information corresponding to the analog output. Synchronously sampling is also referred to as continuously sampling or streaming acquisition. . . . [T]he sampling rate depends on the frequency spectrum of the analog output.

Ex. 1001 at col. 54:24-27.

6. "synchronously sampling the analog output" (claim 46)

A person of ordinary skill would understand the broadest reasonable construction of "synchronously sampling the analog output" to be "sampling to produce digital information corresponding to the analog output." This is true for same reasons stated above with respect to the term "continuous sampling rate."

V. Precise Reasons for Relief Requested

A. Ground 1: Claims 1-3, 5-9, 11-13, 16, 18-19, 21, 28, 32, 40-41, 43-46 Are Unpatentable Over Godavarti 1996 In View Of Leary 2002

As explained in detail below, Godavarti 1996 disclosed each limitation of claims 1-3, 5-9, 11-13, 16, 18-19, 21, 28, 32, 40-41, and 43-46. Godavarti 1996 is a publication describing the work of scientists at the University of Arizona, and their construction and use of a flow cytometer/cell sorter having digital signal processors for analyzing and classifying cells. Ex. 1005 at 330. Godavarti taught the benefits of using digital electronics. *Id*. at 330, abstract (discussing the "limits" of analog processing and the additional features that can be extracted with "direct digitizing."). Godavarti also specifically stated that the goal was "the design of a real-time digital data acquisition system for flow cytometry." *Id*. However, the machine that these scientists built and used did not perform "sorting" of cells in real time, and the authors of Godavarti 1996 recognized that the digital circuitry they were using at the time did not operate fast enough for real-time sorting. *E.g.*, *id*. at 339 ("we have found that the time required for DSP-based calculation of pulse feature values would place an unacceptably low upper bound on the rate of data acquisition."). Thus, while Godavarti 1996 did not report *actual results* of sorting cells using a digital signal processor, it *discloses* how each limitation of claims 1-3, 5-9, 11-13, 16, 18-19, 28, 32, 40-41, and 43-46 could be practiced once fast enough DSPs became available. Ex. 1003 at ¶¶211-214. As discussed in more detail below, there would have been a clear motivation to use Godavarti 1996 for real time sorting once DSPs became fast enough and accessible. Moreover, Leary 2002 discloses that DSPs fast enough for sorting had in fact become available before March 2003. *See* § IV.C.2.b., *supra*. The BD FACSDiVa, which also used DSPs for real time sorting, was also known and discussed in numerous printed publications publications. *See* § IV.C.2.c, *supra*.

1. Godavarti 1996 in view of Leary 2002 renders obvious the Common System Limitations

The challenged independent system claims of the '092 Patent (claims 1, 16, 18, 19, 21, 26, 28, and 32) are largely duplicative. They each include a large number of identical limitations, referred to hereinafter as the "Common System Limitations." For efficiency and simplicity's sake, the Petition will first address how Godavarti and Leary render the Common System Limitations obvious, and will then turn to the small number of differences between individual claims.

	Common System Limitations
	A system for sorting a mixture of stained particles, including stained particles having a characteristic A and stained particles having a characteristic B, the system comprising:
a.	a fluid delivery system for delivering a fluid containing the stained particles in a flow path;
b.	an electromagnetic radiation source for exciting fluorescence emissions from the stained particles having characteristic A and the stained particles having characteristic B in the flow path;
c.	a photodetector for detecting the fluorescence emissions from the stained particles;
d.	a processor in communication with the photodetector for classifying the stained particles according to their fluorescence emissions as either particles having characteristic A or particles having characteristic B;
e.	a sorting system for sorting the stained particles according to the classification to provide at least one population containing desired particles;
f.	an analog to digital converter for sampling a time-varying analog output from the photodetector and providing an output including digital information corresponding to the time-varying analog output wherein the time-varying analog output and the corresponding digital information being indicative of characteristic A or characteristic B; and
g.	a digital signal processor for analyzing and classifying the digital information and providing a sorting signal to the sorting system as a function of the analyzed and classified digital information.

a. "A system for sorting a mixture of stained particles, including stained particles having a characteristic A and stained particles having a characteristic B"

Godavarti 1996 renders obvious "a system for sorting a mixture of stained particles, including stained particles having a characteristic A and stained particles having a characteristic B." Specifically, Godavarti 1996 employs a "Coulter Elite flow cytometer/cell sorter," which is a system for classifying and/or sorting particles. Ex. 1005 at 331; Ex. 1003 at ¶206. The classified particles include "WEHI lymphoma cells and chicken red blood cells (CRBCs)" that "were fixed and stained . . . ." *Id.*

Godavarti 1996 modified the Coulter Elite flow cytometer/cell sorter to use digital processing. *Id.* at 331. However, Godavarti 1996 recognized that the digital electronics available in 1996 were not fast enough to perform real-time cell sorting. Ex. 1003 at ¶¶164-166. Specifically, Godavarti 1996 stated that "the design of the transient capture and processor board combination permits the capture of only a subset of the pulses generated by the flow cytometer." *Id.* at 339. Thus, while the system of Godavarti 1996 was capable of classifying stained particles using a DSP, the commercially available DSPs in 1996 were not powerful enough to provide this processing in real-time, which was required to support the sorting of cells.

Critically, Godavarti 1996 recognized not only this problem, but that it would be resolved in the future when more powerful DSP units became available that would support real-time sorting ::

> [C]lassification [was] implemented in software by using the C programming language. For the purposes of this comparative analysis, the algorithms were run on a Sun Microsystems computer work station to take advantage of the convenient sohare-development environment. However, *for real-time applications, the software would be compiled to run on the DSP chip in the digital analysis system*.

Id. at 333 (emphasis added).

And, in fact, by the priority date of the '092 Patent, commercially available DSPs and related electronics (e.g., ADCs) had increased in speed to the point where they were capable of classifying particles in real time. Ex. 1003 at ¶¶211-214. This was known to those of skill in the art, and it would have been obvious to that person that the digital data acquisition system of Godavarti 1996 could be adapted to use these faster electronics. *Id*. For example, Leary 2002 disclosed a "High Speed Cell Sorter" using a "digital signal processing board." Ex. 1003 at ¶176, ¶178; Ex. 1006 at 204-5, 208. As another example, a person of ordinary skill in March 2002 would have been aware of the TigerSHARC DSP, which was capable of real-time processing, and which is the same DSP used by the '092 patent inventors. *Id*. at ¶212; Ex. 1019 (TigerSHARC DSP Spec Sheet dated

March 2002); Ex. 1032 (TigerSHARC Data Sheet dated February 2002). One of ordinary skill would have recognized that Godavarti 1996 could be used with faster DSPs, such as the TigerSHARC DSP chip disclosed in Exs. 1019 and 1032, to sort particles in real time. And as a matter of common sense, a next-generation DSP would have been used alongside other electronics that allow one to take advantage of the faster DSP speed. Ex. 1003 at ¶¶221. For example, one of ordinary skill would know to use an ADC that was capable of sampling at a rate sufficient for real-time performance. *See id*. at ¶¶218-219.

