UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TRANS OVA GENETICS, LC
Petitioner
v.
XY, LLC
Patent Owner

U.S. Patent No. 7,723,116
Issued: May 25, 2010
Filed: May 25, 2006
Inventors: Kenneth Evans *et al.*

Title: Apparatus, methods and processes for sorting particles and for providing sex-sorted animal sperm

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Case IPR2018-00248

PETITION FOR *INTER PARTES* REVIEW

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1003	Declaration of J. Paul Robinson, Ph.D
1004	Curriculum vitae of J. Paul Robinson, Ph.D
1005	WO 01/85913, published November 15, 2001, to Evans et al. ("Evans")
1006	Tardif et al., "Use of Hoechst 33342 Stain to Evaluate Live Fresh and Frozen Bull Sperm by Computer-Assisted Analysis," *J. Androl.*, 19:201-206 (1998) ("Tardif")
1007	U.S. Patent No. 5,135,759, issued August 4, 1992, to Johnson ("Johnson")
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1013	U.S. Patent No. 5,985,216, issued November 16, 1999, to Rens ("Rens")
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I. INTRODUCTION

Trans Ova Genetics, LC ("Petitioner") requests IPR and cancellation of claims 42-59, 65-67, and 69 of U.S. Patent No. 7,723,116 ("the '116 patent").

The challenged claims are drawn to a system for flow-sorting sperm based on the methods recited in claims 1-41, which are subject to a concurrently-filed IPR. Briefly, in flow-sorting, sperm cells are stained with a fluorescent dye, loaded into a cytometer, flowed through a nozzle and past a radiation source, such as a laser. The laser irradiates the dye, causing it to excite and emit fluorescence. That fluorescence is then measured and analyzed, and the difference in fluorescence signal is used to distinguish between sperm carrying an X-chromosome, which are larger and thus emit relatively more fluorescence, versus sperm carrying a Y chromosome, which are smaller and thus emit relatively less fluorescence. The system of claims 42-59, 65-67, and 69 are merely the components necessary to carry out flow-sorting.

These systems for flow-sorting, however, had been known for years before the '116 patent was filed. Co-inventor Evans, for example, had previously disclosed nearly identical methods and systems in a PCT application ("Evans") pre-dating the '116 patent's critical date. The only notable difference between the two is the '116 patent's disclosure of a pulsed laser in place of the continuous wave

("CW") laser utilized in Evans. But the use of a pulsed laser in flow cytometry, while not explicitly disclosed in Evans, also had been known for years.

Despite this, the '116 patent claims issued, in part because the Patent Owner avoided having to address the most pertinent prior art, such as Evans. This was almost certainly due to the fact that Patent Owner submitted over 1,500 references during prosecution, thereby burying the most pertinent art (including that discussed in this Petition) under a mountain of mostly irrelevant references. Notably, none of the references relied on in this Petition were raised by the Office during prosecution. Instead, the principal prior art reference addressed during prosecution was a patent publication that the Patent Owner ultimately overcame by antedating. Had the Office been aware of the presently-cited art, however, it never would have allowed the patent claims.

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

A. Real Parties In Interest. Trans Ova Genetics, LC and Intrexon Corporation are real parties in interest. No other parties exercised, or could have exercised, control over this Petition; no other parties funded or directed this Petition. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,759-60.

B. Related Matters. A separate petition for IPR of claims 1-26, 33-34, and 39-41 of the 116 patent is being filed concurrently (IPR2018-00247). Petitioner requests that both petitions be reviewed by the same panel.

The '116 patent is the subject of pending litigation in the United States District Court for the District of Colorado (*XY, LLC et al. v. Trans Ova Genetics, LC,* No. 1:17-cv-00944) ("Colorado litigation"), which was transferred from an earlier filed case in the United States District Court for the Western District of Texas between the same parties (No. 6:16-cv-00447). Petitioner will soon also be filing petitions for IPR on two other patents owned by the Patent Owner: U.S. Patent No. 6,372,422 (IPR2018-00249) and U.S. Patent No. 8,652,769 (IPR2018-00250).

C. Lead and Backup Counsel. Petitioner identifies the following:

Lead Counsel	Backup Counsel
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D. Service Information. Please address all correspondence to lead counsel shown above. Petitioner consents to electronic service by email to dkelly@hunton.com and gyao@hunton.com.

III. REQUIREMENTS FOR IPR REVIEW

Pursuant to 37 C.F.R. § 42.104, Petitioner states as follows:

A. Grounds for Standing. Petitioner certifies that the '116 patent is available for IPR and that Petitioner is not barred or estopped from requesting review on the grounds identified herein. The Director is authorized to charge the fee specified by 37 C.F.R. § 42.15(a), and any other fees necessary, to Deposit Account No. 50-0206.

B. Identification of Challenge. Pursuant to 37 C.F.R. § 42.104(b) and § 42.22(a)(1), Petitioner requests review and cancellation of claims 42-59, 65-67, and 69 of the '116 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	References
I	42	§ 102	Evans (Ex. 1005) and Piper (Ex. 1009)
II	42-59, 65, and 69	§ 103	Evans (Ex. 1005), Piper (Ex. 1009), and Tardif (Ex. 1006)
III	51	§ 103	Evans (Ex. 1005), Piper (Ex. 1009), Tardif (Ex. 1006), and Lakowicz (Ex. 1008)

Ground	Claims	Basis	References
IV	66-67	§ 103	Evans (Ex. 1005), Piper (Ex. 1009), Tardif (Ex. 1005), and Fukuda (Ex. 1010)

Pursuant to 37 C.F.R. § 42.22(a)(2), Petitioner sets forth a full statement of the reasons for the relief requested below in Section VIII. These grounds are not redundant with those filed in the co-filed sister petition, which seeks IPR and cancelation of claims 1-26, 33-34, and 38-41. Petitioner's arguments are supported by a Declaration from Dr. J. Paul Robinson (Ex. 1003), SVM Professor of Cytomics and Professor of Bioengineering at Purdue University, who has over 40 years of relevant experience, detailed in his C.V. (Ex. 1003.)

IV. LEVEL OF ORDINARY SKILL IN THE ART

A. Person of Ordinary Skill in the Art

The '116 patent claims priority (through a continuation application) to U.S. Provisional Patent App. No. 60/471,509, filed on May 15, 2003. Without conceding that this priority claim is valid, Petitioner and its expert declarant, Dr. Robinson, use May 15, 2003, as the relevant date for analysis of the level of skill and knowledge of a person of ordinary skill in the relevant art ("POSA").

The '116 patent relates to methods of flow cytometry to separate (*i.e.*, "sort") sperm cells based on whether they carry an X or Y chromosome. A POSA

for purposes of the '116 patent is someone with at least a Bachelor's of Science degree in the biological sciences or closely related discipline and at least 5 years' experience in one or more of the following areas: flow cytometry, sperm sorting, and/or biomedical engineering. Ex. 1003 ¶ 25. Dr. Robinson is qualified to opine from the perspective of a POSA. *Id*.

V. STATE OF THE RELEVANT ART

A. Flow Cytometry Systems For Use In Sorting Sperm Were Well-Known.

Evans details flow cytometry systems used to sort sperm based on differences in DNA content. Ex. 1005, 16:6-18:12. In Evans' system, sperm are stained with a fluorochrome dye, such as Hoechst 33342, deposited within a nozzle of a flow cytometer via an injector tube, and funneled through the nozzle (via fluid hydrodynamics) using a sheath fluid. *Id.,* 16:6-15, 26:18-27:19, Figs. 1 & 2. As the stream of sperm cells flow out of the nozzle, an oscillator acts upon it, breaking the stream into droplets, each containing a single sperm cell. *Id.,* 16:15-23, Fig. 2.

The sperm-containing droplets then pass through an irradiation source, such as a split laser, whose beams excite the dye and cause the sperm cells to emit a fluorescent light. *Id.,* 16:24-17:9, 31:5-19, Figs. 1, 2 & 24. Because the X chromosome contains more DNA than the Y chromosome, X-bearing sperm emit more fluorescent light than Y-bearing sperm. *Id.,* 17:9-14. The emitted fluorescent light is sensed by a detector, such as a photomultiplier tube (PMT), located near

the stream, converted into an electronic signal and multiplied, and then sent to an analyzer coupled to a droplet charger. *Id.,* 17:15-19, 18:13-15, 20:6-22, Figures 1-3.

The droplet charger, responsive to the analyzer, then charges each droplet based on the analyzed characteristics of the sperm contained within the droplet: X-bearing sperm get one charge, and Y-bearing sperm get a different charge (positive or negative). *Id.,* 17:15-18:3 The charged droplets are then passed through a pair of opposing electrostatic deflection plates, which deflect the differentially-charged X- and Y-bearing droplets into respective collection containers. *Id.,* 17:23-27. The droplets that do not entrain a sperm cell or entrain undesired or unsortable cells are left uncharged and thus fall undeflected. *Id.,* 17:27-18:3.

In this way, Evans' system sorts the sperm cells. Evans teaches that the sperm may be sorted at a rate of 2,500 intact sperm per second with a collection rate of 4,000-10,000 sperm per second. *Id.,* 21:10-13 and 27:5-6. The sexual purity of the sperm is 90% or greater. *Id*. 27:6-8. In addition, Evans teaches that the sorted sperm may be used to produce sex-selected offspring in procedures such as artificial insemination ("AI") and *in vitro* fertilization ("IVF"). *Id.,* 7:5-10.

B. Staining Using Less Than The "Maximum" Amount Of Stain Were Well-Known.

Evans discloses staining the sperm with the fluorochrome dye Hoechst 33342. Ex. 1005, 4:5-7, 18:25-27. Evans cautions, however, not to use too much

dye. For one, the dye could be toxic to the sperm. *Id.,* 5:15-18 (noting that UV light "may affect the viability of the spermatozoa," and thus "it may be preferable to use a method that requires less or no stain") Second, Evans warns that too much dye can exacerbate the background noise. *Id.,* 18:25-27 ("The amount of background signal can be further exacerbated when fluorochrome such as Hoechst 33342 can be used to label the nuclear DNA of sperm cells.")

