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. 8,652,769
Issued: February 18, 2014
Filed: August 9, 2010
Inventors: George S. Seidel *et al.*

Title: Methods for separating frozen-thawed spermatozoa into X-chromosome bearing and Y-chromosome bearing populations

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Case IPR2018-00250

PETITION FOR *INTER PARTES* REVIEW
UNDER 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42

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1005	Lu *et al.*, "*In vitro* fertilization with flow-cytometrically-sorted bovine sperm," *Theriogenology* 52-8: 1393-1405 (1999) ("Lu")
1006	WO 99/33956, published July 8, 1999, to Seidel *et al.* ("Seidel")
1007	U.S. Patent No. 5,985,216, issued November 16, 1999, to Rens *et al.* ("Rens")
1008	U.S. Patent No. 5,135,759, issued August 4, 1992, to Johnson ("Johnson '92")
1009	Salisbury *et al.*, "Physiology of reproduction and artificial insemination of cattle," 2nd Ed. (1978) ("Salisbury")
1010	Rens *et al.*, "A novel nozzle for more efficient sperm orientation to improve sorting efficiency of X and Y chromosome-bearing sperm," *Cytometry 33*:476-481 (1998) ("Rens '98")
1011	Fugger *et al.*, "Births of normal daughters after MicroSort sperm separation and intrauterine insemination, in-vitro fertilization or intracytoplasmic sperm injection," *Human Reproduction 13*:9, 2367-2370 (1998) ("Fugger")
1012	Johnson, *et al.*, "Gender preselection in humans? Flow cytometric separation of X and Y spermatozoa for the prevention of X-linked diseases., *Hum. Reprod. 8*, 1733-1739 (1993) ("Johnson '93")
1013	Parrish *et al.*, "Bovine *in vitro* fertilization with frozen-thawed semen," *Theriogenology 25*:591–600 (1986) ("Parrish")
1014	Khatamee *et al.*, "A controlled study for gender selection using swim-up Separation," *Gynecol. Obstet. Invest*. *48*:7–13 (1999) ("Khatamee")

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1015	Johnson, L.A. *et al.*, "Recent advances in sex preselection of cattle: Flow cytometric sorting of X- & Y-chromosome bearing sperm based on DNA to produce progeny," *Theriogenology 41*:51-56 (1994) ("Johnson '94")
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1026	Hong Wei's Master's Thesis, entitled, "Studies on *in vitro* fertilization (IVF) of bovine oocytes with sorted X and Y sperms by flow cytometry," Guangxi Agricultural University, Supervising Professor Lu Kehuan**,** May 1994.
1027	Certified English Translation of Hong Wei's Master's Thesis (Ex. 1026) ("Wei").
1028	Seidel, G. E. and Johnson, L.A., "Sexing Mammalian Sperm – Overview," *Theriogenology 52(8)*:1267-1272 (1999) ("Seidel '99")

I. INTRODUCTION

Trans Ova Genetics, L.C. ("Petitioner") requests IPR and cancellation of claims 1-16 of U.S. Patent No. 8,652,769 ("the '769 patent").

The '769 patent is drawn to methods of fertilizing an egg using sperm cells that have been frozen, thawed, and then "sorted," *i.e.*, separated using flow cytometric staining techniques into two populations, those carrying an X chromosome and those carrying a Y chromosome. The challenged claims recite a method of using the frozen-thawed sorted sperm to fertilize an egg "at success levels of at least about 70% of the success levels with sperm that have not been separated and/or frozen."

The claimed methods were not new. Specifically, it was known that sperm could be frozen, thawed, sorted, and then used to fertilize eggs. Nonetheless, the Patent Owner gained allowance of the claims by persuading the Examiner that the cited art combination—Seidel (Ex. 1006) in view of Lu (Ex. 1005)—failed to disclose the "at least about 70%" success limitation. But, contrary to the Patent Owner's assertions, Lu expressly discloses the claimed success levels.

In particular, Lu's work—much of which was copied *verbatim* into the '769 patent specification to support the claims—showed that frozen-thawed sorted sperm fertilized eggs at greater than 70% of success levels with frozen-thawed unsorted sperm. Had the Examiner recognized that Lu's disclosure not only taught,

but also was the ***sole support for***, the claimed "at least about 70%" claim limitation, he never would have allowed the claims. Petitioner asks this Board to remedy this mistake, correctly apply Lu's teaching, and cancel the challenged claims.

Finally, Petitioner proposes alternative grounds of obviousness based on Lu and Seidel as principal references. Seidel describes essentially the same process as claimed, but does not expressly disclose sorting frozen-thawed sperm. However, as discussed below, it would have been obvious to apply Lu's teaching of sorting frozen-thawed sperm to Seidel's method, or vice-versa.

Accordingly, the challenged claims should be canceled.

II. MANDATORY NOTICES

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

A. Real Parties In Interest. Trans Ova Genetics, L.C. 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. The '769 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 has also filed petitions for IPR against a second patent owned by the Patent Owner here, XY, LLC: U.S. Patent No. 7,723,116 (IPR2018-00247 and IPR2018-00248), and will shortly be filing a petition for IPR against a third patent owned by the Patent Owner, U.S. Patent No. 6,372,422 (IPR2018-00249).

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

Lead Counsel	Backup Counsel
David Kelly Registration No. 53,106 Hunton & Williams LLP 600 Peachtree Street, N.E. Atlanta, GA 30308 Direct: 404.888.4280 Fax: 404.602.8671 dkelly@hunton.com	**Gene J. Yao** Registration No. 47,193 Hunton & Williams LLP 200 Park Ave, New York, NY 10166 Direct: 212.309.1030 Fax: 212.309.1877 gyao@hunton.com

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 '769 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 1-16 of the '769 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	References
I	16	§ 103	Lu (Ex. 1005) and Johnson '94 (Ex. 1015)
II	1-5, 7-12, 14-15	§ 103	Lu (Ex. 1005) and Rens (Ex. 1007)
III	6, 13	§ 103	Lu (Ex. 1005), Rens (Ex. 1007), and Seidel (Ex. 1006)
IV	16	§ 103	Seidel (Ex. 1006), Lu (Ex. 1005), and Johnson '94 (Ex. 1015)
V	1-15	§ 103	Seidel (Ex. 1006), Lu (Ex. 1005), Johnson '94 (Ex. 1015), and Rens (Ex. 1007)

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. Petitioner's arguments are supported by a Declaration from David J. Miller, Ph.D (Ex. 1003), Professor of Animal Sciences at the University of Illinois, who has over 30 years of relevant experience, detailed in his C.V. (Ex. 1004.)

IV. LEVEL OF ORDINARY SKILL IN THE ART

The '769 patent claims priority (through a chain of applications) to U.S. Provisional Application Nos. 60/253,787 and 60/253,785, each filed on November 29, 2000. Without conceding that this priority claim is valid, Petitioner and its expert declarant, Dr. Miller, use November 29, 2000, 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 '769 patent relates to methods of fertilizing eggs using sorted sperm that was previously frozen. A POSA for purposes of the '769 patent includes someone with at least a Bachelor of Science degree in the animal sciences or closely related discipline and at least 5 years of experience in one or more of the following areas: mammalian reproductive technologies, including egg fertilization techniques such as artificial insemination ("AI") and *in vitro* fertilization ("IVF"); study of the various factors that affect fertilization success; handling of mammalian sperm, including cryopreservation, thawing, insemination, and fertilization; genetic, biological, and/or biochemical study of sperm; and the use of flow cytometric techniques to study and/or sort sperm. Ex. 1003 ¶ 18. Dr. Miller is qualified to opine from the perspective of a POSA. *Id*.

V. STATE OF THE RELEVANT ART

In summarizing the state of the art as of November 1999, Petitioner cites additional references beyond "prior art presented as the basis for obviousness," which "legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015).

A. Methods Of Sorting And Freezing Sperm To Then Use For Offspring Preselection (Male Or Female) Were Well-Known.

The use of flow cytometric staining techniques to "sort" mammalian sperm as a means of preselecting the sex of offspring was well-known before November 2000. Ex. 1003 ¶¶ 26-27. In his seminal 1992 patent in this area, Lawrence Johnson described the basic process. *Id*. (citing Ex. 1008 at 2:64-4:58). Briefly, sperm are collected, incubated with a DNA-binding dye, and then extended to a desired concentration. *Id*. The sperm are then loaded into a flow cytometer, where they are encapsulated into droplets and flowed past a laser beam. *Id*. The laser excites the fluorescent dye, which then emits a signal that is collected and analyzed. *Id*. Because X chromosomes contain more DNA than Y chromosomes, the X-containing droplets emit more fluorescent light than the Y-containing droplets. *Id.* For sorting, the X droplets are deflected into one collection vessel, and the Y droplets are deflected into a different collection vessel. *Id*.