Thus by 2002, based on the guidance within Godavarti 1996 itself, one of ordinary skill would have been motivated to use faster electronics in Godavarti 1996 systems once those faster and more capable electronics became available. *Id*. at ¶213. The fact that others (including Leary 2002) *were* using DSPs to analyze, classify, and sort cells in flow cytometers by 2002 proves this. *See* §§ IV.C.2.b and IV.C.2.c, above, discussing Leary 2002 and the BD FACSDiVa machine. Indeed, a real-time classification system using a DSP chip was expressly contemplated by Godavarti 1996. *Id*. As others in the field recognized, "[t]here is NO DOUBT that digital electronics … is the wave of the future—for the good reason that the data we get will be far superior." Ex. 1012 (discussing, *inter alia*, the BD DiVA machine). Thus, there was a clear motivation from the prior art and known to the skilled person to use digital electronics in a flow cytometer/cell sorter to support real time sorting applications.

b. "a fluid delivery system for delivering a fluid containing the stained particles in a flow path"

Godavarti 1996 also disclosed a fluid delivery system for delivering a fluid containing the stained particles in a flow path. Specifically, Godavarti 1996 employed a "Coulter Elite flow cytometer/cell sorter" that included a fluid containing the stained cells in a flow path. Ex. 1005 at 331. Ex. 1003 at ¶207.

c. "an electromagnetic radiation source for exciting fluorescence emissions from the stained particles having characteristic A and the stained particles having characteristic B in the flow path"

Godavarti 1996 also disclosed an electromagnetic radiation source for exciting fluorescence emissions from the stained particles having characteristic A and the stained particles having characteristic B in the flow path. Specifically, Godavarti 1996 included a "488 nm argon laser" to excite fluorescence emissions from the stained particles. Ex. 1005 at 331; Ex. 1003 at ¶208.

d. "a photodetector for detecting the fluorescence emissions from the stained particles"

Godavarti 1996 also disclosed a photodetector for detecting the fluorescence emissions from the stained particles. Specifically, Godavarti 1996 system included a "photomultiplier," which detected the fluorescent emissions. Ex. 1005 at 331; Ex. 1003 at ¶209.

e. "a processor in communication with the photodetector for classifying the stained particles according to their fluorescence emissions as either particles having characteristic A or particles having characteristic B"

Godavarti 1996 also disclosed a processor in communication with the photodetector for classifying the stained particles according to their fluorescence emissions as either particles having characteristic A or particles having characteristic B. Specifically, the Godavarti 1996 utilized a "digital pulse processing system" that was housed in "a personal computer based on the Intel 80486 processor." *Id.*; Ex. 1003 at ¶210.

f. "a sorting system for sorting the stained particles according to the classification to provide at least one population containing desired particles"

Godavarti 1996 would have rendered obvious "a sorting system for sorting the stained particles according to the classification." As explained above for the preamble, the speed of digital processing in Godavarti 1996 was limited by the electronics available in 1996. *See, supra,* at V.A.1.a. By the priority date of the '092 Patent, however, the speed of electronics, including DSPs, had increased to the point where they could support real-time classification. *Id.* One of ordinary skill would have been aware of the faster DSPs (*e.g.*, Leary 2002, the BD FACSDiva, and the TigerSHARC DSP) and it would have been obvious and a matter of routine effort for that person to adapt the system of Godavarti 1996 to use faster electronics. *Id.* Godavarti 1996 itself identified the benefits of using digital processing relative to analog processing, and explained the only limitation in 1996 in doing so was the speed of the available DSPs , a factor that no longer was an impediment by March of 2003. *Id.* Thus, when more powerful digital signal processing units became available, speed ceased to be an obstacle to their use for real-time classification of cells in flow cytometers. At that point, which was before March of 2003, one of ordinary skill would have been motivated to use such faster electronics to obtain the advantages of digital processing identified and proposed by Godavarti 1996. *Id.*

g. an analog to digital converter for sampling a time-varying analog output from the photodetector and providing an output including digital information corresponding to the time-varying analog output wherein the time-varying analog output and the corresponding digital information being indicative of characteristic A or characteristic B

Godavarti 1996 employed an analog-to-digital converter that sampled the time-varying analog output of a photodetector at a rate of 20 MHz. Ex. 1005 at 331. The output of the ADC was "digital information corresponding to the time-varying analog output" and both the analog signal and the corresponding digital information comprised waveform pulses that indicated the presence of characteristics in a cell. Ex. 1003 at ¶220. Indeed, Godavarti 1996 disclosed the use of "digital sampling in which the *complete pulse waveforms* are digitalized" and Godavarti 1996 employed a processor to detect waveform pulses in the digitalized data and classify cells based on those pulses. *Id.*

Godavarti 1996 samples at 20 MHz. Ex. 1005 at 331. As explained above, Patent Owner may contend that "sampling" should be construed to mean sampling at a rate between about 25 to 200 MHz. Even if Patent Owner's construction were adopted, it would not render the claims patentable over Godavarti 1996, given that 20 MHz is effectively indistinguishable (if not within) the lower end of this range; namely, it is either "about" 25 MHz or would make obvious the use of a rate that of about 25 MHz. Ex. 1003 at ¶216. In fact, it would have been obvious to use any reasonable sampling rate—including 25 to 200 MHz—depending upon the application for which one were building a flow cytometry system (e.g., the type of cell to be sorted) and the other attributes of the DSP, laser, and memory capacity. *Id* at ¶¶216-219. In other words, one of ordinary skill would have known to choose an ADC that samples at a rate sufficient to produce enough data points to characterize the cells of interest based upon the chosen system parameters. *Id*. ADCs that sampled at rates of 25 to 200 MHz were widely available at the time of the invention (*see, e.g.,* Ex. 1020 (Oct. 30, 2001 14-BIT Analog to Digital Converter)) and there was nothing unexpected about sampling in this range. Ex. 1003 at ¶219.

Patent Owner may also contend that Godavarti 1996 did not suggest the claimed ADC because Godavarti 1996 digitized only a subset of the signal output of the photodetector. This argument fails for three reasons. First, by definition, an

ADC digitizes an analog signal by "sampling" that signal. Sampling occurs at discrete points in time (i.e., at a sampling rate) and therefore a digital representation of an analog signal is always made up of a discrete, limited number of samples. Ex. 1003 at ¶216. In other words, there is no such thing as an infinite sampling rate. *See* Ex. 1021 (Zilmer 1994) at 105 ("By definition, the values of a continuous analog signal can be infinitely variable; analog-to-digital conversion forces the amplitude values to one of a finite number of values at a discrete set of time intervals."). Thus, every ADC—including the ADC used in the '092 Patent—digitizes "only a subset" of the signal output. Ex. 1003 at ¶216.