Evans also expressly incorporates other references that similarly caution against using too much dye. For example, Johnson specifically warned that, while the dye concentration should be "sufficient to stain sperm uniformly and to detect the small differences in the DNA of X and Y sperm with minimal variation," it must be "minimal to avoid toxicity." Ex. 1007, 4:31-35. To that end, Johnson observed that a "suitable concentration was found to be 5 μg/ml, but this may be varied from 4 to 5 μg/ml." *Id.,* 4:35-36. Thus, it was known that too much dye could harm the sperm and, thus, it was preferable to use less than the "maximum" amount of dye when staining sperm.

C. Flow Cytometry Systems Using A Pulsed Laser Were Well-Known.

Evans does not expressly disclose a pulsed laser. The use of pulsed lasers, however, was widely reported in the prior art. Piper, for example, taught the advantages of pulsed lasers over CW lasers for flow cytometry, including that they are cheaper to purchase and operate, have high instantaneous illumination

intensities, relaxed beam focusing requirements, good beam uniformity, and wavelength versatility. Ex. 1009, 1:38-2:4, 3:19-23, 5:33-35. Similarly, Tardif taught that a pulsed radiation source was preferable over a continuous radiation source in applications involving Hoechst 33342-stained sperm, because a pulsed radiation source reduced the time the sperm cells were exposed to harmful UV illumination. Ex. 1006, 205. Lakowicz, too, taught the use of pulsed lasers to irradiate Hoechst 33342-stained sperm, and disclosed that, for such applications, the laser should be operated at "325-355 nm (UV)," which is the dye excitation/absorption wavelength for Hoechst 33342.

VI. SUMMARY OF THE CLAIMED INVENTION

A. Brief Description Of The Challenged Claims

Claims 42-59, 65-67, and 69 are being challenged. Claim 42, the lone independent claim, recites:

> 42. A flow cytometry system for sperm comprising:
>
> a sheath fluid port to introduce a sheath fluid;
>
> a sample injection element having an injection point through which irradiatable sperm cells may be introduced into said sheath fluid, said irradiatable sperm cells comprises stained sperm cells having a percentage of stain as compared to a standard control, said percentage of stain selected from a group consisting of about 90%, about 80%, about 70%, and about 60% of maximum stain;
>
> a nozzle located in part below said injection point;

an oscillator to which said a sheath fluid is responsive;

a pulsed laser;

a beam splitter;

a sperm cell fluorescence detector to detect fluorescence from said irradiatable sperm cells located in a stream flowing out of said nozzle; said sperm cell fluorescence detector located near said stream of irradiatable sperm cells;

a processing unit connected to said sperm cell fluorescence detector to evaluate detected fluorescence from said irradiatable sperm cells;

a drop charge circuit located near said stream of irradiatable sperm cells flowing out of said nozzle to apply an electrical condition to a stream of said irradiatable sperm cells and sheath fluid, said drop charge circuit is responsive to said processing unit and applies said electrical condition based on said evaluated detected fluorescence;

a first and second deflection plate responsive to said processing unit, each plate disposed on opposite sides of a free fall area in which a drop forms, wherein said first and second deflection plates are oppositely charged; and

a sperm cell collector located below said first and second deflection plates.

Claims 43-59 and 65-69 all depend from claim 42. Each recites one or more elements that are conventional, trivially-limiting, and/or inherent in the system of claim 41. These elements include: a quantitative detector to measure fluorescence

(claims 43 and 44); a rapid sperm sorter (claims 45 and 46); a beam manipulator, such as a mirror (claims 47 and 48); a PMT as the detector (claim 49); a fluorochrome-containing stain (claim 50); a pulsed laser having fluorescence activation wavelength of 355 nm (claim 51) or operating at low power radiation (claims 52 and 53); a Nd:YAG and Nd:YVO4 pulsed laser (claim 69); a detector that distinguishes between X and Y chromosomes (claim 54) and further comprises a high purity population of X and Y sperm (claim 55) or a high resolution of sorted sperm (claim 56); a collector that contains X and Y sperm (claim 57) at high collection rates (claim 58); a low coincidence rate (claim 59); mammalian cells (claim 65); and at least two nozzles (claim 66) along with multiple containers (claim 67).

B. Summary Of The '116 Patent Specification

The '116 patent describes the basics of flow cytometry and, more specifically, conventional systems for flow-sorting dye-stained sperm, which included the following known elements: a sheath fluid flowing into a nozzle (*id.,* 11:47-56); sperm cells stained with less than the "maximum" amount of Hoechst 33342 dye (*id.,* 16:24-37); an injection element for introducing the stained sperm cells into the sheath fluid (*id.,* 11:44-56); a split beam laser to irradiate the stained sperm (*id.,* 8:64-9:5); a detector, such as a PMT, connected to a processing unit to evaluate and process the light (*id.,* 12:45-53, 14:20-21); a drop charge circuit to

charge the X and Y-bearing sperm with either a positive or negative charge (*id.,* 12:53-65); and deflection plates to deflect the X and Y drops into different collectors (*id.,* 13:1-7), thereby sorting the sperm cells based on sex (*id.,* 13:7-14).

Notably, every feature of the flow-sorting system disclosed in the '116 patent had been known and described in one or more of the ***1,500+ references*** cited during prosecution. *Id.,* pp. 1-21. One feature, however, that the patent touts as distinguishing its system over the prior art is the use of a ***pulsed laser*** in place of the more "traditional" CW laser. *Id.,* 2:41-45 ("The traditional type of laser used for the analysis of particles in flow cytometry is a continuous wave (CW) laser. Often this provides a beam of constant intensity. However, in some instances, CW lasers can have particular disadvantages for applications as discussed here."); *id.,* 1:15-18 ("More specifically, the invention relates to the use of a pulsed laser on a flow system for particle analysis which results in more accurate quantification of measurable properties of individual particles.").

However, as detailed below, pulsed lasers had been known for years, including for use in flow cytometry applications and other applications involving dye-stained sperm. *See* Section VIII below; *see also* Ex. 1001, 2:53-3:18 (describing use of pulsed lasers in flow cytometry). Even the specific pulsed laser disclosed in the '116 patent—the "Vanguard Laser"—had been used for years before the '116 patent was filed. *Id.,* 17:37-40 (explaining that the Vanguard Laser

was "manufactured by Spectra-Physics" and was described in "Laser Forefront, Spectra-Physics, No. 30 (2001)"); *see also id.,* 21:35-43, Fig. 17, Tables 1 & 2.

C. Summary Of The Relevant Prosecution History

The '116 patent issued from U.S. App. No. 11/442,735, filed on May 25, 2006, and claims the benefit (through a continuation application) to U.S. Provisional App. No. 60/471,509, filed on May 15, 2003.

The '735 application was filed with 143 claims. Ex. 1015, 59-126. After an initial Office Action rejecting all the claims as anticipated by U.S. Publication No. 2005/0112541 to Durack et al. ("Durack"), the applicants responded by cancelling all then-pending claims and replacing them with a new set of claims drawn to: (A) a "method of flow cytometry sperm processing" (claims 144-199); and (B) a "flow cytometry system for sperm" (claims 200-243). Ex. 1016, 3-7; Ex. 1017, 2-18.

In April 2008, the Office rejected all the claims as both indefinite for various reasons, and as anticipated by Durack, which the Office asserted taught a flow cytometry method using a pulsed laser and beam splitter to sort and classify particles according to one or more characteristics Ex. 1018, 2-8.

In October 2008, the applicants responded by amending the claims, including adding the following limitation after the three "multiply" steps:

> wherein said step of multiply subjecting said irradiatable sperm cells to said radiation for said first amount of time and said step of multiply terminating said radiation of said irradiatable sperm cells for said

> second amount of time and said step of multiply exciting said irradiatable sperm cells with said radiation are performed in a sequential manner then repeated in order at a repetition rate;

Ex. 1019, 3. Although the applicants did not offer an explanation for the amendment, it appears to have been in response to the Office's indefiniteness rejections. *See id.,* 19. The applicants also added the following limitations to overcome the prior art rejection:

> staining sperm cells with a fluorescent dye;
>
> providing a percentage of stain as compared to a standard control, said percentage of stain selected from a group consisting of about 90%, about 80%, about 70%, and about 60% of maximum stain.

Id., 3. They argued that Durack "does not disclose the use of less stain, e.g., about 90%, about 80%, about 70%, and about 60% of maximum stain as presented in claims 144-200." *Id.,* 20.

In November 2008, the Office maintained the indefiniteness rejections over most of the pending claims and modified the anticipation rejection to obviousness based on the amendment. Ex. 1020, 2-6. The Office contended that, while Durack does not explicitly teach the use of the recited amounts of the dye, it would have been obvious for a POSA to use a lower amount of dye since Durack teaches that it is advantageous to use less dye to minimize any harmful impact thereof. *Id*.

In December 2009, the Patent Owner submitted a Rule 131 Declaration from inventors Evans and Gilligan, who averred conception before Durack's March 28, 2003, priority date, and diligent reduction to practice. Ex. 1021. The applicants also argued that the invention was non-obvious over Durack, which they alleged failed to teach using less stain with a pulsed laser. Ex. 1022, 19-20.

The application was subsequently allowed in view of the inventors' Rule 131 Declaration and, according to the Examiner, because the prior art did not teach or suggest staining sperm cells with less than 100% of a maximum amount of fluorescent dye used to stain a standard control material. Ex. 1023, 2.

VII. CLAIM CONSTRUCTION

In an IPR, claim terms are interpreted according to their broadest reasonable interpretation ("BRI") in view of the specification in which they appear. 37 C.F.R. § 42.100(b).[1]

[1] The BRI of claim terms here may be different from the construction that those same terms may receive following claim construction proceedings in district court. *See, e.g., In re Trans Texas Holdings Corp.*, 498 F.3d 1290, 1297 (Fed. Cir. 2007). Thus, the claim constructions presented in this Petition, including where Petitioner does not propose an express construction, do not necessarily reflect the claim constructions that Petitioner believes should be adopted by a district court under *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005).