Methods of freezing sperm for preservation also had been well-known. Ex. 1003 ¶ 28. Salisbury's 1978 chapter, entitled "Principles and Techniques of Freezing Spermatozoa," noted that since the discovery that glycerol protected sperm "freezing has been the preferred method of preserving spermatozoa." Ex. 1009, 494. Salisbury added that sperm stored in liquid nitrogen "survive with relatively high fertility after thawing," though notes that "for optimum fertility[,] larger numbers of spermatozoa are used for frozen than for unfrozen semen." *Id*.

B. Methods Of Sorting Sperm At Higher Speeds, Higher Stain Concentrations, and Higher Sort Purities Were Known.

In the mid-1990s, although the basic process of sorting sperm remained the same, improvements were made to various aspects of the process, most notably, the conditions and speed at which the sperm were stained and sorted, and the average sort purities of the X and Y populations. Ex. 1003 ¶¶ 29-32.

Seidel's July 1999 patent application describes a process of sorting bovine sperm to successfully produce embryos. Ex. 1006, Abstract, 19:24-22:10, 25:1-26:2. Seidel recommends staining the sperm with "higher amounts of stain," such as "at least about 38 μM" Hoechst 33342, and incubating for one hour at 34°C. *Id.,* 20:19–25, 35:22-25 (claim 7). Seidel also discloses sorting the sperm using a MoFlo® high speed sorter. *Id.,* 10:27–29, 25:1-26:2. In this way, "rates of sorting in the thousand and twelve hundred ranges have already been achieved" (*id.* 11:10-

13), and at an "[a]verage sort purity [of] 89% of the desired sex." *Id.,* 22:29–23:1, 25:1-26:2.

To further increase sorting speed, Rens' 1999 patent describes a modified nozzle—the part of the flow cytometer that the sperm line up and pass through. Ex. 1007; Ex. 1003 ¶ 32. Rens' modified nozzle was elliptical-shaped, which oriented the sperm in a manner allowing for theoretical sorting speeds "up to at least 15,000 sperm per second" and demonstrated sorting speeds of about 2,000 sperm per second. Ex. 1007, 4:29-33; 7:46-57 (Example 7). Like Seidel, Rens also was able to achieve "[h]igh purity sort samples" of approximately 90%. *Id.*, 7:8-12; *see also id.*, 7:31-35, 7:4-51.

C. Methods Of Sorting Frozen-Thawed Sperm And Using It In IVF Were Known.

Methods of sorting frozen-thawed sperm also were known before November 2000. Ex. 1003 ¶¶ 33-39. For example, Lu studied the effects of freezing, sorting, and stain concentration on the fertilization potential of bovine sperm. Ex. 1005, 1396-1398, Tables 1-3. According to Lu, sorting frozen-thawed sperm was "very attractive since one then could have access to a wide range of genetics rather than being limited to bulls in the vicinity of the sorting facility." *Id.,* 1397. Put another way, the ability to freeze sperm before sorting it allows for the sperm to be stored

and transported over greater distances, thus providing greater options regarding when and where to sort. Ex. 1003 ¶ 33.

Lu reported fertilization data indicating that "frozen-thawed, stained sorted sperm" yielded blastocysts at comparable levels to both unfrozen sperm and unsorted sperm. Ex. 1005, 1396-1398, Tables 1 & 3. Notably, Lu's methods and data were expressly incorporated into the '769 patent and provide the ***only express support*** in the patent for the claimed "at least about 70%" fertilization success rate. *Compare, e.g., id.* to Ex. 1001 at 9:17-10:23 and Table 1.

Years earlier, Lu's two co-authors, Johnson and Cran, had published a paper describing similar work. Ex. 1015. Specifically, Johnson '94 reported on studies "us[ing] previously frozen sperm for sorting," which had "resulted in fertilized eggs and developed embryos from sperm that had been originally frozen in straws, then thawed, stained and flow sorted." *Id*., 55.

But Lu and his peers were not the only ones sorting frozen-thawed sperm in the 1990s. In a paper published in 1998, Fugger disclosed sorting frozen-thawed human sperm using flow cytometry Ex. 1011, 2367-2678. Following sorting, Fugger used the X-bearing sperm in both IVF and AI procedures, leading to numerous successful gender-selected pregnancies and births. *Id*. Rens had also

described sorting "human cryopreserved-thawed sperm" using its elliptical-shaped nozzle developed to increase sorting efficiency. Ex. 1007, 6:54-67.

D. The Prior Art Taught That Frozen-Thawed Sorted Sperm Used In IVF Was At Least 70% As Effective At Fertilizing Eggs As Compared To Unsorted Or Unfrozen Sperm.

As noted, the prior art already had disclosed sorting frozen-thawed sperm. Moreover, Lu—which published 11 months before the '769 patent's earliest effective priority date—had specifically reported the ***exact same*** fertilization data that the '769 patent inventors would later incorporate and use to support the claimed "at least about 70% fertilization" success rate. Ex. 1005 1396-1398, Tables 1 & 3; *see also* Ex. 1003 ¶ 40.

VI. SUMMARY OF THE CLAIMED INVENTION

A. Brief Description Of The Challenged Claims

Claims 1-5, 7-12, and 14-16 are being challenged. Claims 1 and 16 are independent. The broadest of these, claim 16, recites:

> 16. A method of producing a frozen-thawed sorted sperm sample comprising:
>
> thawing frozen sperm cells;
>
> staining said thawed sperm cells with a concentration of Hoechst 33342 greater than 40 micromolar for a period of time sufficient to achieve uniform staining;
>
> establishing the staining temperature between about 30°C. and about 40 C.°;

> determining a sex characteristic of said sperm cells;
>
> separating said sperm cells according to the determination of their sex characteristic;
>
> isolating sperm cells separated according to the determination of their sex characteristic in a collection element; and
>
> establishing a frozen-thawed sorted sperm sample from said sperm cells isolated in said collection element, the frozen-thawed sorted sperm sample being capable of fertilizing an egg at success levels of at least about 70% of the success levels with sperm cells that have not been separated and/or frozen.

Claim 1 is similar to 16, though it contains a few notable differences. First, it recites that the sample is a "frozen-thawed sorted ***artificial insemination*** sample." Second, it omits the "period of time sufficient to achieve uniform staining" requirement. Third, it requires that the sperm be separated "at a rate of ***greater than 1000 sperm per second*** for either X-chromosome bearing sperm or Y-chromosome bearing sperm." And, finally, rather than merely being "capable of fertilizing an egg," the sample must ***actually*** fertilize an egg.

The remaining challenged claims all depend from claim 1. Claims 2-6 and 9-13 specify some aspect of the sperm sample, such as the type, size, or purity. Claims 2 and 3 recite that the Y-bearing sperm population (claim 2) and X-bearing sperm population (claim 3) are "greater than 85%" pure. Similarly, claims 9 and 10 recite sorting the sperm cells into separate populations and that one of those

populations comprises "at least about 85%" Y-bearing cells (claim 9) or "at least about 85%" X-bearing cells (claim 10).

Claim 4 limits the sperm to "bovine sperm cells." Claim 5 depends from claim 4 and further recites that the sample contain between about 150,000 and 1,000,000 isolated sperm cells. Claim 12, like claim 5, limits the sample to "bovine sperm cells" containing between about 150,000 and 1,000,000 isolated sperm cells. Claim 11 limits the sample to "bovine sperm cells" containing between about 1,000,000 and 3,000,000 isolated sperm cells.

Claims 6 and 13 recite that the sperm sample contain between about 40 million and 100 million equine sperm cells.

Notably, claims 7, 8 14, and 15 specify that the "frozen-thawed sorted artificial insemination sample" of claim 1 be used for ***IVF***. Specifically, claim 7 recites that the fertilizing step further comprises "fertilizing an egg *in vitro*." Similarly, claim 8 recites "fertilizing an egg with said sorted sperm to produce an embryo *in vitro.*" Claim 15 recites "fertilizing an egg with said sorted sperm to produce an embryo *in vitro*.[1] Claim 14 is slightly broader, merely requiring that the frozen-thawed sorted artificial insemination sample of claim 1 be "capable of fertilizing an egg *in vitro*."

[1] Claims 5 and 12 appear to have the same scope, as do claims 7, 8, and 15.