Second, the claims contain no requirement that any particular portion of the analog signal be sampled, or that the digital information somehow correspond to the "entire" analog signal (and indeed it is unclear how one could determine how many samples constitutes the "entire" signal). Instead, the claims require only that the output "include" digital information (in any amount) that corresponds to the analog signal. In other words, the claims do not require the ADC to perform a digital conversion of the entire analog signal. Ex. 1003 at ¶216. Moreover, the claims contain no requirement that a portion of each and every waveform pulse in an analog signal be captured into digital data.

Third, even if the claims of the '092 Patent could be read to require the digitalization of some portion of every waveform pulse in the analog signal, such digitalization would have been obvious when using faster DSPs to sort particles in real-time, as expressly contemplated by Godavarti 1996. Ex. 1003 at ¶216. Indeed, Godavarti 1996 taught that the speed of the digital processor—not the speed of the ADC—was the limiting factor in capturing and classifying data from the photodetector. Godavarti 1996 referred to a 1994 article by Zilmer as describing portions of the digital data acquisition system used. Ex. 1005 at 331. Zilmer 1994 disclosed that a transient capture board ("TCB") performed the analog-to-digital conversion. Ex. 1021 at 103. The TCB stored the converted digital data in a first-in-first-out ("FIFO") buffer. *Id*. The digital processor extracted data from this FIFO buffer and performed the required processing. *Id*. The sooner the processor extracted a piece of data from the buffer, the sooner new data could be written to the buffer. *See id*. Thus, a faster digital processor would have allowed data to move more quickly through buffer and the ADC as a whole. *Id*. at 113 ("The data transfer rate is ***limited by that of the processor board*** (approximately 3 million words/s). Since at the lowest sampling rate the TCB produces an output of 8 million words/s, the FIFO fills and continuous sampling is therefore not possible.") (emphasis added). Godavarti 1996 expressly contemplated real-time sorting of particles using a DSP. Ex. 1005 at 333 ("[F]or real-time applications, the software would be compiled to run on the DSP chip."); *id*. at 339 ("[I]n the next-generation digital data acquisition system, our design calls for real-time performance.”). To accomplish this real-time DSP sorting, it would have been obvious (and necessary) to use a DSP (and ADC) that was capable of processing data at the speeds required for real-time performance. Ex. 1003 at ¶¶211-214; 217-219. And as explained above, such DSPs were widely available by the priority date of the ’092 Patent, including as evidenced by Leary 2002. *See, supra,* at V.A.1.a.

h. a digital signal processor for analyzing and classifying the digital information and providing a sorting signal to the sorting system as a function of the analyzed and classified digital information

Godavarti 1996 also disclosed a DSP for analyzing and classifying the digital information and would thus have rendered obvious the further limitation of “providing sorting signal to the sorting system as a function of the analyzed and classified digital information.” Specifically, the Godavarti 1996 system employed a digital pulse processing system housed in a personal computer based on the Intel 80486 processor that analyzed and classified digital information. *Id.* Godavarti 1996 described numerous algorithms that are used to extract features of the waveform pulses from the digital information and discriminate the waveform pulses as a function of the extracted features. Ex. 1005 at 331-32; Ex. 1003 at ¶160. While Godavarti 1996 acknowledged that real time sorting was limited by the speed of electronics available in 1996, it would have been obvious to use the faster DSPs once they became available to classify and sort particles in real time, which had occurred before March of 2003. *See, supra,* at V.A.1.a. Classifying and sorting particles in real-time using a DSP required that the DSP to provide sort signals as a function of the analyzed and classified digital information and thus this limitation would have been obvious by 2003.

2. Godavarti 1996 In View Of Leary Renders Obvious The Additional Limitations Of Claim 1

As discussed above, Godavarti 1996 in view of Leary would have rendered obvious the Common System Limitations. Claim 1 further requires that "corresponding digital information include[s] a series of waveform pulses." Specifically, Godavarti 1996 disclosed that "pulse waveforms" emitted by the photomultiplier are digitized. Ex. 1005 at 330; Ex. 1003 at ¶¶223. Claim 1 further requires that:

> the digital signal processor includes instructions for detecting the waveform pulses corresponding to the digital information, instructions for extracting features in the detected waveform pulses, and instructions for discriminating the detected waveform pulses as a function of their extracted features.

Ex. 1001, claim 1. Godavarti 1996 disclosed an Intel 80486 processor, along with numerous algorithms, that were used to detect and extract features in the waveform pulses, and to discriminate based on those features. Ex. 1005 at 331; Ex. 1003 at ¶224. Thus, Godavarti 1996 rendered obvious claim 1.

Patent Owner may argue that Godavarti 1996 did not disclose the claimed feature extraction because Godavarti 1996 discussed analyzing pulse features based in the "frequency domain" instead of the "time domain." However, the claims contain no requirement that the features extracted be limited to the time domain. *See, e.g.,* Ex. 1001 at 213:7-12. Regardless, Godavarti 1996 disclosed the previous classification of particles using time-domain features. Ex. 1005 at 330 (referring to previous classification based on "pulse height, pulse integral, and pulse width feature values").

3. Godavarti 1996 In View Of Leary 2002 Renders Obvious Claim 2.

Claim 2 depends from claim 1 and specifies:

> the digital signal processor detects portions of the digital information corresponding to the waveform pulses and classifies the detected portions, and wherein the digital signal processor provides the sorting signal as a function of said detected and classified portions.

Ex. 1001, claim 2. Specifically, Godavarti 1996 disclosed the use of normalization. Ex. 1005 at 332; Ex. 1003 at ¶227. Normalization is the where the "amount of the individual pulses used in calculating the features is normalized with respect to the peak. This was done by measuring the pulse height and then, for feature computation, employing only those waveform values ≥ 20% of the pulse height. This minimized the noise arising due to baseline effects." *Id.* Normalization only employed a portion of the digital information, specifically only those waveform values greater than or equal to 20% of the pulse height. *Id*.; Ex. 1003 at ¶227. Normalization is identified as an algorithm that may be employed in a digital pulse processing system to calculate characteristic feature vectors for each waveform. *Id*. Thus, the processor running the normalization algorithm classifies the detected portions of the digital information. Ex. 1003 at ¶227. It would have been obvious to a person of ordinary skill in the art to provide a sorting signal based on that classification. *Id*. Thus, Godavarti 1996 discloses the additional element of claim 2, and thereby would have rendered this claim obvious.

4. Godavarti 1996 in view of Leary 2002 renders obvious Claim 3.

Claim 3 depends from claim 1 and recites "the particles are cells and characteristics A and B relate to physical characteristics of the cells." Specifically, Godavarti 1996 disclosed the classification of cells, including WEHI lymphoma cells and chick red blood cells. Ex. 1005 at 331; Ex. 1003 at ¶230. Thus, Godavarti 1996 discloses the additional element of claim 3, and thereby would have rendered this claim obvious.