A. "stained sperm cells having a percentage of stain as compared to a standard control, said percentage of stain selected from a group consisting of about 90%, about 80%, about 70%, and about 60% of maximum stain (claims 42-59, 65-67, and 69)

This limitation is not self-explanatory and thus resort to the specification is necessary to shed light on its meaning. The support for the limitations derives principally from the Examples. Specifically, in Examples 1-10, samples of bull sperm are "stained in standard conditions with DNA binding stain Hoechst 33342." Ex. 1001, 26:19-31:7. Examples 5 and 8 further specify that the sperm are stained "with the standard concentration of Hoechst 33342 ***being defined as*** 100% level of stain (control)." *Id.,* 28:4-9 (Ex. 5) (emphasis added), 29:20-25 (Ex. 8). In these two examples, some samples of bull sperm are also "stained with 80% or 60% of the amount of Hoechst 33342 stain, respectively." *Id.,* 28:9-11 (Ex. 5), 29:25-28 (Ex. 8); *see also id.*, Tables 6 and 7. Similarly, in Example 9, bull sperm are stained either with 100% or 80% stain. *Id.,* 30:18-39.

Thus, the specification equates "the standard concentration" of a dye with being the maximum amount of that stain, *i.e.*, "100% level of stain (control)." Ex. 1003 ¶ 60. Put another way, the terms "maximum stain" and "standard concentration of the dye" mean the same thing. *Id.* ¶ 61. Notably, the patent fails to specify a ***particular*** concentration of dye as being the standard concentration (maximum stain). This is for good reason, as the standard concentration of dye will necessarily turn on a variety of factors, including the dye used, the specific

conditions in which the dye is used (*e.g.*, temperature, incubation time, media used, etc.), the species of sperm (*e.g.*, human, bovine, equine, etc.), the nature of the sperm being stained (*e.g.*, fresh, frozen-thawed, etc.), and the precise number of sperm cells in the sample. *Id.* ¶ 62. As such, there is no universal standard control; rather, there is a wide range of dye concentrations that a POSA might select for any given experiment, depending on the foregoing factors.[2] *Id*.

The fact that even the same dye can have varying "standard concentrations" is evidenced by the very documents the '116 patent incorporates by reference, such as Spaulding (Ex. 1012), Rens (Ex. 1013), and Seidel (Ex. 1014). *See* Ex. 1001, column 52. Each of these incorporated patents discloses a process for sorting sperm into X- and Y-bearing populations, just like the '116 patent, yet each discloses a different "standard concentration" (maximum stain) of Hoechst dye, as well as different staining conditions. Ex. 1003 ¶ 63. Spaulding treats mammalian sperm with 10 µg/ml (*i.e.*, ***22 µM***) Hoechst dye for two hours. Ex. 1012, 8:60-9:8. Rens treats mouse and human sperm with ***7.1 µM*** Hoechst dye for 40 minutes at

[2] Petitioner is mindful that indefiniteness is not an appropriate ground of invalidity in an IPR and, to that end, has done its best to ascribe a definite construction to this claim limitation. Petitioner, however, reserves the right to challenge the definiteness of this limitation in the co-pending Colorado litigation, which can address issues beyond those available in an IPR, including indefiniteness.

32°C, and uses a similar dye preparation diluted with propidium iodide for bull sperm. Ex. 1013, 5:2-10. And Seidel treats bull sperm with ***38 μM*** Hoechst dye for 1 hour at 34°C. Ex. 1014, 15:2-5.

Accordingly, the maximum stain for any given dye appears to be the highest amount of effective stain used in any particular experiment (or set of experiments). Ex. 1003 ¶ 64. And a "percentage of [maximum] stain" is simply some amount less than that. *Id*. Thus, the phrase "providing a percentage of a fluorescent dye stain as compared to a standard control" means "providing some amount of dye less than the standard concentration." *Id*. That amount of dye is further specified by the claim as "about 60%, about 70%, about 80%, or about 90%" of the maximum stain. *Id*.

In sum, a POSA reading the claims in view of the specification would understand the limitation "stained sperm cells having a percentage of a fluorescent dye stain as compared to a standard control, said percentage of stain selected from a group consisting of about 90%, about 80%, about 70% or about 60% of maximum stain" to mean, simply, "sperm cells stained with about 60%, 70%, 80%, or 90% of the highest concentration of dye shown to be effective at staining the sperm in any particular experiment (or set of experiments)." Ex. 1003 ¶ 65.

B. "about [X]%" (claims 42-59, 65-67, and 69)

The term "about" in the phrase "about 90%, about 80%, about 70%, and about 60%" is not defined in the '116 patent. However, the use of the term "about" is generally understood to "avoid[] a strict numerical boundary" and must, rather, "be interpreted in its technologic and stylistic context." *Pall Corp. v. Micron Separations, Inc*., 66 F.3d 1211, 1217 (Fed. Cir. 1995). Here, a POSA reading the '116 patent would understand the term "about" in the phrase "about [X]%" to embrace a variance of a few percentage points of the recited value. Ex. 1003 ¶ 66. This is because, for a fluorescent dye to be excited within a cell, the molecules must be "saturated" by the radiation, and saturation would require a moderately broad concentration related to the intensity of the radiation. *Id*.

Thus, a POSA would understand the phrases "*about* 60%" would range from, *e.g.*, 54% to 66%; "*about* 70%" would range from, *e.g.*, 63% to 77%; "*about* 80%" would range from, *e.g.*, 72% to 88%; and "*about* 90%" would range from, *e.g.*, 81% to 99%. That is, each recited value would have a ±10% variance. *Id*.

C. "wherein said sperm cell fluorescence detector comprises [a] detector between an X chromosome bearing sperm and a Y chromosome bearing sperm" (claims 44 and 54-56)

This limitation makes no sense on its face. It is not at all clear what a "detector between" X and Y-bearing sperm means. Ex. 1003 ¶ 67. While the claim language suggests that the detector physically reside between the X and Y sperm,

that is nonsensical as the detector must lie outside the stream of sperm. *Id*. Resort to the specification is also unhelpful as this phrase appears nowhere in the specification other than in the original claims set appended to the end of the specification. Petitioner is thus left to speculate as to the inventors' intent when drafting this claim. To that end, Petitioner proposes that the phrase be construed to mean "wherein said sperm cell fluorescence detector is capable of distinguishing between an X chromosome bearing sperm and a Y chromosome bearing sperm."[3] *Id*. ¶ 68.

D. "a nozzle" (claims 42-59, 65-67, and 69) / "said nozzle comprises at least two nozzles" (claims 66 and 67)

Claim 42 recites "a nozzle." This term is self-explanatory and would otherwise need no construction. However, claims 66 and 67, which depend from claim 42, further recite that "said nozzle comprises at least two nozzles." This limitation is nonsensical as the claims currently read. Specifically, it is physically impossible for "a nozzle" (claim 42) to comprise "at least two nozzles." Again, Petitioner is left to divine the inventors' intent. To that end, Petitioner proposes

[3] Petitioner is mindful that indefiniteness is not an appropriate ground of invalidity in an IPR and, to that end, has done its best to ascribe definite constructions to the '116 patent claim terms/phrases. It, however, reserves the right to challenge the definiteness of any of these terms/phrases in the co-pending Colorado litigation.

curing claims 66-68, which are facially defective, by construing the term "a nozzle" in claim 42 as "at least one nozzle." This not only remedies the lack of antecedent basis in claims 66 and 67, but also mirrors how the inventors claimed the "nozzle" in the method claims. Ex. 1001, claim 1 ("at least one nozzle"); claims 35-37 ("at least two nozzles").

VIII. DETAILED DISCUSSION OF HOW EACH GROUND RAISES A REASONABLE LIKELIHOOD OF UNPATENTABILITY

Pursuant to Rule 42.104(b), this section demonstrates that the challenged claims are unpatentable. (Ex. 1003, ¶ 77-139.)

A. Each of the Relied-Upon References is Authentic, Admissible Prior Art to the '116 Patent

Petitioner relies on the following references:

1. Evans (Ex. 1005) - Evans is a PCT application that published in November 2001, and is thus prior art to the '116 patent claims under pre-AIA 35 U.S.C. § 102(b). Exhibit 1005 is an authentic, admissible copy of the Evans reference under the Federal Rules of Evidence. Ex. 1002.

2. Piper (Ex. 1009) - Piper is a PCT application that published in May 1992, and is thus prior art to the '116 patent claims under pre-AIA 35 U.S.C. § 102(b). Exhibit 1009 is an authentic, admissible copy of the Piper reference under the Federal Rules of Evidence. Ex. 1002.

3. Tardif (Ex. 1006) - Tardif published in the March/April 1998 volume of the *Journal of Andrology*, and is thus prior art to the '116 patent under pre-AIA 35 U.S.C. § 102(b). As detailed in the accompanying declaration of Jonathan H. Hartnett, a librarian with the law firm of Hunton & Williams (Ex. 1002), Exhibit 1006 is an authentic, admissible copy of the Tardif reference under the Federal Rules of Evidence.

4. Lakowicz (Ex. 1008) - Lakowicz is United States patent issued in April 1996. As such, it is prior art to the '116 patent under pre-AIA 35 U.S.C. § 102(b). Exhibit 1008 is an authentic, admissible copy of the Lakowicz reference under the Federal Rules of Evidence. Ex. 1002.

5. Fukuda (Ex. 1010) - Fukuda is a United States patent that issued in December 1992. As such, it is prior art to the '116 patent under pre-AIA 35 U.S.C. § 102(b). Exhibit 1010 is an authentic, admissible copy of the Fukuda reference under the Federal Rules of Evidence. Ex. 1002.