B. Summary of the '769 Patent Specification

The '769 patent specification is short on disclosure, but long on incorporation by reference. Indeed, the written portion of the patent is less than 12 full columns. Ex. 1001, 1:17-12:17. And much of that is filled with "background" (*id.,* 1:35-2:62), "objects" of the invention (*id.,* 2:64-4:12), and descriptions of prior art devices (*id.,* 6:45-8:13, Figs. 2&3) and others' work (*id.,* 8:14-10:23 (describing the work disclosed in seven previous references). The patent concludes with a ***18-column table of art*** containing nearly a thousand references, each of which the patent purports to "incorporate[] by reference." *Id.,* 12:15-17; *see also id.,* 12:18-30:30 (table of references).

The principal support for the claims—and the ***only*** support for the "at least about 70%" success rate—is located in two passages. The first passage summarizes Lu's staining concentration experiments and findings. *Compare* Ex. 1001, 6:3-44, *with* Ex. 1005, 1397-1398 & Table 3. The second passage begins by incorporating Lu (*id.,* 9:7-16), and then summarizes Lu's staining concentration experiments and data (*id.,* 9:17-10:23). Indeed, portions of this passage are taken nearly *verbatim* from Lu, including Lu Table 3 ("Effect of stain concentration on cleavage and development rates of frozen-thawed, stained, sorted sperm"), which was copied and pasted into the '769 patent. *Compare* Ex. 1005, 1398 (Table 3), *with* Ex. 1001, 9:53-10:13 (Table 1).

The inventors introduce Table 1 (*i.e.*, Lu Table 3) with the following summary of Lu's data:

> With conventional procedures, blastocyst production with separated spermatozoa can be 70-90% of controls with spermatozoa that have not been separated. For example, development of blastocyst has been shown to be 17% with bovine oocytes inseminated with separated spermatozoa, compared with >25% which might be expected with IVF using unseperated [*sic*] spermatozoa.

Ex. 1001, 9:48-55.

The patent concludes with a fulsome discussion of how the foregoing description of embodiments, terms, and concepts should be read as expansively as possible. *See, e.g., id*., 10:43-63.

C. Summary Of The Relevant Prosecution History

The '769 patent issued from U.S. App. No. 12/853,196, filed August 9, 2010, which claims the benefit to two provisional applications filed November 29, 2000.

Following a preliminary amendment and election, the broadest claim recited a "method of producing frozen-thawed sorted artificial insemination sample" that was "capable of fertilizing an egg." Ex. 1018, cl. 89. A dependent claim recited the "at least about 70%" fertilization success rate. *Id*., cl. 90.

In August 2011, the Office rejected the claims containing the "capable of fertilizing an egg" language as indefinite since actual fertilization was not required. Ex. 1019, 8. The Office also rejected the claims as obvious over Seidel in view of Lu, which the Examiner asserted taught all of the claim limitations except the "at least about 70%" fertilization success rate in claim 90. *Id*., 10-12. But the Examiner deemed this limitation to be inherent given that the claim did not require actual fertilization of an egg. *Id.*, 12.

In November 2011, the applicants traversed the indefiniteness rejection, arguing that the "capable of" language relates to the properties of the AI sample, such as its viability and fertilization ability. *See* Ex. 1020, 8. They asserted that sperm viability can be measured, for example, by "comparing the percentage of embryos which cleave, which reach the blastocysts stage of development, ***or*** which reach other stages of embryotic development among different sperm subjected to different treatments." *Id*. (emphases added).

In December 2011, the Office reiterated its indefiniteness and prior art rejections. Ex. 1021, 2-13. In March 2012, the applicants responded to the indefiniteness rejection by deleting the "capable of" language from the rejected claims. Ex. 1022, 2-5; *id*. at 9 ("With this response, the limitation in question ['capable of'] has been deleted in claims 89 and 90 [and] replaced with the

affirmative step of fertilizing an egg."). The applicants also amended the specification to include the following passage:

> With conventional procedures, blastocyst production with separated spermatozoa can be 70-90% of controls with spermatozoa that have not been separated. For example, development of blastocyst has been shown to be 17% with bovine oocytes inseminated with separated spermatozoa, compared with >25% which might be expected with IVF using unseperated [*sic*] spermatozoa.

Id., 7. This passage was apparently added to provide support for the claimed "at least about 70%" fertilization success rate. (However, as discussed herein, the foregoing passage merely summarizes the data from Table 3 of Lu—the very reference applicants were simultaneously arguing failed to teach the 70% limitation.)

In May 2013, the Office withdrew the obviousness rejection over dependent claim 90, finding that the "at least about 70%" success level sufficiently distinguished the claim from the cite art. Ex. 1023, 3. But the Office maintained the Seidel/Lu obviousness rejection over both independent claims (89 and 106), which failed to recite this fertilization success rate. *Id*., 8-13.

In October 2013, the applicants amended the independent claims to incorporate the "at least about 70%" fertilization success limitation, and argued that Seidel and Lu failed to teach this limitation. Ex. 1024, 2, 6-7. Interestingly,

they also amended independent claim 106 (*i.e.*, claim 16 of the '769 patent) to include the same "capable of" language they had previously deleted from the other claims to overcome the indefiniteness rejection. Ex. 1024, 5-6.

In the Notice of Allowability, the Examiner made a few minor amendments, but found the claims to be in condition for allowance. Ex. 1025, 6-7. In his "reasons for allowance," the Examiner made clear that the claims' recited fertilization success rate was the perceived point of novelty:

> The closest prior art of record, Seidel ... in view of Lu ... teach a method of obtaining frozen sperm cells, thawing said cells, staining said cells with a fluorochrome, determining a sex characteristic of said cells, separating the cells according to the sex characteristic, establishing a frozen-thawed sorted artificial insemination sample from said separated cells, and artificially inseminating a female animal to produce an offspring of the desired sex, but ***do not teach that the fertilization of an egg with the frozen-thawed sorted artificial insemination sample in an artificial insemination procedure at success levels of at least about 70% of the success levels with sperm cells that have not been separated and/or frozen.***

Id., 6 (emphasis added).

As detailed herein, the Examiner failed to appreciate that Lu ***did***, in fact, disclose the "at least about 70%" success limitation. Ironically, it was ***Lu's own***

data that the applicants added to the specification to support the ***very limitation*** they were ***simultaneously*** arguing distinguished their claims invention ***over Lu***.

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). This standard is different from—and broader than—that applied in district court litigation. *Versata Dev. Grp., Inc. v. SAP Am., Inc.*, 793 F.3d 1306, 1327-28 (Fed. Cir. 2015).[2]

A. "frozen-thawed sorted artificial insemination sample" (claims 1-15)

A POSA would understand this phrase to mean "a sample of sperm cells that has been frozen, thawed, and sorted; the sorted sample contains sufficient numbers of sperm to be suitable for artificial insemination (AI), but its use is not limited to artificial insemination and it may ultimately be used for *in vitro* fertilization (IVF)." Ex. 1003 ¶¶ 64-71. Notably, the sample need only have a sufficient number of sperm to be ***suitable*** for AI, but the sample need not ***actually*** be used for AI. *Id*.,

[2] Because the BRI standard may be different than that used in litigation, the claim constructions presented in this Petition, including where Petitioner does not propose an express construction, do not necessarily reflect the claim constructions Petitioner believes should be adopted by a district court under *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005).

¶ 65. The claims leave no doubt about this, as they expressly cover embodiments in which the frozen-thawed AI sample is actually used for ***IVF***, and not AI.[3] *Id*., ¶ 66. Indeed, claims 7, 8 and 15 specify that the AI sample of claim 1 be used for IVF. Ex. 1001, claim 7 (using the frozen-thawed AI sample of claim 1 for "fertilizing an egg ***in vitro***."); claim 8 ("producing an embryo ***in vitro*** *in vitro* [*sic*] comprising sorting sperm by the method of claim 1"); cl. 15 (same).