5. Godavarti 1996 in view of Leary 2002 renders obvious Claim 5

Claim 5 depends from claim 1 and recites that:

> the flow path is formed to contain particles following generally one after another in a series which includes sequential sets of particles, including first particle sets each including one or more particles having characteristic A, second particle sets each including one or

> more particles having characteristic B, and third particle sets each including two or more closely spaced particles at least one of which has characteristic A and at least one of which has characteristic B.

Ex. 1001, claim 5. Godavarti 1996 shows this additional element. Specifically, Godavarti 1996 discloses a digital data acquisition system for use with a Coulter Elite flow cytometer / cell sorter. Ex. 1005 at 331. The Coulter Elite flow cytometer / cell sorter was a droplet sorter, and was known to include a conventional fluid system. Ex. 1003 at ¶233.

As the '092 patent recognizes, in any random mixture, the sequence of cells will be divided into particle series. Ex. 1001 at col. 126:48-61. Claim 5 simply describes this phenomenon which occurs when any mixture of particles passes through a flow cytometer. *See* Ex. 1003 at ¶233. For example, in any droplet cell sorting system, the droplets comprise sequential sets of particles, and some droplets will include one or more particles having characteristic A (i.e., a first particle set) while other droplets will include one or more particles having characteristic B (i.e., a second particle set). Furthermore, in any droplet sorting system, at least some droplets will occasionally contain a series of cells, one of which may be an unwanted cell and one of which may be a desired cell. Ex. 1003 at ¶233. These droplets thus constitute a third particle set that include two or more closely spaced particles where at least one has characteristic A (desired cell) and one has characteristic B (unwanted cell). *See id*. Thus, Godavarti 1996 discloses the additional element of claim 5, and thereby would have rendered this claim obvious.

6. Godavarti 1996 in view of Leary 2002 renders obvious Claim 6

Claim 6 specifies the system of claim 1 where "the sorting system is a droplet sorting system or a photo-damage sorting system or a fluid-switching sorting system," Because Godavarti 1996's Coulter Elite flow cytometer / cell sorter was a droplet sorting system, Godavarti 1996 discloses this additional requirement of claim 6. Ex. 1005 at 331; Ex. 1003 at ¶236. Thus, Godavarti 1996 discloses the additional element of claim 6, and thereby would have rendered this claim obvious.

7. Godavarti 1996 in view of Leary 2002 renders obvious Claim 7

Claim 7 depends from claim 1 and recites:

> the digital signal processor includes a pulse detection processor for detecting waveform pulses represented by the digital information, and in that the digital signal processor classifies the digital information as a function of the detected waveform pulses.

As described in regards to claim 1, Godavarti 1996 disclosed an Intel 80486 processor that detected waveform pulses that were digitized, employed numerous algorithms to extract features in the detected waveform pulses, and discriminated based on those features. *See, supra*, at V.A.1-2; Ex. 1003 at ¶239. Thus, Godavarti 1996 discloses the additional element of claim 7, and thereby would have rendered this claim obvious.

8. Godavarti 1996 in view of Leary 2002 renders obvious Claim 8

Claim 8 depends from claim 1 and recites "wherein the digital signal processor includes a sort processor responsive to the classifying for providing the sort signals to the sorting system." As explained above, a "sort processor" is simply "hardware that generates sorting instructions." *See, supra,* at IV.D.3.; Ex. 1003 at ¶242. Also as explained above, it would have been obvious to use the system of Godavarti 1996 with faster DSPs that had become available before March of 2003 to make it possible to sort cells in real time. *See, supra,* at V.A.1.a. When a DSP is used as described in Godavarti 1996 to sort cells in real time, it is "hardware that generates sorting instructions" and therefore is a "sort processor." Thus, Godavarti 1996 discloses the additional element of claim 8, and thereby would have rendered this claim obvious.

9. Godavarti 1996 in view of Leary 2002 renders obvious Claim 9

Claim 9 depends from claim 8 and specifies "the sort processor enumerates the number of classified particles having characteristic A or having characteristic B." As explained above, the broadest reasonable interpretation of this term is to "keep track of or count the number of cells classified as having characteristic A and characteristic B."

Godavarti 1996 disclosed the accuracy of classification decisions for different cell types. Ex. 1005 at 337, Table 2. One of ordinary skill would have understood that one way to arrive at these accuracy measurements would have been to keep track of the number of cells classified as having each characteristic. Ex. 1003 at ¶245. Furthermore, it would have been trivial for one of ordinary skill to store the classification decisions of the DSP. *Id.* Indeed, storing a classification decision would require only a few simple lines of code in which each classification was written to a table, database, array, or other storage location. *Id.* Thus, Godavarti 1996 discloses the additional element of claim 9, and thereby would have rendered this claim obvious.

10. Godavarti 1996 in view of Leary 2002 renders obvious Claim 11

Claim 11 depends from claim 1 and specifies "the digital signal processor extracts features from the waveform pulses corresponding to the digital information." As explained with regard to claim 1, Godavarti 1996 disclosed use of an Intel 80486 processor that detected waveform pulses that had been digitized, employed numerous algorithms to extract features in the detected waveform pulses, and discriminated based on those features. *See, supra*, at V.A.1-2; Ex. 1003 at ¶248. Godavarti 1996 would have rendered obvious providing a sorting signal for all the reasons discussed above with respect to claim 1. *See, supra*, at

V.A.1.f; Ex. 1003 at ¶249. Thus, Godavarti 1996 discloses the additional element of claim 11, and thereby would have rendered this claim obvious.

11. Godavarti 1996 in view of Leary 2002 renders obvious Claim 12

Claim 12 depends from claim 11 and recites:

> the digital signal processor includes a pulse detection processor for detecting waveform pulses represented by the digital information and for classifying the detected waveform pulses and the time varying output includes waveform pulses wherein the waveform pulses and the corresponding digital information are indicative of characteristic A or characteristic B and the a digital signal processor discriminates the digital information as indicative of characteristic A or as indicative of characteristic B and provides a sorting signal to the sorting system as a function of the discriminated digital information.

Ex. 1001, claim 12. As explained with regard to claim 1, Godavarti 1996 disclosed an Intel 80486 processor that detected waveform pulses that had been digitized, employed numerous algorithms to extract features in the detected waveform pulses, and discriminated based on those features. *See, supra,* at V.A.1.; Ex. 1003 at ¶252. In addition, it would have been obvious to use the system of Godavarti 1996 with faster DSPs as they became available in order to sort cells in real time. *See, supra,* at V.A.1.f.; Ex. 1003 at ¶253. When such a faster DSP is used as described in Godavarti 1996 to sort cells in real time, it would discriminate the digital information as indicative of particular characteristics and provided a sorting signal to the sorting system as a function of the discriminated digital information, as provided in claim 12. *Id*. Thus, Godavarti 1996 discloses the additional element of claim 12, and thereby would have rendered this claim obvious.