Each one of Exhibits 1008 (Lakowicz), 1009 (Piper), and 1010 (Fukuda) is over 20 years old, and each was prepared before January 1, 1998, and thus each qualifies as an ancient document under Fed. R. Evid. 803(16), both before and after the pending Dec. 1 2017 amendment to the Rule. Moreover, each of these Exhibits, as well as Exhibits 1005 (Evans) and 1006 (Tardif), also meets the residual exception to hearsay under Fed. R. Evid. 807 as each (i) has equivalent

circumstantial guarantees of trustworthiness, (ii) is offered as evidence of a material fact, (iii) is more probative on the point for which it is offered than any other evidence that Petitioner can obtain through reasonable efforts, and as (iv) admitting the Exhibit will best serve the purposes of the Federal Rules of Evidence and the interests of justice. Additionally, Exhibits 1005 (Evans) and 1009 (Piper) are Publications of the World Intellectual Property Organization and Exhibits 1008 (Lakowicz) and 1010 (Fukuda) are issued United States Patents. As such, they meet the public records exception to hearsay under Fed. R. Evid. 803(8).

B. Summary Of The Grounds Of Rejection

The principal reference in the proposed grounds of rejection, Evans, shares a co-inventor with the '116 patent and discloses strikingly similar apparatuses for flow-sorting sperm. Embodiments of Evans' apparatus are recited in claims 121, 124-126, 131, 134-137, and 139-141, appearing at the end of the document. As can be seen, these claims, which are reproduced below, contain ***nearly every element*** of the challenged '116 patent system claims:

> 121. A particle differentiation apparatus, comprising:
>
> a fluid stream;
>
> intact live sperm cells introduced into said fluid stream;
>
> a nozzle having a orifice through which said fluid stream exits;
>
> an oscillator responsive to said fluid stream; and

droplets breaking off from said fluid stream, wherein a plurality of said droplets entrain said intact live sperm cells, and wherein said droplets have sufficient size to encapsulate one of said live sperm cells.

124. A particle differentiation apparatus as described in claim 123, further comprising a light emission source generating light.

125. A particle differentiation apparatus as described in claim 124, further comprising a detector responsive to said light.

126. A particle differentiation apparatus as described in claim 125, wherein said intact live sperm cells have at least one sex differentiation characteristic.

131. A particle differentiation apparatus as described in claim 126, an irradiation source generating an irradiation beam responsive to said intact live sperm cells.

134. A particle differentiation apparatus as described in claim 131, wherein said at least one sex differentiation characteristic comprises a difference in amount of nuclear DNA of said intact live sperm cells, and wherein said light emission source comprises a light emission material bound to nuclear DNA, and wherein said light emission material emits light differentially based upon said difference in amount of said nuclear DNA, and wherein and wherein said detector generates at least one signal in response to said light.

135. A particle differentiation apparatus as described in claim 134, further comprising an analyzer responsive to said detector, wherein

said analyzer differentiates between said at least one intact live sperm cell based upon said difference in amount of nuclear DNA.

136. A particle differentiation apparatus as described in claim 135, wherein said difference in said amount of said nuclear DNA comprises a difference between X chromosome bearing sperm cells and Y-chromosome bearing sperm cells.

137. A particle differentiation apparatus as described in claims 136, further comprising a droplet charger coupled to said analyzer, wherein said droplet charger generates a charge on said droplets differentially based upon said difference in amount of said nuclear DNA.

139. A particle differentiation apparatus as described in claims 137 or 138, further comprising a droplet separator, wherein said droplet separator separates said droplets based upon charge of said droplets.

140. A particle differentiation apparatus as described in claim 139, further comprising at least one collection container in which droplets containing said X-chromosome bearing sperm cells are collected as an X-chromosome bearing population.

141. A particle differentiation apparatus as described in claim 139, further comprising at least one collection container in which droplets containing Y-chromosome bearing sperm cells are collected as a Y-chromosome bearing population.

Ex. 1005, 76:8-79:16 (claims 121, 124-126, 131, 134-137, and 139-141).

The foregoing apparatuses, as well as various alternatives and preferred embodiments, are detailed in Evans, which specifically describes performing

sperm-sorting on a "Cytomation SX MoFlo® sorting flow cytometer." *Id.,* 20:6-23:16; *see also id.,* Figs. 3-12. Notably, this is the ***very same*** machine that Petitioner uses to sort sperm, and which forms the basis of Patent Owner's assertions of infringement in the co-pending Colorado litigation. Ex. 1011, Ex. B. In other words, the Patent Owner is accusing Petitioner of infringing the '116 patent claims by performing ***the same methods*** on ***the same machine*** that Evans disclosed more than a year before the '116 patent's earliest priority date.

In any event, as detailed below, Evans expressly discloses or suggests every element of the challenged '116 patent claims. Any claimed feature not expressly recited in Evans was conventional and/or expressly taught by other, closely-related art.

For example, Piper taught the use of a pulsed laser, as well as its advantages over conventional, continuous wave (CW) lasers. Piper also taught the use of a pulsed laser in systems for flow cytometry. Similarly, Tardif taught the use of a pulsed radiation source in systems involving evaluating Hoechst 33342 dye-stained sperm cells. Tardif also taught using the pulsed radiation source at a wavelength of 327 to 395 nm. Moreover, Lakowicz, which also disclosed a pulsed laser, taught that cells stained with Hoechst 33342 should be irradiated at 325-355 nm. And Fukuda disclosed a flow cytometer comprising two nozzles, which it taught increased the efficiency of the cytometer.

C. Ground 1: Claim 42 Is Obvious Over Evans In View Of Piper.

Claim 42 (preamble): ***A flow cytometry system for sperm comprising:***

Evans discloses a system of flow cytometry for sorting stained sperm cells. Ex. 1005, 16:6-18:12 (detailing system for flow-sorting sperm), 8:22-9:2; *see also id.,* 76:8-79:16 (claims 121, 124-126, 131, 134-137, and 139-141). Figure 1 depicts the basic system:

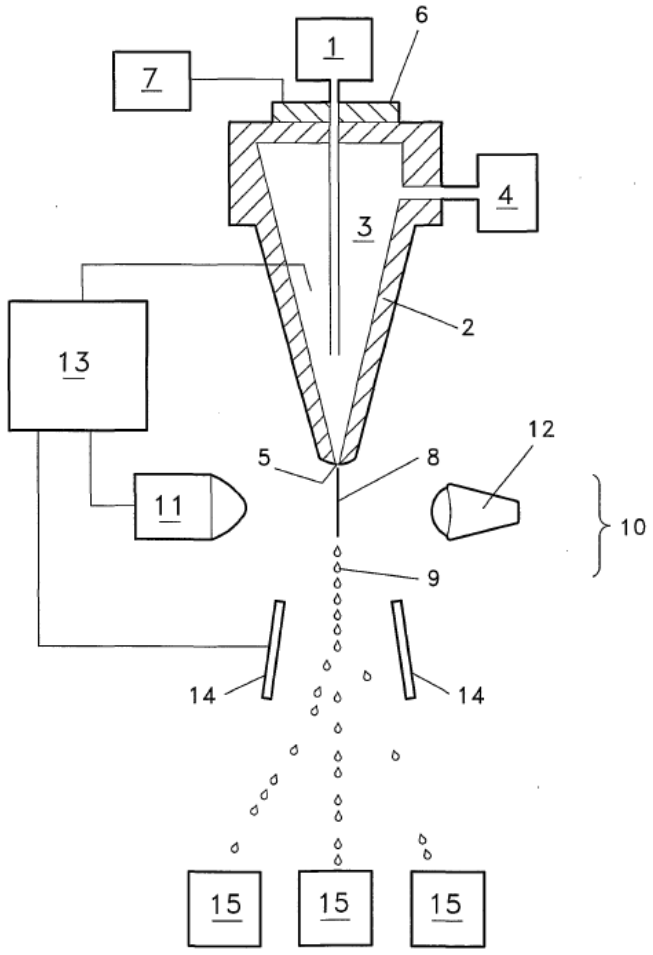

Fig. 1

Key:

(1) = Cell source
(2) = Nozzle
(3) = Fluid stream / Sheath fluid
(4) = Sheath fluid source
(5) = Nozzle orifice
(6) = Oscillator
(7) = Oscillator control
(8) = Exiting stream
(9) = Drops
(10) = Cell sensing system
(11) = Detector / sensor
(12) = Irradiation source (laser)
(13) = Analyzer
(14) = Deflection plates
(15) = Collection containers

Id., Fig. 1; *see also id.,* 16:6-17:23 (describing the parts of Fig. 1).

<u>Claim 42(a):</u> a sheath fluid port to introduce a sheath fluid;

Evans expressly discloses this step. Ex. 1003 ¶ 81. Referring to Figures 1 and 2, Evans states:

> Now referring to Figures 1 and 2, a flow cytometer embodiment of the invention is shown which includes a particle or cell source (1) which acts to establish or supply particles or cells stained with at least one fluorochrome for analysis. ***The particles or cells are deposited within a nozzle (2) in a manner such that the particles or cells are introduced into a fluid stream or sheath fluid (3). The sheath fluid (3) is usually supplied by some sheath fluid source (4)*** so that as the particle or cell source (1) supplies the particles or cells into the sheath fluid (4) they are concurrently fed through the nozzle (2)**.**

Ex. 1005, 16:6-12 (emphasis added), Fig. 1; *see also id.,* 76:8-15 (claim 121).

<u>Claim 42(b):</u> a sample injection element having an injection point through which irradiatable sperm cells may be introduced into said sheath fluid,

See Claim 42(a) above and Evans Fig. 1. Additionally, Evans specifically discloses injecting the stained sperm cells into a sheath fluid. Ex. 1005, 27:2-5 ("Spermatozoa introduced into the laminar flow of sheath fluid maintained by an embodiment of the injector tube invention having the paddle shaped beveled blade allows for a 20%, 30%, 40%, 50% or even greater increase in spermatozoa sorting rates over conventional injection tube technology."); *see also id.,* 76:8-15 (claim 121).