This construction of AI sample is also consistent with the specification, which indicates that an "artificial insemination sample" is merely one that "***can***" be utilized for AI, which, in turn, depends on the number of sperm cells. Ex. 1001, 8:14-20 (explaining that, after the artificial insemination samples are prepared, they "***can then be*** utilization [*sic*] in artificial insemination protocols.") (emphasis

[3] AI and IVF are distinct fertilization protocols. In AI, sperm is deposited into the female's reproductive tract (specifically the uterus in cattle) and conception happens otherwise normally. Ex. 1003 ¶ 50. In IVF, by contrast, the sperm and eggs are combined outside of the female body, and the resulting embryo is placed in the female's uterus. *Id*. Because AI involves depositing sperm directly inside the uterus, the procedure typically requires more sperm than is required for IVF, which is performed in a more controlled environment. *Id*. It thus follows that an adequate number of sperm for AI is typically more than sufficient for IVF. *Id*. Additionally, some AI procedures are performed with so-called "low-dose" samples of sperm, which contain numbers of sperm similar to that used in IVF. *Id*.

added). A POSA reading the specification would understand this teaching to mean that an AI sample is one that is suitable for utilization in AI protocols, but that it does not ultimately have to be used for AI. Ex. 1003 ¶ 67; *see also, e.g., CIF Licensing, LLC v. Agere Sys. Inc.*, 565 F. Supp. 2d 533, 546 (D. Del. 2008) ("The plain meaning of the phrase 'can be' is permissive, rather than mandatory.").

Further, the specification expressly requires that the claims be read expansively. Ex. 1001, 10:43-63 ("Neither the description nor the terminology is intended to limit the scope of the claims…. Further, each of the various elements of the invention and claims may also be achieved in a variety of manners. This disclosure should be understood to encompass each such variation.").

As for the number of sperm needed to be suitable as an AI sample, the claims and specification make clear that as few as 150,000, or even 100,000 sperm cells, are all that is required. Ex. 1003 ¶ 69. Specifically, the patent explains, "***[l]ow dose*** artificial insemination samples for bovine artificial insemination can contain ... ***as few as 150,000 spermatozoa***." Ex. 1001, 8:14-20 (emphasis added). Similarly, WO 99/33956 to Seidel *et al.* (Ex. 1006)—which is expressly incorporated into the '769 patent (*see* Ex. 1001, 13:20) and thus forms part of the

specification[4]—states that "artificial insemination with good percentages of success has been shown with levels of insemination of sperm at ***100,000*** and 250,000 sperm." Ex. 1006, 19 (emphasis added). Thus, the '769 patent makes clear that "low dose" samples of sperm containing as few as 150,000, or even as few as 100,000 sperm cells, could be successfully used for AI in cows. Ex. 1003 ¶ 70.

Additionally, claims 5 and 12 of the '769 patent specifically recite AI samples containing as few as 150,000 sperm. Ex. 1001, claim 5 ("said frozen-thawed sorted artificial insemination sample has a number of isolated sperm cells ***between about one hundred and fifty thousand*** to about one million.") (emphasis added); *id.*, claim 12 (same). And since independent claim 1 is presumed to be broader than claims 5 and 12, *see* pre-AIA 35 U.S.C. § 112(4), it conceivably covers AI samples containing ***even fewer*** than about 150,000 sperm cells.

In sum, the '769 patent inventors specifically and unequivocally intended the term "frozen-thawed sorted artificial insemination sample" to cover samples of sperm that, after being frozen, thawed, and sorted, contain a sufficient number of

[4] *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001) ("When a document is 'incorporated by reference' into a host document, such as a patent, the referenced document becomes effectively part of the host document as if it were explicitly contained therein.").

sperm to be suitable for either AI or IVF. This would include samples containing as few as 100,000 sperm cells. Ex. 1003 ¶¶ 70-71.

B. "frozen-thawed sorted sperm sample" (claim 16)

This phrase appears nowhere in the specification. Accordingly, it should be accorded its customary and ordinary meaning, *i.e.*, "a sample of sperm cells that has been frozen, thawed, and sorted." Ex. 1003 ¶ 72. Notably, unlike the frozen-thawed sorted ***AI*** sample of claim 1, there is no requirement that the "sperm sample" of claim 16 even be suitable for AI. *Id*.

C. "fertilizing an egg with said frozen-thawed sorted artificial insemination sample at success levels of at least about 70% of the success levels with sperm cells that have not been separated and/or frozen (claims 1-15)

This limitation—the purported point of novelty in the claims—does not appear in the specification. It consists of several subsidiary concepts that require construction, including "fertilizing an egg ... at success levels," "at least about 70%," and "have not been separated and/or frozen." Petitioner takes these in turn.[5]

Beginning with the concept of fertilization success, support for this passage was added to the specification in March 2012. Ex. 1022, 7. That passage provides:

[5] 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. It, however, reserves the right to challenge the definiteness of this limitation in the co-pending Colorado litigation.

> With conventional procedures, ***blastocyst production*** with separated spermatozoa can be 70-90% of controls with spermatozoa that have not been separated. For example, ***development of blastocyst*** has been shown to be 17% with bovine oocytes inseminated with separated spermatozoa, compared with >25% which might be expected with IVF using unseperated [*sic*] spermatozoa.

Id. (emphasis added); *see also* Ex. 1001, 9:48-55.

In this passage—and in the table that immediately follows it—the '769 patent squarely equates "blastocyst production" with fertilization success.[6] *Id.,* 9:48-10:13. This is consistent with the applicants' statements during prosecution, where they indicated that measuring blastocyst development was at least one accepted methodology for measuring fertilization. *See* Ex. 1020, 8 (arguing that "accepted" methodologies for measuring fertility characteristics "can include comparing percentage of embryos which cleave, which reach the blastocysts stage of development, or which reach other stages of embryotic development among different sperm subjected to different treatments").

[6] Petitioner notes that "fertilization" and "blastocyst production" are not the same. Rather, they are distinct concepts in mammalian embryonic development. Ex. 1003 ¶ 74. Fertilization is the fusion of the sperm cell and egg into a diploid cell called a zygote. *Id*. A blastocyst, by contrast, is a differentiated structure in which different cells develop specific fates (such as fetus and placenta), and which typically occurs 5 to 9 days after fertilization. *Id*.

Accordingly, while there may be several different "accepted" methodologies for measuring fertilization success, both the specification and prosecution history indicate that at least one such methodology—and the only one expressly mentioned in the specification—is to measure "blastocyst production," *i.e.,* compare the number of eggs inseminated to the number of blastocysts produced therefrom. Ex. 1003 ¶¶ 74-77. Under BRI, blastocyst production is thus clearly at least one way to measure fertilization success levels. *Id*. ¶ 77.

Turning to the phrase "at least about 70%," the scope of this range is unclear. The specification only literally supports "70-90%," yet the term "about" suggests that the claimed range goes below 70%. For purposes of this proceeding, Petitioner proposes that the phrase means "at least 70%, give or take a few percent." Ex. 1003 ¶ 78.

Finally, Petitioner turns to the phrase "have not been separated ***and/or*** frozen." The term "and/or" is generally construed to mean "having element A alone, element B alone, or elements A and B taken together." *Ex Parte John Nicholas Gross*, Appeal 2011-004811 (Patent Tr. & App. Bd., Dec. 31, 2013). As the claimed phrase is expressed in the negative, however ("have ***not*** been separated ***and/or*** frozen"), the appropriate construction must also be stated in the negative: "have not been separated, have not been frozen, or have been neither separated nor

frozen." (The specification and claims use the terms "separated" and "sorted" interchangeably, and thus either term can be used in this construction.)

In sum, a POSA would understand that fertilization success can be measured by "blastocyst production," *i.e.*, comparing the number of eggs inseminated to the number of blastocysts produced. Ex. 1003 ¶¶ 73-77. The POSA would further understand that he or she would need to compare the fertilization success of eggs inseminated with the frozen-thawed AI sample to the fertilization success of eggs inseminated with a reference sperm sample that: (i) has not been separated, (ii) has not been frozen, ***or*** (iii) has been neither sorted nor frozen. *Id*., ¶¶ 78-80. Finally, the POSA would understand that the percentage of successful fertilizations achieved with the frozen-thawed AI sample must be at least 70% (give or take a few percent) of that achieved with at least one of the three reference samples. *Id*.

D. "*in vitro*" (claims 7-8 and 14-15)

A POSA would understand the phrase "*in vitro*" to mean "occurring outside of the organism, such as in a laboratory." Ex. 1003 ¶ 81. Thus, the claims' recitation of "fertilizing an egg *in vitro*" (claims 7 and 14) and "fertilizing an egg with said sorted sperm to produce an embryo *in vitro*" (claim 15) simply means fertilizing an egg outside the body of the female mammal. *Id.*

E. "capable of fertilizing an egg" (claims 14 and 16)

A POSA would understand the phrase "capable of" in claims 14 and 16 to mean that the frozen-thawed sperm sample "has the ability to fertilize an egg, but need not actually do so." Ex. 1003 ¶ 82. The term "capable of," like its synonyms "can be" and "may be," are typically interpreted as permissive unless the specification indicates otherwise. *CIF Licensing, LLC*, 565 F. Supp. 2d at 546 ("'[T]he plain meaning of the phrase 'can be' is permissive, rather than mandatory."); *see also, Alloc, Inc. v. ITC,* 342 F.3d 1361, 1378 (Fed. Cir. 2003) (Schall, J., dissenting) ("'Can' and 'may' are commonly used by patentees to show that a limitation is permissive."). Here, neither the language of the claims nor the specification demonstrates an intent to depart from this plain meaning.