12. Godavarti 1996 in view of Leary 2002 renders obvious Claim 13

Claim 13 depends from claim 11 and specifies that "the extracted features corresponds to one or more of the following features: pulse area, pulse peak, pulse inner area, pulse width, pulse gaussianity, pulse lagging peak or pulse slope." Specifically, Godavarti 1996 identified multiple algorithms employed in the digital pulse processing system to extract features including pulse integral (i.e. pulse area), and pulse height (i.e. pulse peak). Ex. 1005 at 331; Ex. 1003 at 256. Thus, Godavarti 1996 would have rendered obvious claim 13.

13. Godavarti 1996 in view of Leary 2002 renders obvious Claim 16

In addition to the Common System Limitations, claim 16 specifies "the digital signal processor includes a data management processor for assembling the digital information into a continuous stream." Godavarti 1996 disclosed that "[a]n alternative to analog pulse processing involves the use of digital sampling, in which the ***complete pulse waveforms are digitized*** at the point of detection." Ex. 1005 at 330 (emphasis added). Godavarti 1996 employed a processor that detected waveform pulses in the digitalized data and employed algorithms to extract features in the detected waveform pulses, and classified cells based on those pulses. *See, supra,* at V.A.1-2. Thus, Godavarti 1996's processor assembled the digital information into a digital stream that is a rendition of a pulse (i.e., a continuous stream) which constitutes the claimed data management processor. Ex. 1003 at ¶259. Thus, Godavarti 1996 in view of Leary 2002 would have rendered obvious claim 16.

14. Godavarti 1996 in view of Leary 2002 renders obvious Claim 18

In addition to the Common System Limitations, claim 18 specifies "the analog to digital converter further comprises a continuous sampling rate." As explained above, "continuous sampling rate" means "sampling to produce digital information corresponding to the analog output." In Godavarti 1996, the ADC sampled at a rate of 20 MHz. Ex. 1005 at 331; Ex. 1003 at ¶261. The digital information resulting from this sampling corresponded to the photodetector's analog output. If the digital information did not correspond to the analog output, it would not have been possible to use it to accurately classify cells. Ex. 1003 at ¶261.

Claim 18 also further specifies:

> "a filter for filtering the analog output at a frequency equal to or less than one half the continuous sampling rate of the analog to digital converter, wherein the analog to digital converter converts the filtered analog output into corresponding digital information, and in that the digital signal processor classifies the digital information as a function of a discrimination boundary."

Ex. 1001 at Cl. 18. The ’092 patent recognizes that “[i]t is well understood that when sampling a time varying signal it is necessary for the sampling frequency to be at least twice the maximum frequency contained in the signal being sampled. This is known as the Nyquist sampling theorem.” Ex. 1001 at col. 54:41-54; Ex. 1003 at ¶262. Filters, including low-pass filters such as the one disclosed by the ’092 Patent, were commercially available and well known as of the priority date. *Id*. Depending on the chosen sampling rate, it would have been obvious to one of ordinary skill to use such a filter to keep the frequency of the analog signal at less than half of the sampling rate—as required by the Nyquist theorem.

As explained above, Godavarti 1996 also disclosed an ADC to convert analog output to corresponding digital information. *See, supra,* at V.A.1.g. Moreover, Godavarti 1996 disclosed a DSP that “classifies the digital information as a function of a discrimination boundary.” In particular, Godavarti 1996 disclosed the use of neural networks that can be used to form “decision boundaries” which are used to discriminate between cells. *See, e.g.,* Ex. 1005 at 331 (“The strength of neural networks lies in their ability to draw arbitrarily complex decision boundaries between different clusters.”) These decision boundaries were discrimination boundaries. Ex. 1003 at ¶262. Thus, Godavarti 1996 in view of Leary 2002 rendered obvious claim 18.

15. Godavarti 1996 in view of Leary 2002 renders obvious Claim 19.

The only material difference between independent claim 18 and independent claim 19 is that claim 19 omits the final phrase in limitation "h" that is present in claim 18. Because Godavarti 1996 in view of Leary 2002 rendered obvious claim 18, claim 19 would have been obvious as well.

16. Godavarti 1996 in view of Leary 2002 renders obvious Claim 21.

In addition to the Common System Limitations, claim 21 specifies "the analog to digital converter further comprises a continuous sampling rate." Godavarti discloses this limitation as described above with respect to claim 18. *See, supra*, at V.A.14. Godavarti 1996 also rendered obvious a sampling rate of "about 105 MHz or higher," as required by claim 21. Although Godavarti 1996 disclosed a sampling rate of 20 MHz, one of ordinary skill would understand that a higher sampling rate could have been used. Ex. 1003 at ¶270. By 2002, ADCs having a higher sampling rate were well known, and the particular 105 MHz ADC used in the '092 patent was commercially available. *Id.*; Ex. 1020. It was well understood that a faster sampling rate would provide more data about the pulse. *See* Ex. 1003 at ¶219. It is simply common sense that one of ordinary skill in the art would have understood that a higher sampling rate provided by these off-the-shelf ADCs might provide additional data that could be useful in analyzing and classifying cells, depending on the application. Thus, Godavarti 1996 in combination with Leary 2002 rendered obvious claim 21.

17. Godavarti 1996 in view of Leary 2002 renders obvious Claim 28

In addition to the Common System Limitations, claim 28 specifies:

> "the digital signal processor determines background characteristics of the time-varying analog output from the digital information; detects waveform pulses represented by the digital information as a function of the determined background characteristics; and provides a sorting signal to the sorting system as a function of the detected waveform pulses."

Ex. 1001 at Cl. 28. Godavarti 1996 described 14 algorithms that were "employed in the digital pulse processing system." Ex. 1005 at 331; Ex. 1001 at ¶272. The first algorithm was "baseline restoration" and involved the calculation of a "baseline value" by averaging "8,000 digital samples taken in the absence of pulse waveforms." *Id.* Another algorithm normalized "[t]he amount of the individual pulses used in calculating the features" in order to "minimize[] the noise arising due to baseline effects." *Id.* at 332. The normalized feature vectors were used with Godavarti 1996's artificial neural network for "automated cell classification based on these feature values." *Id.* at 331. Godavarti 1996 also disclosed that the neural network classification was "implemented in software" and that "for real-time applications, the software would be compiled to run on the DSP chip in the digital analysis system." *Id*. at 333. Thus, Godavarti 1996 disclosed the use of a DSP to determine background characteristics of the analog signal such as baseline noise and detected waveform pulses as a function of the background characteristics. Ex. 1003 at ¶272. As explained above, Godavarti 1996 rendered obvious providing a sorting signal because DSPs had increased in speed to the point where real-time sorting was possible by the priority date of the '092 Patent. *See, supra,* at V.A.1.h; Ex. 1003 at ¶272. Thus, Godavarti 1996 in view of Leary 2002 rendered obvious claim 28.