<u>Claim 42(c):</u> said irradiatable sperm cells comprises stained sperm cells having a percentage of stain as compared to a standard control, said percentage of stain selected from a group consisting of about 90%, about 80%, about 70%, and about 60% of maximum stain;;

As discussed in Section VII above, this limitation requires that the sperm cells be stained with "about 60%, 70%, 80%, or 90% of the highest concentration of dye shown to be effective at staining the sperm in any particular experiment (or set of experiments)." Although Evans does not expressly disclose the concentration of dye used in its experiments, Evans expressly (and repeatedly) incorporates Johnson—widely considered to be one of the pioneering patents in the field of flow sorting.[4] Ex. 1005, 2:15-25; *see also* Ex. 1003 ¶ 83.

As Johnson is expressly incorporated into Evans' disclosure, it is deemed a part of that disclosure.[5] *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1382, n.3 (Fed. Cir. 2007) ("We have further explained that material incorporated by reference 'is effectively part of the host document as if it were explicitly contained therein.'") (internal citation omitted); *see also Callaway Golf Co. v.*

[4] The Johnson patent is so foundational to the field of flow-sorting sperm that Evans incorporates it by reference not once, but ***three different times.*** *See* Ex. 1005, 1:11-12, 2:24-25, and Table on pg. 38, row 3.

[5] Should the Board determine that Johnson should not be treated as a part of Evans' disclosure, Petitioner respectfully requests that the Board, in that case, treat Johnson as a secondary reference to be combined with Evans.

Acushnet Co., 576 F.3d 1331, 1346-47 (Fed. Cir. 2009) (holding that material properly incorporated by reference into a prior art document is generally treated as being within the "four corners" of the document itself).

Like Evans, Johnson describes methods of flow-sorting Hoechst 33342 dye-stained sperm. Ex. 1003 ¶ 84. Additionally, Johnson specifically teaches using lower amounts of Hoechst 33342 to avoid harming the sperm. Ex. 1007, 4:27-36. Johnson explains:

> Concentration of the fluorochrome ***must be minimal to avoid toxicity***, and yet be sufficient to stain sperm uniformly and to detect the small differences in the DNA of X and Y sperm with minimal variation. A suitable concentration was found to be 5 µg/ml, but this may be varied ***from 4 to 5 µg/ml.***

Id., 4:27-36 (emphasis added). Thus, Johnson provides both the motivation to use lower amounts of stain than the maximum, as well a ***specific*** range of concentrations, namely, "from 4 to 5 µg/ml." Significantly, this range encompasses from 80% to 100% of the maximum amount of dye disclosed by Johnson as "suitable" for staining X and Y sperm. Ex. 1003 ¶ 84. Johnson, therefore, both recommends using less than the maximum amount ***and*** discloses an amount of dye (4 µg/ml) that reads directly onto the claimed "about 80%" maximum stain. *Id.*

Accordingly, a POSA practicing Evans' method of flow-sorting sperm would have been prompted by Johnson, which is expressly incorporated into

Evans' disclosure, to use less than the maximum amount of dye necessary or suitable to stain sperm. Ex. 1003 ¶ 85. Further, the POSA would have been instructed by Johnson to choose, for example, 80% of maximum stain, as taught therein. *Id.* Guided by Johnson's instruction and informed by its own teaching, the POSA would have reasonably expected this concentration to be both effective in staining the X and Y chromosomes, yet generally safer for sperm than using the maximum amount. *Id.*

Claim 42(d): a nozzle located in part below said injection point;

See Claim 42 (preamble) and Claim 42(a) above. As shown in Evans Figure 1 (reproduced above), the nozzle (2) is located in part below the point at which the sample injection point, *i.e.*, cell source (1).

Claim 42(e): an oscillator to which said a sheath fluid is responsive;

See Claim 42 (preamble). Additionally, Evans specifically discloses an oscillator that "acts upon the sheath fluid":

> By providing some type of ***oscillator*** (6) which may be very precisely controlled through an oscillator control (7), pressure waves may be established within the nozzle (2) and transmitted to the fluids exiting the nozzle (2) at nozzle orifice (5). ***Since the oscillator (6) acts upon the sheath fluid (3)***, the stream (8) exiting the nozzle orifice (5) eventually and regularly forms drops (9)."

Ex. 1005, 16:16-20 (emphasis added); *see also id.,* 76:8-15 (claim 121).

Claim 42(f): a pulsed laser;

See Claim 42 (preamble). Additionally, Evans specifically discloses "an irradiation source such as a laser exciter (12) generating an irradiation beam to which the particle can be responsive." Ex. 1005, 17:45; *see also id.,* 31:5-11, 32:8-9. Yet Evans does not expressly indicate whether the "laser exciter" can be pulsed.

Pulsed lasers, however, were widely reported in the art of flow-sorting cells. Ex. 1003 ¶ 89. For example, Piper disclosed a pulsed laser in 1992. Ex. 1009. More specifically, Piper disclosed a system for flow-sorting cells that included a high-repetition pulsed laser. *Id.,* 1:3-4 ("The invention pertains to flow cytometry and more particularly to a pulsed laser light source in a flow cytometer."); *id.,* 3:37-32. Significantly, Piper explained the disadvantages of continuous lasers in flow cytometry, including that they are more expensive to purchase, install, and operate (*id.,* 1:33-2:3), have a relatively short laser tube lifetime (*id.,* 2:3-10), and are difficult to align (*id.,* 2:11-20). "[H]igh repetition rate pulse lasers," by contrast, "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.,* 3:27-32.

Piper noted that other advantages of certain pulsed lasers, such as neodymium:YAG lasers, is that their "output may be frequency-doubled to

generate high repetition rate pulsed output in the visible [spectrum]." *Id.,* 3:17-23. Such devices, Piper explained, "are expected to increasingly dominate in laser applications requiring long-term reliability in the low-power regime; their compact size and projected low cost are especially appropriate to applications requiring multiple sources as in flow cytometry."[6] *Id.,* 3:24-27. Piper also disclosed splitting the laser beam. *Id.,* 10:7-8 (claim 10: "the laser source comprises a multi-wavelength laser whose beam is split using a beam splitter into separate beams of individual wavelengths").

In view of the above, it would have been obvious for a POSA to modify Evans' flow cytometry system with Piper's pulsed laser. Ex. 1003 ¶ 93. The POSA would have been motivated to make this substitution given the many advantages of pulsed lasers taught by Piper, including lower costs and increased performance, higher instantaneous illumination intensities, relaxed beam focusing requirements, good beam uniformity, and wavelength versatility. *Id.* Moreover, the POSA would have reasonably expected Piper's pulsed laser to work in a flow cytometry system

[6] Piper notes that a perceived difficulty with the use of pulsed lasers had been the difficulty in ensuring that each cell is illuminated as it passes through the interaction region; however, Piper explains, it had overcome that difficulty by synchronizing the pulse rate with the droplet flow rate and by adjusting the focal spot size of the beam. *Id.,* 3:33-4:11.

since Piper specifically taught that its pulsed laser was particularly useful and effective in flow cytometry application like those taught by Evans. *Id.*

Claim 42(g): a beam splitter;

Evans discloses this element. Ex. 1003 ¶ 94. Specifically, Evans discloses an embodiment utilizing various optical elements, including a beam splitter:

> Components of an embodiment of the invention may be arranged in line with each other and consist of: … a spectral adjustment element, for example, a bandpass filter; a polarization adjustment element (49)… ; a light condenser (51) allowing the light to be condensed onto the particle or sperm cell, for example, a condenser lens, or set of lenses, or microscope objective; … a light collector (45) to collect the light from the particle or cell, for example a 50x high working distance microscope objective and a tube lens; ***a beam splitter (50) to split up the beam into two, or more, components***…; image light selector (55) to select only the light corresponding to the particle or sperm cell….

Ex. 1005, 32:8-21; *see also* Fig. 24.

> ***Claim 42(h): a sperm cell fluorescence detector to detect fluorescence from said irradiatable sperm cells located in a stream flowing out of said nozzle; said sperm cell fluorescence detector located near said stream of irradiatable sperm cells;***

See Claim 42(a) above and Evans Fig. 1. As shown in Figure 1 (reproduced above), in Evans' system, the detector (11) is located just below the nozzle orifice (5) and adjacent the existing stream (8) so as to detect the fluorescence of the

sperm cells as they stream pass. Additionally, Evans specifically discloses that "emitted light can be received by sensor (11) and fed to some type of separation discrimination system or analyzer…." Ex. 1005, 17:15-17; *id.,* 25:25-29 ("[T]he light emitted (31) by laser excitation of fluorochrome(s) bound to the DNA contained within spermatozoa can be detected by photomultiplier tubes (32) … as it flows through the excitation laser beam pattern."); *see also id.,* 77:3-4 (claim 125).

Claim 42(i): ***a processing unit connected to said sperm cell fluorescence detector to evaluate detected fluorescence from said irradiatable sperm cells;***

See Claim 42(a) above and Evans Fig. 1. As shown in Figure 1 (reproduced above), in Evans' system an analyzer (13) is connected to the detector (11). Evans states:

> In order to achieve separation and isolation based upon particle or cell characteristics, ***emitted light can be received by sensor (11)*** and ***fed to some type of separation discrimination system or analyzer (13) coupled to a droplet charger*** which ***differentially charges each droplet (9)*** based upon the characteristics of the particle or cell contained within that droplet (9). In this manner the separation discrimination system or analyzer (13) acts to permit the ***electrostatic deflection plates (14) to deflect drops (9) based on whether or not they contain the appropriate particle or cell.***

Ex. 1005, 17:15-21 (emphasis added). More specifically, Evans discloses that, "by ***measuring*** the fluorescence emitted by the bound fluorochrome upon excitation, it is possible to differentiate between X-bearing spermatozoa and Y-bearing spermatozoa." *Id.,* 17:12-14 (emphasis added); *see also id.,* 77:11-21 (claims 134 and 135, reciting "an analyzer responsive to said detector, wherein said analyzer differentiates between" sperm based on the amount of light detected).