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 ¶¶ 83-196.

A. Each of the Relied-Upon References is Authentic, Admissible Prior Art to the '769 Patent

Petitioner relies on the following references:

1. Lu (Ex. 1005) – Lu published in a 1999 volume of the journal *Theriogenology*, and is thus prior art to the '769 patent claims under pre-AIA 35 U.S.C. § 102(a). As detailed in the accompanying declaration of Jonathan Hartnett,

a librarian with the law firm of Hunton & Williams, LLP, Exhibit 1005 is an authentic, admissible copy of the Lu reference under the Federal Rules of Evidence. Ex. 1002.

2. Johnson '94 (Ex. 1015) – Johnson '94 published in a 1994 volume of the journal *Theriogenology*, and is thus prior art to the '769 patent claims under pre-AIA 35 U.S.C. § 102(b). As detailed in Mr. Hartnett's Declaration, Exhibit 1015 is an authentic, admissible copy of the Johnson '94 reference under the Federal Rules of Evidence. Ex. 1002.

3. Rens (Ex. 1007) – Rens is a United States patent issued on November 16, 1999, and is thus prior art to the '769 patent under pre-AIA 35 U.S.C. § 102(b). Exhibit 1007 is an authentic, admissible copy of the Rens reference under the Federal Rules of Evidence.

4. Seidel (Ex. 1006) – Seidel is a PCT application that published July 8, 1999, and is thus prior art to the '769 patent under pre-AIA 35 U.S.C. § 102(b). Exhibit 1006 is an authentic, admissible copy of the Seidel reference under the Federal Rules of Evidence.

Exhibits 1005 (Lu), 1007 (Rens), 1006 (Seidel), and 1015 (Johnson '94) each meet 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; and (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 such Exhibit will best serve the purposes of the Federal Rules of Evidence and the interests of justice. Additionally, as Exhibit 1015 (Johnson '94) is over 20 years old, and was prepared before January 1, 1998, it 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, Exhibit 1006 (Seidel) is a WIPO publication, and Exhibit 1007 (Rens) is an issued U.S. Patent; as such, each meets the public records exception to hearsay under Fed. R. Evid. 803(8).

B. Invalidity Grounds Relying On Lu As The Principal Reference[7]

1. Ground 1: Claim 16 Is Obvious Over Lu In View Of Johnson '94.

As claim 16 is the broadest of the claims, Petitioner begins with it. As detailed below, Lu expressly discloses every element of claim 16, with the possible

[7] Petitioner recognizes that raising grounds of rejection based on art overcome during prosecution is generally disfavored. However, because Lu literally describes the ***exact same*** methods and results as those disclosed and claimed in the '769 patent, and since the Examiner appears to have allowed the claims only because he failed to appreciate this fact, Petitioner feels more than justified in raising Lu-based grounds in this Petition.

exception of the staining temperature ("between about 30° and about 40°C"). However, this temperature range was conventional. In fact, the only mention Lu makes of any staining temperature is a previous experiment in which sperm had been stained at 35°C. Moreover, Johnson '94 discloses that a 35°C staining temperature is central to achieving uniform stain penetration. A POSA would thus have understood Lu's experiments to have been optimally performed at or near 35°C. *Id.* ¶¶ 91-92.

***Claim 16 (preamble):* A method of producing a frozen-thawed sorted sperm sample comprising:**

Lu studied how freeze-thawing and stain concentration affected the ability of bovine sperm to fertilize eggs. Ex. 1005, 1396-1398; Tables 1 & 3. Lu Table 1 reports blastocyst development rates of eggs inseminated with "Sorted-fresh," "Sorted-frozen," "Unsorted-fresh," and "Unsorted-frozen" sperm. *Id*., 1396. Lu Table reports the effect of Hoechst 33342 dye concentrations (224 μM and 2,240 μM) on blastocyst development rates of "frozen-thawed, stained, sorted sperm." *Id*., 1398. Lu also reports on experiments performed in 1992 in the U.K. in which "frozen-thawed sperm ... were stained ... [and] sorted." *Id*., 1397-1398.

Importantly, Lu explains the advantage of freezing sperm ***before*** sorting them: "Being able to sex frozen sperm would be very attractive since one then

could have access to a wide range of genetics rather than being limited to bulls in the vicinity of the sorting facility." *Id*.

Claim 16(a): thawing frozen sperm cells;

As discussed above, Lu expressly discloses thawing a sample of frozen sperm cells. *Id.*, 1395-1398, Tables 1 & 3. Lu also describes earlier experiments on frozen-thawed sperm samples performed in the U.K. *Id*., 1397-1398.

Claim 16(b): staining said thawed sperm cells with a concentration of Hoechst 33342 greater than 40 micromolar for a period of time sufficient to achieve uniform staining;

Lu expressly discloses staining frozen-thawed sperm cells "either at the standard 224 μM or 2,224 μM of Hoechst 33342" before sorting. *Id.*, 1398. Lu observes better cleavage and blastocyst percentages with the 2,224 μM concentration of stain, and attributes this as likely due to the decreased amount of time required to stain (60 minutes versus 190 minutes for the 224 μM concentration). *Id*.; *see also id.*, Table 3 (reporting that frozen-thawed, sorted sperm stained with 2,224 μM Hoechst 33342 at 60 minutes had a 23% blastocyst success rate).

Claim 16(c): establishing the staining temperature between about 30°C and about 40 C°;

Lu discloses staining frozen-thawed sperm at "***standard*** stain concentration and incubation temperature." *Id.*, 1398 (emphasis added). A POSA would have

understood this to be between 30°C to 40°C, as such was conventional when staining sperm with Hoechst 33342. Ex. 1003 ¶¶ 90-93.

This is corroborated by Lu itself, which references previous studies showing that "[s]taining sperm with Hoechst 33342 ***at 35°C*** [did] not greatly affect motility of fresh sperm." Ex. 1005, 1394 (emphasis added). A POSA thus would have understood 35°C to be a "standard" sperm staining temperature. Ex. 1003 ¶ 93.

However, should additional evidence of obviousness be needed, Johnson '94 explains that one of the "central" advances made in sex preselection of cattle using flow cytometric sorting was "incubating sperm at 35 C with a vital fluorochrome (Hoechst 33342) to get uniform stain penetration." Ex. 1015, Abstract, 52. Thus, Johnson '94 establishes that staining Hoechst 33342 dye-stained sperm at or near 35°C was not just known, but was critically important. Ex. 1003 ¶ 91.

In sum, a POSA would have understood that Lu would have established a staining temperature within the claimed range of about 30°C to 40°C, and would have both been motivated to do the same and expected this temperature range to be optimal for sorting frozen-thawed sperm. Ex. 1003 ¶ 93.

<u>Claim 16(d):</u> determining a sex characteristic of said sperm cells;

Lu describes sorting sperm based on their sex characteristic. Lu begins by describing the "great interest in sex predetermination in cattle," especially given the "clear economic and management advantages to be gained," such as increased

milk and calves from female cows and beef from bulls. Ex. 1005, 1394. To that end, Lu studies the effects of freezing and staining concentrations on the ability of sorted and unsorted sperm to fertilize eggs. Ex. 1005, 1396-1398; *see also* Tables 1-3. Lu also reports on earlier studies showing that frozen-thawed sperm could be sorted and the "sexed sperm" utilized to successfully inseminate heifers. *Id*., 1397-1398. Lu concludes: "Sexed bovine sperm, whether frozen or unfrozen, can be used successfully in IVF systems." *Id.,* 1403.

Claim 16(e): separating said sperm cells according to the determination of their sex characteristic;

As discussed above, Lu explains that "[b]eing able to sex frozen sperm would be very attractive," as it allows sperm to be sorted from bulls housed at great distance from the flow cytometers, expanding the possible number of bulls to which this technology can be applied and enhancing its impact. Ex. 1005, 1397. Lu describes earlier studies using sex-sorted sperm to successfully inseminate cattle, including studies conducted in the U.K. that had inseminated heifers with frozen-thawed, sex-sorted sperm, thereby producing sexed embryos. *Id*., 1394, 1397-1398.