18. Godavarti 1996 in view of Leary 2002 renders obvious Claim 32

In addition to the Common System Limitations, claim 32 specifies:

> "the digital processor employs a detection threshold for defining waveform pulses corresponding to the digital information, and wherein said detection threshold is a function of a background mean estimate and a standard deviation of the digital information computed within a moving window of samples ending with the current sample."

Ex. 1001 at Cl. 32. As explained above with respect to claim 28, Godavarti 1996 used at least 14 algorithms to calculate "feature vectors" which were used by an artificial neural network to determine "decision boundaries" for "automated cell classification." *See, supra,* at V.A.17; Ex. 1003 at ¶275; *see* Ex. 1005 at 332 ("[F]eature values were derived for the individual pulse waveforms, and these were presented as the inputs to the [neural] network."); *id*. at 338 ("Neural networks . . .

function through a straightforward training process that requires minimal user interaction and, thereafter, can handle large amounts of data, efficiently extracting the desired features or drawing the ***appropriate decision boundaries***.") (emphasis added). The algorithms used to calculate the feature vectors included a background mean estimate ("baseline value") and standard deviations (*see* algorithms 5, 8, and 11). *Id*. at 331-32. Thus, Godavarti 1996 employed a decision boundary (i.e., detection threshold) that was a function of a background mean estimate and a standard deviation of the digital information. Ex. 1003 at ¶175. Thus, Godavarti 1996 in view of Leary 2002 rendered obvious claim 32.

19. Godavarti 1996 in view of Leary 2002 renders obvious Claim 40

Godavarti 1996 rendered obvious "a method for sorting a mixture of stained particles, including stained particles having a characteristic A and stained particles having a characteristic B." Specifically, Godavarti 1996 employed a Coulter Elite flow cytometer/cell sorter, which was a system for classification and/or sorting particles. Ex. 1005 at 331; Ex. 1003 at ¶278. Such particles included "WEHI lymphoma cells and chicken red blood cells (CRBCs)" that "were fixed and stained . . . ." *Id*. As explained above with regard to claim 1, performing real-time sorting with the system of Godavarti 1996 would have been obvious by the priority date of the '092 Patent because faster DSPs were widely available, as taught for example by Leary 2002. *See, supra,* at V.A.1.a; Ex. 1003 at ¶283.

Godavarti 1996 disclosed the step of "forming a stream containing stained particles." Specifically, Godavarti 1996 employed a "Coulter Elite flow cytometer/cell sorter" that included a stream containing the stained cells as explained above regarding claim 1. *See, supra,* at V.A.1.b; Ex. 1003 at ¶279.

Godavarti 1996 disclosed the step of "generating an analog output with a photodetector detecting stained particles in the stream." Specifically, Godavarti 1996 system included a "photomultiplier." Ex. 1005 at 331; Ex. 1003 at ¶280. The photomultiplier detected pulse waveforms that are emitted from stained particles in the stream of the flow cytometer as explained above regarding claim 1. *See, supra,* at V.A.1.d; Ex. 1003 at ¶280.

Godavarti 1996 disclosed the step of "sampling the analog output from the photodetector with an analog to digital converter and generating corresponding digital information wherein the analog output is indicative of characteristic A or characteristic B." *See, supra,* at V.A.1.g (addressing claim 1).Specifically, the Godavarti 1996 system employed an ADC that sampled the pulse waveforms at a rate of 20 MHz. Ex. 1005 at 331.; Ex. 1003 at ¶281.

Godavarti 1996 disclosed the step of:

> "analyzing and classifying the digital information, wherein the step of analyzing and classifying further comprises detecting waveform pulses represented by the digital information, extracting features of the waveform pulses from the digital information, and discriminating

> the detected waveform pulses as a function of their extracted features."

Ex. 1001 at Cl. 40. Specifically, as explained above with respect to claim 1, Godavarti 1996 disclosed an Intel 80486 processor that detected waveform pulses that have been digitized, employed numerous algorithms to extract features in the detected waveform pulses, and discriminated based on those features. *See, supra*, at V.A.1-2; Ex. 1003 at ¶282.

Godavarti 1996 rendered obvious "sorting the stained particles as a function of the analyzed and classified digital information" for the reasons discussed above with respect to claim 1's limitation of "a sorting system for sorting the stained particles according to the classification." *See, supra*, at V.A.1.f; Ex. 1003 at ¶283.

Godavarti 1996 did not report that had had performed the step of "collecting the sorted particles" because, as explained above, Godavarti 1996 did not report results from sorting due to the speed limitations of electronics available in 1996. *See, supra,* at V.A.1.a; Ex. 1003 at ¶284. However, as a matter of common sense, one of ordinary skill would have known to collect the sorted particles into one or more populations based on the characteristic for which sorting was conducted. Ex. 1003 at ¶284. Indeed, collection into populations was the reason one would engage in sorting in the first place and systems that performed such collection were well known. *Id*. Thus, Godavarti 1996 in view of Leary 2002 renders obvious claim 40.

20. Godavarti 1996 in view of Leary 2002 renders obvious Claim 41

Claim 41 depends on claim 40, and further requires that "the particles are cells and characteristics A and B relate to physical characteristics of the cells." Godavarti 1996 disclosed the classification of cells based on their physical characteristics, including WEHI lymphoma cells and chick red blood cells. Ex. 1005 at 331; Ex. 1003 at ¶287; *see also* discussion of claim 3 above. Thus, Godavarti 1996 discloses the additional element of claim 41, and thereby would have rendered this claim obvious.

21. Godavarti 1996 in view of Leary 2002 renders obvious Claim 43

Claim 43 depends on claim 40, and further requires:

> "the step of forming the stream to contain particles following generally one after another in a series which includes sequential sets of particles, including first particle sets each including one or more particles having characteristic A, second particle sets each including one or more particles having characteristic B, and third particle sets each including two or more closely spaced particles at least one of which has characteristic A and at least one of which has characteristic B."

Ex. 1001 at 43. Godavarti 1996 discloses this limitation for all the reasons discussed above with respect to claim 5. *See, supra,* at V.A.5; Ex. 1003 at ¶289.

22. Godavarti 1996 in view of Leary 2002 renders obvious Claim 44

Claim 44 depends on claim 40, and further requires "the step of sorting uses a droplet sorting process, or a photo-damage sorting process, or a fluid-switching sorting process." Godavarti disclosed a droplet sorter, as discussed above with respect to claim 6. *See, supra,* at V.A.6; Ex. 1003 at ¶291. Thus, Godavarti 1996 discloses the additional element of claim 44, and thereby would have rendered this claim obvious

23. Godavarti 1996 in view of Leary 2002 renders obvious Claim 45

Claim 45 depends on claim 40, and further requires "the step of defining a decision boundary discriminating between the extracted features representing characteristics A and the extracted features representing characteristic B." As explained above for claim 18, Godavarti 1996 used at least 14 algorithms to calculate "feature vectors" which were employed by an artificial neural network to determine "decision boundaries" which were used for "automated cell classification." *See, supra,* at V.A.14; Ex. 1003 at ¶294; *see* Ex. 1005 at 332 ("[F]eature values were derived for the individual pulse waveforms, and these were presented as the inputs to the [neural] network."); *id*. at 338 ("Neural networks . . . function through a straightforward training process that requires minimal user interaction and, thereafter, can handle large amounts of data, efficiently extracting the desired features or drawing the ***appropriate decision boundaries***.") (emphasis added). Thus, Godavarti 1996 disclosed the step of "defining a decision boundary discriminating between the extracted features representing characteristics A and the extracted features representing characteristic B" and thereby would have rendered obvious claim 45. Ex. 1003 at ¶294.