> ***Claim 42(j):*** ***a drop charge circuit located near said stream of irradiatable sperm cells flowing out of said nozzle to apply an electrical condition to a stream of said irradiatable sperm cells and sheath fluid, said drop charge circuit is responsive to said processing unit and applies said electrical condition based on said evaluated detected fluorescence;***

See Claim 42(i) above and Evans Fig. 1. Although Figure 1 does not depict the "droplet charger, Evans explains that it is coupled to the analyzer and acts to "differentially charge[] each droplet (9) based upon the characteristics of the particle or cell contained within that droplet (9)." Ex. 1005, 17:15-21; *see also id.,* 78:28-79:1 (claim 137: "A particle differentiation apparatus as described in claims 136, further ***a droplet charger coupled to said analyzer,*** wherein said droplet charger ***generates a charge on said droplets differentially based upon said difference in amount of said nuclear DNA.***") (emphasis added).

> ***Claim 42(k):*** ***a first and second deflection plate responsive to said processing unit, each plate disposed on opposite sides of a free fall area in which a drop forms, wherein said first and second deflection plates are oppositely charged; and***

See Claim 42(i) above and Evans Fig. 1. As shown in Figure 1 (reproduced above), in Evans' system electrostatic deflection plates (14) responsive to the analyzer are disposed on opposite sides of a freefall area in which the drops form. Additionally, Evans provides:

> [T]he flow cytometer acts to separate the particle or cells (16) by causing them to be directed to one or more ***collection containers*** (15). For example, when the analyzer differentiates sperm cells based upon a sperm cell characteristic, the droplets entraining X-chromosome bearing spermatozoa can be ***charged positively*** and thus ***deflect in one direction***, while the droplets entraining Y-chromosome bearing spermatozoa can be ***charged negatively*** and thus ***deflect the other way***, and the wasted stream (that is droplets that do not entrain a particle or cell or entrain undesired or unsortable cells) can be left uncharged and thus is collected in ***an undeflected stream*** into a suction tube or the like . . . .

Ex. 1005, at 17:15-29 (emphasis added); *see also id.,* 54:8-17 (claim 11).

> ***Claim 42(j):*** ***a sperm cell collector located below said first and second deflection plates.***

See Claim 42 (k) and Evans Fig. 1; *see also* Ex. 1005, 79:11-16 (claims 140 and 141 reciting that the apparatus further comprises "at least one collection container" for each of the X and Y-bearing cells).

D. Ground 2: Claims 42-59, 65, And 69 Are Obvious Over Evans In View Of Piper And In Further View of Tardif.

1. Tardif provides additional motivation to use the claimed staining conditions and pulsed laser recited in claim 42.

Claim 42(c):

If any additional motivation was needed to use less than the "maximum" amount of stain—*see* Claim 42(c) above—Tardif provides it. Ex. 1003 ¶ 101. Tardif studied how to improve procedures for evaluating Hoechst 33342 dye-stained bull sperm. Ex. 1006, Abstract. To that end, Tardif studied how factors such as dye concentration, dye exposure time, media content, and pulse illumination affected the sperm. *Id.*, Abstract, 201-202. In Experiments 2 and 3, Tardif reported that frozen-thawed samples of bull sperm stained with 40, 50, and 60 μg/ml of Hoechst 33342 dye and pulse-illuminated for 20 minutes all showed similar sperm motility. Ex. 1007, 202-205; Figs. 1 & 2. Tardif thus concluded that 40 to 60 μg/ml of Hoechst 33342 was the "optimal" range to when staining frozen-thawed bull sperm. *Id*., Abstract.

Thus, Tardif discloses both (i) a ***range*** of "optimal" Hoechst 33342 dye concentrations (*i.e.*, "40 to 60 μg/ml"), as well as (ii) several ***specific*** concentrations falling within that range, namely, 40, 50, and 60 μg/ml. Ex. 1003 ¶ 102. As 60 μg/ml is the highest effective concentration of dye disclosed in Tardif, it is the "maximum stain." *Id.* As such, the disclosed range of "40 to 60 μg/ml" encompasses about 67% to 100% of the maximum stain, which nearly completely

subsumes the claimed ranges of "about 60%, about 70%, about 80% or about 90%" maximum stain. *Id.* This alone is sufficient to render the claimed ranges *prima facie* obvious. *See, e.g., In re Wertheim*, 541 F.2d 257, 267 (CCPA 1976) (claimed ranges *prima facie* obvious where they "overlap or lie inside ranges disclosed by the prior art"); *see also In re Geisler*, 116 F.3d 1465, 1469-71 (Fed. Cir. 1997) (prior art disclosure of "not less than about [100 Angstroms]" rendered obvious "50 to 100 Angstroms").

In addition, Tardif's explicit disclosure of staining sperm with 40 and 50 µg/ml of Hoechst 33342 constitutes a ***specific*** disclosure of two of the claimed ranges. Specifically, 40 µg/ml is 67% of the maximum stain disclosed in Tardif, or "***about*** 70%"; and 50 µg/ml is 83% of maximum stain, or "***about*** 80%." Ex. 1003 ¶ 103 (explaining that a POSA would understand 40 and 50 µg/ml to constitute "about 70%" and "about 80%", respectively, of the maximum stain disclosed in Tardif); *see also, e.g., In re Woodruff*, 919 F.2d 1575 (Fed. Cir. 1990) (prior art disclosure of "about 1-5%" deemed to overlap with the claimed range of "more than 5%.").

Moreover, even if 67% and 83% are deemed just outside the claimed concentrations of "about" 70% and 80%, they are sufficiently close to render those concentrations *prima facie* obvious, as there is no indication that the claimed concentrations produce a result different in kind to the disclosed concentrations.

See, e.g., *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996) (claimed thickness of 0.180 or more obvious over prior art disclosure of 0.111 to 0.142 where the modification did not "produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art"); *In re Aller*, 220 F.2d 454, 455 (CCPA 1955) (claimed process performed at 40° to 80°C and an acid concentration of 25% to 70% was obvious over prior art method performed at 100°C and an acid concentration of 10%).

Here, very little experimentation would have been required to decrease the dye concentration from, say, 50 μg/ml (*i.e.*, 83% of maximum stain), as taught by Tardif, to 48 μg/ml (*i.e.*, 80% of maximum stain), as claimed in the '116 patent. Ex. 1003 ¶ 104; *see, e.g.*, *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990) (claimed range obvious where increasing and decreasing concentration was "a matter of routine optimization"). Moreover, there was ample motivation in the art to do so. Ex. 1003 ¶ 105. For example, Johnson—incorporated by reference into Evans—specifically recommended using "minimal" concentrations of dye "to avoid toxicity." Ex. 1007, 4:27-36. Thus, there was incentive for a POSA to experiment with decreasing the dye concentration. Ex. 1003 ¶ 105. Moreover, given the modest differences in dye concentrations between those disclosed by Tardif and those claimed, the POSA would have reasonably expected the claimed amounts to work just as well in distinguishing X and Y chromosomes. *Id.*

Claim 42(f):

If any additional motivation was needed to use a pulsed laser (like that expressly taught in Piper) in Evans' system—*see* Claim 42(f) above—Tardif also would have provided this. Ex. 1003 ¶ 106. Tardif discloses a system that utilizes a pulsed radiation source to evaluate Hoechst 33342 dye-stained bull sperm. Ex. 1006, Abstract; *see also id.,* 201 (explaining the device is "equipped with strobe light UV illumination to be used with the DNA-specific Hoechst 33342 stain for CASA [Computer-Aided Sperm Analysis]."). Tardif explained that the advantage of using a pulsed radiation source on stained sperm instead of a conventional continuous light source was that it minimized the time sperm are subjected to potentially harmful UV exposure:

> Although continuous exposure of fluorescently stained cells to UV illumination is ***often harmful***, the illumination in the Hamilton Thorn IVOS unit is not continuous. The exposure to the strobe light is about 10 to 15 microseconds, with a frequency of 60 cycles/second, so sperm are exposed ***very briefly***.

Id., 205 (emphasis added). Thus, Tardif not only disclosed a pulsed radiation source to evaluate Hoechst 33342 dye-stained sperm (as is done in flow-sorting), but also provided explicit motivation for substituting a pulsed radiation source for the more conventional continuous radiation source. Ex. 1003 ¶ 107.

In view of the above, in addition to the advantages of a pulsed laser taught by Piper, a POSA would have been further prompted by Tardif to use a pulsed radiation source, such as a pulsed laser, when evaluating fluorescently-stained sperm. *Id.* ¶ 108. More specifically, a POSA would have sought to minimize the harm to the sperm known to be caused by the UV light of a laser beam. *Id.* To that end, the POSA would have been motivated by Piper and Tardif to replace Evans' CW laser with a pulsed laser. *Id.* Moreover, the POSA would have reasonably expected such a modification to succeed in a flow-sorting system given Tardif's teaching that it worked well for irradiating and evaluating Hoechst 33342-stained sperm. *Id.*

2. Claims 43-59, 65, and 69 are similarly obvious over Evans in view of Piper and in further view of Tardif.

As detailed below, claims 43-59, 65 and 69 recite trivial modifications to the system of claim 42. As such, each is also rendered obvious by Evans in view of Piper and (if needed) Tardif.

Claim 43: ***A flow cytometry system for sperm according to claim 42 wherein said sperm cell fluorescence detector comprises a sperm cell fluorescence quantitative detector.***

See Ground 1, Claim 42(h) above. Additionally, Evans discloses that, "by ***measuring*** the fluorescence emitted by the bound fluorochrome upon excitation, it is possible to ***differentiate between X-bearing spermatozoa and Y-bearing spermatozoa.***" *Id.,* 17:12-14 (emphasis added); *see also id.,* 2:10-13 ("One-by-one

assessment of sperm cells can provide advantages in that the actual separation process can be monitored, and objective quantitative data can be generated even during the separation process, and separation parameters altered as desired."); *see also* Figs. 4-10 (univariate and bivariate histograms).