Lu reports testing data on numerous sperm samples, including sperm that were sex-sorted and then frozen, and sperm that were frozen and then bulk-sorted.[8]

[8] Bulk-sorting was done "without regard for DNA content" to speed up collection rates. Ex. 1005, 1395. As Lu explains, bulk-sorted sperm "were

Ex. 1005, 1396-1398, Tables 1 & 3. Based on the results, Lu concludes that "[s]exed bovine sperm, whether frozen or unfrozen, can be used successfully in IVF systems." *Id.* 1403.

Claim 16(f): ***isolating sperm cells separated according to the determination of their sex characteristic in a collection element;***

See Ground 1, Claim 16(e) above. The separated sperm cells are necessarily collected in a "collection element." Ex. 1003 ¶ 100.

Claim 16(g): ***and establishing a frozen-thawed sorted sperm sample from said sperm cells isolated in said collection element, the frozen-thawed sorted sperm sample being capable of fertilizing an egg at success levels of at least about 70% of the success levels with sperm cells that have not been separated and/or frozen.***

As with all the '769 patent claims, this is the *critical* limitation. This was the limitation that the Examiner (wrongly) concluded distinguished the claimed invention over the prior art. Undoubtedly, the confusing nature of the limitation, with its indistinct concepts of "being capable of fertilizing," "success levels," "at least about 70%," and "have not been separated and/or frozen," hampered the Examiner's ability to fairly apply the art to the limitation.

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subjected to the ***same conditions*** as for sorted X and Y sperm." *Id*. (emphasis added). Given that the bulk-sorted sperm were subject to the "same conditions" as the sex-sorted sperm, a POSA would have understood that the type of sorting conducted (*i.e.*, sexed vs. bulk) would have had no impact on Lu's reported fertilization success results. Ex. 1003 ¶ 98, n. 1.

In any event, to the extent this limitation's meaning can be reasonably discerned, Lu necessarily discloses it. Ex. 1003 ¶¶ 101-106. Lu Table 1, reproduced below, reports the "[c]leavage and embryonic development" of eggs inseminated with either: (i) sorted, unfrozen sperm; (ii) unsorted, unfrozen sperm; (iii) sorted, frozen sperm; and (iv) unsorted, frozen sperm:

Table 1. Cleavage and embryonic development of oocytes inseminated with sorted and unsorted sperm

Sperm type	No. oocytes	No. cleaved (%)	No. blastocysts (%)
Sorted-fresh	792	523 (66)[a]	128 (16)[a]
Unsorted-fresh	721	544 (76)[b]	172 (24)[b]
Sorted-frozen	554	394 (71)	100 (18)[a]
Unsorted-frozen	566	423 (75)	140 (25)[b]

[a,b] Percentages within columns with different superscripts differ, (P<.01), χ^2.

Ex. 1005, 1396, Table 1.

Lu Table 3, reproduced below, reports the effect of stain concentration and staining time "on cleavage and [blastocyst] development rates of frozen-thawed, stained, sorted sperm":

Table 3. Effect of stain concentration on cleavage and development rates of frozen-thawed, stained, sorted sperm (Green, et al., unpublished)

Bull	No. ejaculates	Hoechst 33342 conc. (μM)	Staining time required (min)	No. oocytes	% cleaved	% blastocysts/ oocyte
1	3	224	190	368	44[a]	17
1	3	2,240	60	373	60[b]	23
2	1	224	190	86	23[a]	0[a]
2	1	2,240	60	81	42[b]	16[b]

[a,b] Percentages within bulls within columns with different superscripts differ (P<.025, χ^2).

Id., 1398, Table 3.

As can be seen from the two tables, the "frozen-thawed, stained sorted sperm" of Table 3, while generally requiring longer staining times or higher dye concentrations, yielded relatively high blastocyst percentages. Ex. 1003 ¶ 103 (citing Ex. 1005, 1396-1398, Tables 1 & 3). Specifically, Table 3 reports that frozen-thawed sperm stained with the "standard concentration" of 224 μM for 190 minutes produced blastocysts ***17%*** of the time. *Id*. The blastocyst success rate for frozen-thawed sperm stained with 2,240 μM for 60 minutes was even higher, at ***23%***. *Id*. These success rates compare favorably to the blastocyst success rates reported in Table 1 for sperm that had not been frozen and/or sorted. *Id*. Specifically, Table 1 reports a ***16%*** and ***24%*** blastocyst success rate for eggs inseminated with "Sorted-fresh" and "Unsorted-fresh" sperm, respectively. *Id*.

Thus, both the 224μM/190min and the 2,240μM/60min samples of frozen-thawed sperm from Table 3 were ***at least 70%*** as successful at producing blastocysts as the unfrozen-sorted and unsorted samples from Table 1. *Id.* ¶ 104 (citing Ex. 1005, 1396-1398, Tables 1 & 3). This success rate is derived by dividing the blastocyst percentage of the frozen-thawed, sorted samples from Table 3 (17% and 23%, respectively) by the blastocyst percentage of the two unfrozen samples (sorted and unsorted) from Table 1 (16% and 24%, respectively). *Id*. The comparative success levels of the former range ***from 71%*** (the 224μM/190 min

frozen-thawed sorted sample compared to the unsorted-fresh sperm, *i.e.*, 17 ÷ 24) ***to 144%*** (the 2,240μM/60min frozen-thawed sorted sperm compared to the sorted-fresh sperm, *i.e.*, 23 ÷ 16). *Id*.

Lu's data thus plainly meets the "at least about 70%" requirement in at least ***two different ways***. *Id*. ¶ 105. Specifically, Lu discloses that the two frozen-thawed sorted sperm samples in Table 3 are capable of fertilizing eggs at greater than 70% the success of: (i) sperm cells that have not been frozen; ***and*** (ii) sperm cells that have been neither sorted nor frozen. *Id*.

Lu's Disclosure = '769 Patent Support For "At Least 70%" Limitation

In this IPR, the Patent Owner will presumably try to distinguish Lu. However—and this cannot be emphasized enough—***any*** argument that the Patent Owner makes to distinguish over Lu must be squared with the fact that it is the ***very same*** Lu experiments discussed herein that the '769 patent expressly relies on to support the "at least about 70%" success limitation. As discussed above, the '769 patent reports:

> With conventional procedures, blastocyst production with separated spermatozoa can be 70-90% of controls with spermatozoa that have not been separated. For example, development of blastocyst has been shown to be ***17% with bovine oocytes inseminated with separated spermatozoa***, compared with >25% which might be expected with IVF using unseperated spermatozoa.

Ex. 1001, 9:48-54 (emphasis added). This passage, added during prosecution to provide support for the claimed "at least about 70%" success" limitation, is summarizing ***Lu's data***. Indeed, immediately following this passage, the patent reproduces Lu Table 3, which includes the 17% figure cited in the foregoing passage. *Compare id.,* 9:57-10:13 (Table 1), *with* Ex. 1005, 1398 (Table 3).

As discussed above, Lu Table 3 reports the fertilization success rates of sperm frozen, thawed, stained at different dye concentrations, and then bulk-sorted at 1,000 sperm per second. Ex. 1005, 1398. Whatever the Patent Owner argues to distinguish over these experiments and data, it must be remembered that it is these ***same experiments and data*** that form the only support the '769 patent has for the claimed "at least about 70%" success limitation.

In short, the Patent Owner cannot have it both ways. It copied Lu's disclosure to provide express support for its claims; it cannot now credibly argue that Lu does not disclose its invention.

2. Ground 2: Claims 1-5, 7-12, and 14-15 Are Obvious Over Lu In View Of Rens.

Unlike claim 16, claim 1 (i) recites "an artificial insemination sample," (ii) requires "fertilizing an egg" with the sample, and (iii) recites a sorting rate "of greater than 1000 sperm per second" per X- or Y-bearing sperm. As detailed below, Lu teaches or suggests each of these limitations. Additionally, Rens

provided ample motivation to select the recited conditions (*i.e.*, staining temperature and sorting speed), as well as a reasonable expectation of success. Similarly, this combination of references also teaches or suggests all the limitations of claims 2-5, 7-12, and 14-15. The references all relate to sorting bovine semen using flow cytometry; they share common authors/inventors; each is directed to improving the accuracy, efficiency, and/or purity of sex-selected sperm; and Lu and Rens each disclose sorting frozen-thawed semen. Ex. 1003 ¶¶ 107-144.