24. Godavarti 1996 in view of Leary 2002 renders obvious Claim 46

Claim 46 depends on claim 40, and further requires "synchronously sampling the analog output from the photodetector." As explained above in the claim construction section, synchronously sampling meant sampling to produce digital information corresponding to the analog output. Synchronously sampling was also referred to as continuously sampling or streaming acquisition. Ex. 1001 at 54:21-27; Ex. 1003 at ¶296. Godavarti 1996 discloses continuous sampling for all the reasons discussed above with respect to claim 18. *See, supra,* at V.A.14. Thus, Godavarti 1996 discloses the additional element of claim 46, and thereby would have rendered this claim obvious

B. Ground 2: Claims 4, 26-27, 42 and 49 Are Unpatentable Over Godavarti 1996 in View of Leary 2002 and Further In View of Johnson 1999

A person of ordinary skill would have been motivated to combine Godavarti 1996, modified with a faster DSP as disclosed, e.g., in Leary 2002, with Johnson 1999. Both Godavarti 1996 and Johnson 1999 addressed problems associated with the real-time sorting of cells using flow cytometry.

Johnson 1999 discloses a flow cytometry-based system for sorting sperm cells into X- and Y- bearing populations. Ex. 1007 (Johnson 1999); Ex. 1003 at ¶¶192-199. Sperm sorting was one well known application for a cell sorter, and Johnson 1999 shows use of a modified general purpose cell sorter for this purpose . Ex. 1007 at 1323. While Godavarti reported on results of sorting two particular types of cells, Godavarti's work was intended to have a general application, and nothing in Godavarti suggested that it was limited to any particular type of cell. Ex. 1003 at ¶299. Thus, it would have been obvious to apply the improved digital signal processing advances of Godavarti 1996 to the sperm sorting application disclosed in Johnson 1999. *Id*. at ¶297. *See KSR*, 550 U.S. at 417 ("if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

1. Godavarti 1996 and Leary 2002 in Combination With Johnson 1999 Renders Obvious Claim 4.

Claim 4 depends on claim 3, and further requires that the stained particles are stained sperm cells. Godavarti 1996 did not expressly describe the sorting of sperm cells. However, it was well known that flow cytometers using droplet sorters could be used to sort sperm cells, as taught by Johnson 1999. Ex. 1003 at ¶299. Thus, a person of skill in the art would have known that the digital data acquisition system of Godavarti 1996 could be used to sort sperm cells by applying the adaptations to a conventional cell sorter described in Johnson 1999 to enable the sorting of sperm. Moreover, a person of ordinary skill in the art would have known, well prior to the invention date of the ’092 patent, that sorting sperm cells is desirable. Ex. 1003 at ¶299. Thus, a person of ordinary skill in the art would have been motivated to modify the digital data acquisition system disclosed in Godavarti 1996 to enable sorting of sperm cells as taught by Johnson 1999.

2. Godavarti 1996 and Leary 2002 in Combination With Johnson 1999 Renders Obvious Claim 26.

In addition to the Common System Limitations, claim 26 further requires:

> “the digital signal processor classifies the digital information such that a population of the particles having characteristic A and a population of the particles having characteristic B correspond to a computer model of three populations including a first model population of particles having characteristic A, a second model population of particles having characteristic B and a third model population of unaligned particles, said model estimating population statistics for each of the first, second and third model populations.”

Ex. 1001 at Cl. 26. It was well known that in the sorting of sperm cells, a significant number of the sperm cells are not identified as either male or female. Ex. 1003 at ¶303; Ex. 1007 at 1324. Johnson 1999 taught the use of sort windows to differentiate between X- and Y-chromosome-bearing sperm must account for the unaligned sperm cells. Ex. 1003 at ¶303; Ex. 1007 at 1330; *id* at Fig. 3. In particular, Johnson 1999 showed classifying cells into three population models: (1)

X-chromosome-bearing sperm, (2) Y-chromosome-bearing sperm, and (3) X and Y sperm that were not resolved, including because they are unaligned. *Id*.; Ex. 1003 at ¶303; *See also* Ex. 1007 at 1328-29 (discussing orientation). Johnson 1999 also taught the estimation of population statistics for each model, and including populations of unaligned cells. Ex. 1007 at 1330 at Fig. 3 (showing frequency of X and Y bearing populations); *id*. at 1332, Table 1 (showing tracking of % oriented); Ex. 1003 at ¶303. Thus, Godavarti 1996 in view of Leary 2002, and further in view of Johnson 1999 would have rendered obvious claim 26.

3. Godavarti 1996 and Leary 2002 in Combination With Johnson 1999 Renders Obvious Claim 27.

Claim 27 depends from claim 26 and further requires that "the third model population includes two populations of unaligned particles, and the model estimates the population statistics for the two populations of unaligned particles." Johnson 1999 describes a third model population which includes unaligned X-chromosome-bearing sperm cells and Y-chromosome-bearing sperm cells. Ex. 1007 at 1330. In the population that was not properly oriented, the X- and Y-bearing sperm would be expected to occur in roughly equal numbers. Ex. 1003 at ¶307. Thus, the model taught by Johnson 1999 estimates the population statistics for two populations of unaligned particles. *Id*. Thus, Johnson 1999 discloses the additional element of claim 27, and thereby would have rendered this claim obvious.

4. Godavarti 1996 and Leary 2002 in Combination With Johnson 1999 Renders Obvious Claim 42.

Claim 42 depends on claim 41, and further requires that the "particles are sperm cells, and characteristic A is indicative of a live X-chromosome bearing sperm cell and characteristic B is indicative of other than a live X-chromosome bearing cell (~X)." The sorting method of claim 42 would have been obvious for all the same reasons discussed above with respect to claim 4. *See, supra,* at V.B.1; Ex. 1003 at ¶310. Thus, Godavarti 1996 in view of Leary 2002 and Johnson 1999 would have rendered obvious claim 42.

5. Godavarti 1996 and Leary 2002 in Combination With Johnson 1999 Renders Obvious Claim 49.

Claim 49 depends on claim 40, and further requires that

> "the step of classifying the digital information includes classifying the digital information such that a population of the particles having characteristic A and a population of the particles having characteristic B correspond to a computer model of three populations including a first model population of particles having characteristic A, a second model population of particles having characteristic B and a third model population of unaligned particles, said model estimating population statistics for each of the first, second and third model populations."