> ***Claim 44:*** ***A flow cytometry system for sperm according to claim 43 wherein said sperm cell fluorescence quantitative detector comprises a detector between an X chromosome bearing sperm and a Y chromosome bearing sperm.***

See Ground 2, Claim 43 above. (As discussed in Section VII, Petitioner construes this claim to mean that the system comprises a fluorescence quantitative detector that is capable of distinguishing between an X chromosome bearing sperm and a Y chromosome bearing sperm.)

> ***Claim 45:*** ***A flow cytometry system for sperm according to claim 42 and further comprising a rapid sperm sorter having a sort rate of greater than 500 cells per second.***

See Ground 2, Claim 43 above. Additionally, Evans specifically discloses:

> The mean sort rates of live spermatozoa after the above-mentioned conversion was about 40.3 x 10^6/ 4.5 hour sort (i.e. about ***2,500 sorts per second per stream***) at about 90.8% purity with a range of 89% to about 92%. The events per second were 13,000, 15,000, and 19,500 respectively for the three sorts.

Ex. 1005, 21:10-13 (emphasis added); *see also id.,* 80:11-81:2 (claim 147, reciting sperm separation rates ranging from 500 to 11,000 per second).

Claim 46: ***A flow cytometry system for sperm according to claim 42 and further comprising a rapid sperm sorter having a sort rate selected from a group consisting of greater than 1000 cells per second; greater than 1500 cells per second; greater than 2000 cells per second; and greater than 3000 cells per second.***

See Ground 2, Claim 45 above.

Claim 47: ***A flow cytometry system for sperm according to claim 42 and further comprising a radiation beam manipulator.***

See Ground 1, Claim 42 above. Additionally, in addition to disclosing "a beam splitter (50) to split up the beam into two, or more, components" (Ex. 1005, 32:17-19), Evans also discloses a "mirror (57) [that] breaks up the light (44)" (*id.,* 34:2-3), an "objective lens (45)" that can focus the light "onto a detector" (*id.,* 31:11-14), and "additional filters (48), such as color filters" (*id.,* 31:24-25). Each of these elements is a "beam manipulator" as that term is exemplified in the '116 patent. Ex. 1001, 8:39-44 ("Beam manipulators may include ***mirrors*** …, deflectors, ***beam splitters***, refractive objects, ***lenses***, ***filters***, prisms, lenses, or the like.") (emphasis added).

Additionally, Piper also expressly discloses using a beam splitter, optical lenses, and a prism/diode array—all "beam manipulators" under the patent. Ex. 1009 at 4:27-29, 6:15-16, 10:7-8.

Claim 48: ***A flow cytometry system for sperm according to claim 47 wherein said radiation beam manipulator is selected from a group consisting mirrors, deflectors, beam splitters, prisms, refractive objects, lenses and filters.***

See Ground 2, Claim 47 above.

<u>Claim 49:</u> A flow cytometry system for sperm according to claim 42 wherein said sperm cell fluorescence detector comprises a photomultiplier tube.

See Ground 1, Claim 42 above. Additionally, Evans specifically discloses using a photomultiplier tube as the sperm cell fluorescence detector:

> Now referring to Figures 8 and 9, which show bivariate histograms from separation or sorting of intact live equine spermatozoa with the SX MoFlo® flow cytometer before using this embodiment of the invention (Figure 8) and upon using this embodiment of the invention (Figure 9). When using this embodiment of the invention, live equine spermatozoa were separated or sorted with the laser power ***at 100mW*** with the ***photomultiplier tube*** voltage below 300 volts. The separation rates or sort rates exceeded 4,800 sorts per second average at 12,000 events per second.

Ex. 1005, 22:10-16 (emphasis added); *see also id.,* 18:13-15 ("the detector, which can be a photomultiplier tube…."); *id.,* 19:7-20:22 (detailing the properties of the photomultiplier tube); *id.,* 79:16-22 (claim 142: "wherein said detector comprises at least one photomultiplier tube").

Moreover, if any additional motivation were needed to use a photomultiplier tube in a pulsed laser, Piper discloses this. Ex. 1009 at 4:36-5:1 ("The collection optics 15 images the collected light onto a detection device 16 such as a ***photomultiplier tube*** where an electrical signal is generated for each incident pulse.") (emphasis added); *see also* Ex. 1003 ¶ 118.

Claim 50: ***A flow cytometry system for sperm according to claim 42 wherein said stain comprises fluorochrome.***

See Ground 2, Claim 43 above.

Claim 51: ***A flow cytometry system for sperm according to claim 42 wherein said pulsed laser comprises a fluorescence activation wavelength of 355 nm.***

See Ground 1, Claim 42 above. Additionally, while Evans does not expressly disclose irradiating the Hoechst 33343 dye-stained sperm at a wavelength of 355 nm, such would have been obvious. Ex. 1003 ¶ 120. Tardif, for example, discloses that when irradiating sperm cells stained with Hoechst 33342 dye with a pulsed radiation source, a wavelength of 327 to 395 nm should be used:

> For all experiments, the IVOS (version 10 model, Hamilton Thorne Research) equipped with UV illumination was used. This unit has a strobed xenon light source with a double band-pass filter. For fluorescence, the 50% excitation band-pass is ***327 to 395 nm .*** . . .

Ex. 1006, 202 (emphasis added). Tardif's disclosure that the excitation range for Hoechst 33342 dye is "327 to 395" nm renders obvious the claimed range of 355 nm, which falls directly in the middle of the disclosed range. Ex. 1003 ¶ 120. *See also*, *e.g., Wertheim*, 541 F.2d 257 (claimed range lying inside disclosed range is *prima facie* obvious).

Claim 52: ***A flow cytometry system for sperm according to claim 42 wherein said pulsed laser comprises low power radiation of less than about 300 mW.***

See Ground 2, Claim 49 above.

Claim 53: ***A flow cytometry system for sperm according to claim 42 wherein said pulsed laser comprises low power radiation selected from a group consisting of: less than 350 milliwatt; less than 200 milliwatt; less than 175 milliwatt; less than 100 milliwatt; less than 88 milliwatt; less than 50 milliwatt; and less than 25 milliwatt.***

See Ground 2, Claim 49 above.

Claim 54: ***A flow cytometry system for sperm according to claim 42 wherein said sperm cell fluorescence detector comprises detector between an X chromosome bearing sperm and a Y chromosome bearing sperm.***

See Ground 2, Claim 43 above. (As discussed in Section VII, Petitioner construes this claim to mean that the system comprises a fluorescence detector that is capable of distinguishing between an X chromosome bearing sperm and a Y chromosome bearing sperm.)

Claim 55: ***A flow cytometry system for sperm according to claim 54 and further comprising a high purity population of said X chromosome bearing sperm and said Y chromosome bearing sperm selected from a group consisting of: greater than 85% purity; greater than 90% purity; greater than 95% purity; greater than 96% purity; and greater than 98% purity.***

See Ground 2, Claim 54 above. Additionally, Evans specifically discloses:

> The mean sort rates of live spermatozoa after the above-mentioned conversion was about 40.3 x 10^6/ 4.5 hour sort (i.e. about 2,500 sorts per second per stream) at ***about 90.8% purity*** with a ***range of 89% to about 92%.*** The events per second were 13,000, 15,000, and 19,500 respectively for the three sorts.

Ex. 1005, 21:10-13 (emphasis added); *see also id.,* 21:3-9 (disclosing "range of 84% to 93% purity"); 22:20-22 (disclosing sort purity of X and Y populations of

"about 93%); 52:1-12 (claim 1, reciting sorting "purity of greater than 90%); 80:3-10 (claim 145, reciting ranges of sorting purity, including "between 90% to about 100%, between about 91% to about 100%, between about 92% to about 100%, between about 93% to about 100%, between about 94% to about 100%, between about 95% to about 100%, between about 96% to about 100%, between about 97% to about 100%, between about 98% to about 100%, [and] between about 99% to about 100%.").

> ***Claim 56:*** ***A flow cytometry system for sperm according to claim 54 and further comprising sorted sperm cells at a high resolution selected from a group consisting of: greater than 7.0; greater than 7.5; greater than 8.0; greater than 8.5; greater than 9.0; and greater than 9.2.***

See Ground 2, Claim 54 above. Additionally, while Evans does not disclose particular resolution numbers, a "significant object" of Evans' invention was to "increase the apparent resolution of chromatograms or histograms resulting from sorting fluorochrome stained sperm . . . having small differences in emitted light flux upon excitation of the bound fluorochrome(s)." Ex. 1005, 8:15-18. Moreover, in comparing the resolution of a pulsed laser against that of a CW laser like the one used by Evans, the '116 patent discloses that the CW laser provides a resolution of 7.6 (as compared to a resolution of between 8.0 to 9.8 for the pulsed laser). Ex. 1001, 29:40-58. Thus, the '116 patent establishes that Evans' CW laser inherently "provid[es] high resolution of said sorted sperm . . . of greater than 7.0." Moreover, based on the '116 patent's teaching, substituting a pulsed laser in place of Evans'

CW laser would only have led to higher resolutions, not lower. *See id.; see also* Ex. 1003 ¶ 126.

> ***Claim 57:*** ***A flow cytometry system for sperm according to claim 42 wherein said sperm collector comprises a X chromosome bearing sperm collector and a Y chromosome sperm collector.***

See Ground 1, Claim 42(preamble) above and Evans Fig. 1. As shown in Figure 1 (reproduced above), in Evans' system, collection containers (15) are situated below each of the X-bearing droplets and Y-bearing droplets. Additionally, Evans provides that "the flow cytometer acts to separate the particle or cells (16) by causing them to be directed to one or more ***collection containers*** (15)." Ex. 1005, at 17:15-29 (emphasis added); *see also id.,* 79:11-16 (claims 140 and 141, reciting a "collection container" for each of the X and Y-bearing sperm cells).