***Claim 1 (preamble):* A method of producing a frozen-thawed sorted artificial insemination sample comprising:**

As discussed above in Ground 1, Lu expressly discloses a frozen-thawed sperm sample. Ex. 1005, 1396-1398. Moreover, although Lu's fertilization experiments involved IVF, not AI, claim 1 is not limited to samples ***only*** used for AI. As discussed in section VII above, the frozen-thawed sample need only be suitable for AI, but the claim plainly covers samples that are ***actually*** used for IVF. *See also* Ex. 1003 ¶¶ 64-71, 107. Indeed, IVF is the ***only*** application of the AI sample recited in the dependent claims. *See* Ex. 1001, claims 7 and 15 (reciting "fertilizing an egg in vitro") and claim 8 (reciting "fertilizing an egg with said sorted sperm to produce an embryo in vitro"). Notably, none of the dependent claims actually specifies using the AI sample of claim 1 ***for AI***.

Moreover, should the Patent Owner argue, as it has in the co-pending Colorado litigation, that Lu's sample contained too few sperm to be an "AI sample," this too is belied by the dependent claims. Lu estimated that its frozen-thawed sorted sample contained a theoretical maximum of about 1.5 x 10^6 sperm, less any losses during preparation for insemination. Ex. 1005, 1397. Notably, this number is ***10 times*** the amount of sperm needed for an AI sample, which the '769 patent makes clear can contain as few as 150,000 (or, possibly, even as few as 100,000) sperm. Ex. 1001, claims 5 & 12 (claiming the AI sample of claim 1 having "between about one hundred and fifty thousand to about one million" isolated sperm cells); *see also id.,* 8:14-20 ("Low dose artificial insemination samples for bovine artificial insemination can contain ... as few as 150,000 spermatozoa."); *id.,* 13:20 (incorporating Seidel, Ex. 1006, which states on page 19 that "artificial insemination with good percentages of success has been shown with levels of insemination of sperm at ***100,000*** and 250,000 sperm").

Thus, under BRI, Lu's frozen-thawed sperm sample is a "frozen-thawed sorted artificial insemination sample" as that term is specifically defined in the '769 patent claims and specification, and as it would be understood by a POSA. Ex. 1003 ¶¶ 107-109.

Further, even if the number of sperm initially collected using Lu's methods did not contain sufficient numbers of sperm to be suitable for a particular AI application, it would have been both obvious and routine for a POSA to simply conduct one or more additional sorts to arrive at a sufficient number of sperm cells. *Id*., ¶ 110.

Claim 1(a): thawing frozen sperm cells;

See Ground 1, Claim 16(a).

Claim 1(b): staining said thawed sperm cells with a concentration of a Hoechst 33342 greater than 40 micromolar;

See Ground 1, Claim 16(b).

Claim 1(c): establishing the staining temperature between about 30°C and about 40 C°;

See Ground 1, Claim 16(c). Based on Lu's disclosure alone, coupled with the general knowledge in the art, a POSA would have understood Lu's experiments with frozen-thawed sperm to have been conducted between 30° and 40°C. Ex. 1003 ¶ 113. However, should any additional motivation be needed to stain the sperm at the claimed temperature, Rens describes a "Sperm Preparation and Staining" protocol in which sperm are stained "over a 40-min period at 32°C." Ex. 1007, 4:54-5:6. Rens adopted this protocol from earlier methods taught by Larry Johnson (*id*., 4:61-64) and applied it to all of the Examples, including Example 4, where Rens stained frozen-thawed human sperm cells. *Id*., 6:55-67 (Example 4).

Thus, a POSA would have understood Lu to have been staining at between 30° and 40°C, as this was the "standard" sperm staining temperature in flow cytometry applications. Ex. 1003 ¶ 115. This is further evidenced by Lu's own disclosure, which described previous studies that stained frozen-thawed sperm at 32°C, and also by Rens, which, adopting conventional staining methods, used a staining temperature of 32°C on both unfrozen and frozen-thawed mammalian sperm. *Id*.

Claim 1(d): determining a sex characteristic of said sperm cells;

See Ground 1, Claim 16(d).

Claim 1(e): separating said sperm cells according to the determination of their sex characteristic;

See Ground 1, Claim 16(e).

Claim 1(f): isolating sperm cells separated according to the determination of their sex characteristic in a collection element at a rate of greater than 1000 sperm per second for either X-chromosome bearing sperm or Y-chromosome bearing sperm;

As discussed above in Ground 1, claim 16(f), Lu isolates sperm cells according to their sex. Ex. 1005, 1396-1398; 1403. Lu also reports on earlier studies that had similarly isolated sperm cells based on their sex. *Id*., 1397-1398.

Although Lu does not expressly disclose sex-sorting sperm at a rate "greater than 1,000 sperm per second" for X- or Y-bearing sperm, it does disclose that such speeds can be attained with known high-speed sorters:

> [W]ith the advent of high-speed sorters and technical improvements (21) leading to ***sort speeds approaching 10 x 10^6 sexed sperm/h*** [*i.e.*, 2,777 sorts per second], AI with sorted sperm has become a possibility (25).

Ex. 1005, 1394 (emphasis added); *see also* Ex. 1003 ¶ 119-121.

The article Lu cites—reference 21—is a 1998 article co-authored by Rens and Johnson (Ex. 1010) describing the very same "high–speed sorters and technical improvements" disclosed and claimed in Rens. Ex. 1003 ¶ 120.

Specifically, Rens discloses "a high speed sorter" modified with an elliptical-shaped nozzle designed to orient sperm in a way so as to increase sort speed yet maintain high sort purity. Ex. 1007, 2:22-32, 2:40-42. Rens' high-speed sorter "increases the yield of sorted X- and Y-chromosome bearing sperm 10-fold." *Id.,* 4:43-48; 5:13-18. Notably, Rens reports, "[w]e have found that with the elliptical nozzle, the proportion of proper orientation is maintained at sample rates up to at least 15,000 sperm per second." *Id.*, 4:29-34.

Rens Example 7 discloses that "up to 25 millionxsperm [*sic*] (50 million, total X and Y) were required to be sorted between 9am and 4pm." Ex. 1014, 7:52-54 (Example 7). Example 7 thus teaches sorting at least 1,984 X- and Y-bearing

sperm cells per second (*i.e.*, 50 million X and Y sperm divided by 25,200 seconds).[9] Ex. 1003 ¶ 123.

In sum, it would have been both obvious and desirable to a POSA sorting frozen-thawed sperm to do so as efficiently as possible, particularly if the POSA wanted to use Lu's method for low-dose AI applications. Ex. 1003 ¶ 126. To this end, the POSA would have been directed by Lu to use "high-speed sorters," such as Rens' sorters, which had a theoretical sample speed of 15,000 sorts per second and a demonstrated sort speed of about 2,000 sperm/second. *Id*.; *see also* Ex. 1016 (PTAB explaining why a POSA would have the desire and ability with reasonable expectation of success in combining Rens' high-speed sorting teaching with the prior art sorting methods).

[9] In IPR 2014-01161, the Patent Owner, XY, took the (ultimately unavailing) position that Rens Example 7 achieves a sort rate of only 992 X or Y sorts per second, not 1,984 sorts per second. Ex. 1016, 18-19. The PTAB rejected the Patent Owner's narrow reading of the phrase "sorts per second." *Id*., 10-12, 18-19. But even if the Patent Owner's strained interpretation of "sorts per second" were adopted in this case, it would require no more than routine optimization to increase the sort rate from 992 sorts per second to "greater than 1000 sperm per second." Ex. 1003 ¶ 125; *see also In re Aller*, 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.").

Moreover, the POSA would have reasonably expected the modified, high-sorting method to work on frozen-thawed sperm because Rens specifically discloses using its modified high-speed sorters on frozen-thawed human sperm. Ex. 1007, 6:53-67 (Example 4, describing sorting frozen-thawed human sperm, and noting that it orients in the elliptical nozzle at about the same proportion as fresh mouse sperm); *see also* Ex. 1003 ¶ 126.

Claim 1(g): ***establishing a frozen-thawed sorted artificial insemination sample from said sperm cells isolated in said collection element;***

As detailed above in the analysis of Ground 1, Claim 1 (preamble), Lu discloses a frozen-thawed sorted AI sample from sperm cells that are separated and isolated. Ex. 1005, 1395-1398; 1403.

Claim 1(h): ***and fertilizing an egg with said frozen-thawed sorted artificial insemination sample at success levels of at least about 70% of the success levels with sperm cells that have not been separated and/or frozen.***

This claim limitation is substantially similar to claim 16(g), except that it requires ***actual*** fertilization at the recited success level. As discussed above for Ground 1, claim 16(e) and (g), Lu discloses successfully fertilizing eggs with frozen-thawed sorted sperm, and thus expressly teaches this claim limitation. Ex. 1005, 1394-1399; Tables 1-3; *see also* Ex. 1003 ¶ 129.