The sorting method of claim 49 would have been obvious for all the same reasons discussed above with respect to claim 26. *See, supra,* at V.B.2; Ex. 1003 at ¶312.

Thus, Godavarti 1996 in view of Leary 2002 and Johnson 1999 would have rendered obvious claim 49.

C. Ground 3: Claim 10 is Unpatentable Over Godavarti 1996 in View of Leary 2002 and Further in View of Piper 1992

Claim 10 depends from claim 1 and further requires that the electromagnetic radiation source further comprises a pulsed illumination device. Godavarti did not expressly teach use of a "pulsed laser." However, before March of 2003, it was well known that pulsed lasers could be used in flow cytometers, as described in Piper 1992. Ex. 1022 (Piper 1992) at 3.

Piper 1992 identifies the benefits of using pulsed lasers in flow cytometric cell sorting, explaining

> [H]igh repetition rate pulsed lasers have particular advantages in application as flow cytometry sources including high instantaneous illumination intensities (giving high signal levels), relaxed beam focussing [sic] requirements, good beam uniformity and especially wavelength versatility which can be effectively utilised by temporal multiplexing techniques.

Id. One of ordinary skill would have been motivated by this explanation in Piper 1992 to modify Godavarti 1996 to use a pulsed laser, which would have resulted in a cell sorting apparatus of claim 10. Ex. 1003 at ¶¶314, 316. This combination would have been a matter of common sense and would have been seen by the skilled person to be a routine application of known elements to achieve predictable results.

VI. Conclusion

For the foregoing reasons, the Petitioner respectfully requests that Trial be instituted and that claims 1-13, 16, 18-19, 21, 26-28, 32, 40, 41-46, and 49 of the ’092 Patent be cancelled.

Date: April 21, 2016

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PETITION FOR INTER PARTES REVIEW

OF U.S. PATENT NO. 8,198,02

Attachment A:

Proof of Service of Petition

CERTIFICATE OF SERVICE

I hereby certify that on this 21st day of April 2016, a copy of this PETITION FOR INTER PARTES REVIEW has been served by Federal Express on the following address for patent owner(s):

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PETITION FOR INTER PARTES REVIEW

OF U.S. PATENT NO. 8,198,02

Attachment B:

List of Evidence and Exhibits Relied Upon in Petition

Exhibit No.	Reference Name
1001	U.S. Patent No. 8,198,092 (filed May 17, 2011)
1002	U.S. Patent No. 8,198,092 File Wrapper
1003	Declaration of J. Paul Robinson
1004	Curriculum Vitae of J. Paul Robinson
1005	Godavarti, M. et al., “Automated Particle Classification Based on Digital Acquisition and Analysis of Flow Cytometric Pulse Waveforms.” *Cytometry* 24 (1996): 330-339. (Godavarti 1996)
1006	Leary, J.F., et al. “Advanced real-time classification methods for flow cytometry data analysis and cell sorting.” *Proc. SPIE* 4622, Optical Diagnostics of Living Cells V, 204 (May 28, 2002). (Leary 2002)
1007	Johnson, L.A. et al., “Sex Preselection: High-Speed Flow Cytometric Sorting of X and Y Sperm for Maximum Efficiency.” *Theriogenology* 52:1323-41 (1999). (Johnson 1999)
1008	Durack, G., “Cell—Sorting Technology.” *Emerging Tools for Single-cell Analysis* (2000): 1-20. (Durack 2000)
1009	Ormerod, M.G., “Analysis of DNA—General Methods.” *Flow Cytometry: A Practical Approach, ed 2* (2000): 83-97. (Ormerod 2000)
1010	“BD’s DiVa” post by Mario Roederer, Feb. 27, 2001
1011	Shapiro, Howard M., “Principles of Data Acquisition and Display.” *Methods in Cell Biology* 63 (2001): 149-167 (Shapiro 2001)
1012	“Digital Flow Electronics????” post by Mario Roederer, May 17, 2001
1013	“HiPerFACS and DIVA” post, Feb. 27, 2001
1014	“The Digital ‘Disadvantage’?” post by Mario Roederer, Jan. 23, 2002
1015	“The Digital ‘Disadvantage’?” post by Kathleen Schell, Jan. 24, 2002
1016	“BD vs. Coulter: quality and precision.” post by Joern Schmitz, Oct. 16, 2001
1017	BD FACSDiVa Option White Paper

Exhibit No.	Reference Name
1018	"FACSVantage DIVA specs and performance" post by Marty Bigos, May 2, 2001
1019	TigerSHARC DSP Hardware Specification
1020	"14-BIT Analog to Digital Converter" Oct. 30, 2001
1021	Zilmer, Nick A., et al., "Flow Cytometric Analysis Using Digital Signal Processing." *Cytometric* 20:102-117 (1995) (Zilmer 1995)
1022	WO 92/08120 ("Pulsed Laser Flow Cytometry"). (Piper 1992)
1023	Van Den Engh, Ger., "High speed cell sorting." *Emerging Tools for Single Cell Analysis* (2000): 21-48. (van Den Engh 2000)
1024	WO 01/28700 ("Transiently Dynamic Flow Cytometer Analysis System"). (Ellison 2001)
1025	Shapiro, A., *Practical Flow Cytometry* (1985). (Shapiro 1985)
1026	Herzenberg, L.A. et al., "Fluorescence-activated cell sorting." *Sci Am* 234.3 (1976): 108-117. (Herzenberg 1976)
1027	Fulwyler, M., "Electronic Separation of Cells." *Science* 150:910-911 (1965). (Fulwyler 1965)
1028	Peters, D., et al., "The LLNL High-Speed Sorter: Design Features, Operational Characteristics, and Biological Utility." *Cytometry* 6:290-301 (1985). (Peters 1985)
1029	Carter, N. P., et al., "Introduction to the principles of flow cytometry." *Flow Cytometry: A Practical Approach, ed* 2 (2000): 1-22. (Carter 2000)
1030	U.S. Patent No. 5,021,244
1031	Fridman, J., et al., "The Tigersharc DSP Architecture." *IEEE micro* 1 (2000): 66-76. (Fridman 2000)
1032	TigerSHARC DSP Microcomputer
1034	U.S. Patent No. 5,135,759 (Johnson 1992)
1035	Johnson, L.A. et al., "Sex Preselection in Rabbits: Live Births from X and Y Sperm Separated by DNA and Cell Sorting." *Biology of Reproduction* 41.2 (1989): 199-203. (Johnson 1989)
1036	U.S. Patent No. 5,204,884 (Leary 1993)
1037	U.S. Patent No. 5,804,143 (Leary 1996)

Exhibit No.	Reference Name
1038	"The Digital 'Disadvantage'?" post by Howard Shapiro, Jan. 24, 2002