> ***Claim 58:*** ***A flow cytometry system for sperm according to claim 57 and further comprising a high collection rate selected from a group consisting of: greater than 2400 sperm per second; greater than 2600 sperm per second; greater than 2900 sperm per second; greater than 3000 sperm per second; and greater than 3100 sperm per second.***

See Ground 2, Claim 45 above; *see also* Ex. 1005, 6:22-26 ("The high speed separation can produce live sperm of each sex at rates of about 500, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8,000, 9,000 or even 10,000 per second, or higher."); *id.* at 21:10-13 (disclosing "about 2,500 sorts per second per stream"); 22:15-16 (disclosing "separation rates or sort rates exceed[ing] 4,800 sorts per

second average at 12,000 events per second."); *id.,* 80:11-81:2 (claim 147, reciting sperm separation rates ranging from 500 to 11,000 per second).

> ***Claim 59:*** ***A flow cytometry system for sperm according to claim 42 and further comprising a low coincidence rate selected from the group consisting of: less than 4400; less than 4000; less than 3700; and less than 3600.***

See Ground 1, Claim 42 above. Additionally, while Evans does not disclose particular coincidence rates, another "significant object" of Evans' invention was "to provide beam shaping optics which minimizes coincidence of objects within the excitation/detection path." Ex. 1005, 9:11-13. Moreover, in comparing the coincidence rate of a pulsed laser against that of a CW laser like the one used by Evans, the '116 patent discloses that the CW laser provides a coincidence rate of 4380 (as compared to a coincidence rate of between 3500 and 3600 for the pulsed laser). Ex. 1001, 29:40-58. Thus, the '116 patent establishes that the CW laser by Evans inherently "sort[s] said sperm cells at a low coincidence rate . . . of less than 4400." Moreover, based on the '116 patent's teaching, substituting a pulsed laser in place of Evans' CW laser would only have led to lower coincidence rates, not higher. *See id.; see also* Ex. 1003 ¶ 129.

> ***Claim 65:*** ***A flow cytometry system for sperm according to claim 42 wherein said sperm cells comprises sperm cells selected from a group consisting of mammal sperm cells, bovine sperm cells, equine sperm cells, porcine sperm cells, ovine sperm cells, camelid sperm cells, ruminant sperm cells, and canine sperm cells.***

See Ground 1, Claim 42 above. Additionally, Evans discloses that "spermatozoa from any male of a species of mammal" can be utilized in the invention, "including, but not limited to, spermatozoa from humans and spermatozoa from commonly known animals such as bovids, equids, ovids, canids, felids, goats, or swine, as well as less commonly known animals such as elephants, zebra, camels, or kudu." Ex. 1005, 14:13-21; *see also id.,* 1:8-10. More specifically, much of Evans' own work was done on bovine and equine sperm. *See, e.g., id.,* 11:14-16 ("Figure 5 shows univariate and bivariate histograms illustrating improved resolution between X-chromosome bearing and Y-chromosome bearing populations of ***bovine spermatozoa*** using a particular embodiment of the amplification invention.") (emphasis added); *id.,* 12:46 ("Figure 9 shows univariate and bivariate histograms illustrating the improved resolution between X-chromosome bearing and Y-chromosome bearing populations of ***equine spermatozoa*** using a particular embodiment of the amplification invention.") (emphasis added).

> ***Claim 69:*** ***A flow cytometry system for sperm according to claim 42 wherein said pulsed laser is selected from a group consisting of Nd:YAG and Nd:YVO4.***

See Ground 1, Claim 42, and Ground 2, Claim 42(f), above. Additionally, as discussed above, Piper expressly discloses using a pulsed laser, such as "neodymium:YAG" laser, whose "output may be frequency-doubled to generate

high repetition rate pulsed output in the visible [spectrum]." Ex. 1009, 3:17-23. Such devices, Piper predicts, will likely "increasingly dominate in laser applications requiring long-term reliability in the low-power regime; their compact size and projected low cost are especially appropriate to applications requiring multiple sources as in flow cytometry." *Id.,* 3:24-27. Thus, it would have been obvious to use an Nd:YAG pulsed laser, like the one taught by Piper, in Evans' flow-sorting system. Ex. 1003 ¶ 131.

E. Ground 3: Claim 51 Is Obvious Over Evans In View Of Piper And Tardif And In Further View Of Lakowicz.

Claim 51 recites a flow cytometry system according to claim 42 wherein the pulsed laser comprises a fluorescence activation wavelength of 355 nm. As discussed in Ground 2 above, this claim is rendered obvious by Evans in view of Piper and Tardif. Tardif, for example, teaches using a pulsed radiation source on Hoechst 33342 dye-stained sperm at a wavelength of 327 to 395 nm. Ex. 1006, 202. However, should any additional motivation be necessary to use a laser comprising a fluorescence activation wavelength of 355 nm to irradiate Hoechst dye-stained DNA, Lakowicz expressly provides it. Ex. 1008, Table 1.

More specifically, Lakowicz discloses a flow cytometer system that differentiates fluorescently-dyed cells. *Id*., Abstract; 1:10-12. In Lakowicz's system, cells are stained with Hoechst 33342 and then irradiated with a periodically pulsed laser. *Id.,* 2:11-30; 8:62-64, Figs. 1 and 2; Table 1.) The laser

"can produce pulses at a repetition frequency in the Mhz-range which is sufficient to illuminate each cell with a pulse of light at least one time as it passes through the observation point of flow chamber 3." *Id.,* 9:1-5; Fig. 2.) Importantly, Lakowicz teaches that, for cells stained with Hoechst 33342 dye, the laser should be operated at "***325-355 nm (UV)***," which is the "dye excitation/absorption wavelength" for Hoechst 33342. *Id.*, Table 1.

Thus, a POSA practicing Evans' flow-sorting system modified with a pulsed laser, as taught by Piper, would have known, from Tardif's general disclosure or Lakowicz's more specific disclosure, to use a beam of light providing a 355 nm wavelength of radiation when irradiating DNA stained with Hoechst 33342 dye. Ex. 1003 ¶ 134. The POSA would also have had a reasonable expectation of success in exciting Hoechst 33342 dye-stained sperm using this light at this wavelength given that it falls right in the middle of the range provided by Tardif and is precisely taught by Lakowicz to be appropriate for exciting Hoechst 33342 dye-stained DNA. *Id.*

F. <u>Ground 4:</u> Claims 66 and 67 Are Obvious Over Evans In View Of Piper And Tardif, And In Further View Of Fukuda.

Claim 66 depends from claim 42 and further recites "wherein nozzle comprises at least two nozzles." (As discussed in Section VII above, Petitioner proposes construing the term "nozzle" in claim 42 as "at least one nozzle," which would provide proper antecedent basis for this otherwise nonsensical limitation.)

As detailed in Grounds 1 and 2 above, Evans, as modified by Piper and (if needed) Tardif, teaches a flow cytometry system for staining and sorting sperm using a pulsed laser. Neither of these disclosures, however, expressly mentions irradiating a fluid stream flowing from "at least two nozzles." This feature, however, is expressly taught by Fukuda. Ex. 1010.

Specifically, Fukuda describes an improved flow cytometer containing two oppositely-opposed nozzles from which a sample fluid may flow into a flow cell. *Id.,* 2:9-46; Figures 1-9. Fukuda teaches that a benefit to using two nozzles is increased efficiency. *Id*., Abstract (explaining that with "two liquid specimen nozzles [] disposed opposite to each other . . . the analysis processing time can be notably shortened."); *see also id.,* 5:21-27 (same). As depicted in Figure 1 of Fukuda, the fluid sheath streams from both nozzles (labeled 18) are irradiated by the "light emitting element such as a laser source" (labeled 29) inside a flow cell (11). *Id*., Fig. 1; *see also id.,* 3:42-4:22 (Embodiment 1).

Accordingly, a POSA seeking to increase to increase the efficiency of Evans' flow-sorting method, would have been motivated by Fukuda to modify the method by increasing the number of nozzles used to disperse the sheath fluid and sample. Ex. 1003 ¶ 138. The POSA would also have had a reasonable expectation of success in using the modified two-nozzle flow cytometer given Fukuda's disclosure of a working example. *Id.* Of course, the POSA would also have known

how to make any necessary modifications to Fukuda's two-nozzle approach should such be necessary to maximize the use of two nozzles for flow-sorting sperm. *Id., see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007) ("[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle. . . . A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton.").

Claim 67 depends from claim 66 and further recites that the "sperm cell collector is selected from the group consisting of multiple containers and a combined collector having a [*sic*] individual containers." This claim is obvious for the same reasons claim 66 is. In addition, as discussed above for Claim 57, Evans expressly discloses a sperm cell collector comprising ***multiple*** containers. More specifically, as shown in Evans Figure 1 (reproduced above), Evans' system includes collection containers (15) situated below each of the X-bearing droplets and Y-bearing droplets. Additionally, Evans provides that "the flow cytometer acts to separate the particle or cells (16) by causing them to be directed to one or more ***collection containers*** (15)." Ex. 1005, at 17:15-29 (emphasis added); *see also id.,* 79:11-16 (claims 140 and 141, reciting that the apparatus comprises a "collection container" for each of the X and Y-bearing sperm cells).

IX. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that trial be instituted and that claims 42-59 and 65-67, and 69 of the ‘116 patent be cancelled.

Dated: November 30, 2017

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CERTIFICATION OF WORD COUNT UNDER 37 CFR § 42.24(d)

Pursuant to 37 C.F.R. § 42.24, I certify that the foregoing **PETITION FOR *INTER PARTES* REVIEW** contains 12,663 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: November 30, 2017

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CERTIFICATE OF SERVICE

I hereby certify that on this 30th day of November, 2017, a copy of this **PETITION FOR *INTER PARTES* REVIEW** has been served by Federal Express at the following address for the Patent Owner:

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