Finally, should the Patent Owner attempt to argue that Lu somehow fails to teach all the claim elements, or fails to teach the elements in the exact order they

appear in the claim, or is somehow non-enabling, it bears reiterating that it is ***Lu's disclosure***—which the '769 patent inventors copied and pasted into their patent—that provides the ***only*** express support for the claimed "at least about 70%" success rate. Thus, if Lu does not disclose and/or enable the claimed invention, then the '769 patent also necessarily fails to disclose and/or enable the invention. This is true not only for claim 1, but also for the dependent claims, which Petitioner addresses next.

> ***Claim 2:*** ***The method according to claim 1, wherein the sperm cells isolated in said collection element comprise spermatozoa sorted into separate populations, wherein the spermatozoa of one of the populations comprises a purity greater than 85% Y chromosome bearing sperm cells.***

See Ground 2, Claim 1. As discussed above, a POSA practicing Lu's method would have understood that improved sort speed and purity were desirable, and thus would have naturally turned to Rens. Ex. 1003 ¶ 131. Rens, in turn, discloses X- and Y-bearing sperm populations with "purities of approximately 90%." Ex. 1007, 4:29-37; *see also id.,* 7:9-12.

> ***Claim 3:*** ***The method according to claim 1, wherein the sperm cells isolated in said collection element comprise spermatozoa sorted into separate populations, wherein the spermatozoa of one of the populations comprises a purity greater than 85% X chromosome bearing sperm cells.***

See Ground 2, Claim 2.

Claim 4: ***The method according to claim 1 wherein the frozen sperm cells comprise bovine sperm cells.***

See Ground 2, Claim 1. Lu expressly discloses sorting frozen-thawed bovine sperm cells. Ex. 1005, 1397-1398; Table 3.

Claim 5: ***The method according to claim 4 wherein said frozen-thawed sorted artificial insemination sample has a number of isolated sperm cells between about one hundred and fifty thousand to about one million.***

As discussed above, Lu discloses a frozen-thawed sorted artificial insemination sample having a theoretical "maximum" of about 1.5 million sperm cells, less "any losses during preparation for insemination." *See* Ground 2, Claim 1; *see also* Ex. 1005, 1397. A POSA would understand this disclosure as teaching a frozen-thawed, sorted sperm sample for insemination containing somewhere between a few hundred thousand sperm (assuming heavy losses during preparation for insemination) to about 1.5 million sperm (assuming little to no losses during preparation). Ex. 1003 ¶ 136. Put another way, a POSA would expect the concentration of the frozen-thawed, sorted sperm sample to fall within the recited range—"between about one hundred and fifty thousand to about one million" isolated sperm cells. *Id*.

Thus, Lu teaches a frozen-thawed sperm sample containing "about one hundred and fifty thousand to about one million" isolated sperm. *Id*. At the very least, Lu renders the recited range obvious. M.P.E.P. 2144.05 ("[W]here the

claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a prima facie case of obviousness exists.") (citing cases); *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003) ("[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness.").

Claim 7: ***The method according to claim 1 wherein the step of fertilizing an egg further comprises: fertilizing an egg in vitro.***

See Ground 2, Claim 1. As noted above, Lu discloses fertilizing eggs *in vitro* with the frozen-thawed sorted sperm. Ex. 1005, 1396-1398; Table 1.

Claim 8: ***A method of producing an embryo in vitro in vitro [sic] comprising sorting sperm by the method of claim 1, and fertilizing an egg with said sorted sperm to produce an embryo in vitro.***

See Ground 2, Claim 7. The fertilized eggs disclosed in Lu developed into embryos and then blastocysts. Ex. 1005, 1396-1398; Table 1.

Claim 9: ***The method according to claim 1 wherein the sperm cells isolated in said collection element comprise spermatozoa sorted into separate populations, wherein the spermatozoa of one of the populations comprises at least about 85% Y chromosome bearing sperm cells.***

See Ground 2, Claim 2.

Claim 10: ***The method according to claim 1 wherein the sperm cells isolated in said collection element comprise spermatozoa sorted into separate populations, wherein the spermatozoa of one of the populations comprises at least about 85% X chromosome bearing sperm cells.***

See Ground 2, Claim 2.

Claim 11: ***The method according to claim 1 wherein the frozen sperm cells comprise bovine sperm cells and wherein said frozen-thawed sorted artificial insemination sample has a number of isolated sperm cells between about one million to about three million.***

See Ground 2, Claims 4 and 5. As noted, Lu expressly discloses that, after sorting a frozen-thawed sample of sperm, a theoretical maximum of 1.5 million sexed sperm, less the inevitable losses incurred during preparation, could be available for insemination. A POSA would understand this disclosure as teaching a frozen-thawed, sorted sperm sample for insemination containing somewhere between a few hundred thousand sperm (assuming heavy losses during preparation for insemination) to about 1.5 million sperm (assuming little to no losses during preparation). Ex. 1003 ¶ 138. Put another way, a POSA would expect the concentration of the frozen-thawed, sorted sample to fall within the recited range—*i.e.*, above "about 1 million" isolated sperm cells. *Id*.

Claim 12: ***The method according to claim 1 wherein the frozen sperm cells comprise bovine sperm cells and wherein said frozen-thawed sorted artificial insemination sample has a number of isolated sperm cells between about one hundred and fifty thousand to about one million.***

See Ground 2, Claims 4 and 5.

Claim 14: ***The method according to claim 1 wherein the frozen-thawed sorted artificial insemination sample is capable of fertilizing an egg in vitro.***

See Ground 2, Claim 7.

Claim 15: ***A method of producing an embryo in vitro comprising sorting sperm by the method of claim 1, and fertilizing an egg with said sorted sperm to produce an embryo in vitro.***

See Ground 2, Claim 8.

3. Ground 3: Claims 6 and 13 Are Obvious Over Lu In View Of Rens, And In Further View of Seidel.

As discussed in Ground 2, claim 1 is obvious over Lu in view of Rens. Claims 6 and 13 merely recite that the sample comprises about 40 to 100 million equine sperm cells. These claims would have been obvious in further view of Seidel, which specifically discloses sorting equine sperm for AI. Ex. 1003 ¶ 142; *see also* Ex. 1006, 7:4-6 (disclosing sorting equine sperm); *id*., claim 3 (claiming same). Seidel also teaches that "[t]ypical artificial insemination is presently conducted with ... ***hundreds of millions of sperm*** for equine species," but that for "low dose" AI, "the dosage of sperm utilized in the insemination event are ***less than one-half or preferably even less than about 10%*** of the typical number of sperm provided in a typical artificial insemination event." Ex. 1006, 19:6-10 (emphases added).

Seidel also explains the desire in the art for sorting equine sperm: "For ages it has been desired to select the sex of specific offspring," which "has significant economic consequences when one considers its application to food producing animals such as cattle as well as celebrated trophy animals such as horses and the

like." Ex. 1006, 1:12-14. Thus, a POSA would have been motivated by Seidel to apply Lu's method of sorting frozen-thawed sperm, as modified by Rens, to equine sperm cells. Ex. 1003 ¶ 143.

Additionally, the POSA would have known from Seidel's teaching that using lower dosages of equine sperm, such as "less than one-half or preferably even less than 10%" of the "hundreds of millions" of equine sperm normally used for AI, are preferred. *Id*. (citing Ex. 1006, 3:9-18, 19:6-10). The POSA would also have had a reasonable expectation of success, as Seidel specifically discloses that its equine sperm sample may be used for AI. *Id*.

C. Invalidity Grounds Relying On Seidel As The Principal Reference

1. Ground 4: Claim 16 Is Obvious Over Seidel In View Of Lu and Johnson '94.

Seidel describes a process in which mammalian sperm is stained, sorted, and then used for AI. Although the sperm in Seidel is not frozen-thawed, a POSA would have had ample motivation to apply Seidel's method to a frozen-thawed sperm sample, as detailed below. Ex. 1003 ¶¶ 145-161.

Claim 16 (preamble): A method of producing a frozen-thawed sorted sperm sample comprising:

Seidel discloses a method of producing a sorted sperm sample for use in AI. Ex. 1006, 19:24-25, 20:4–6, 23:1–5. Seidel's goal was to minimize the stress on sperm during the sorting process by providing improved sheath and collection

media for the sperm. *Id*., Abstract, 6:15-19. In Example 1, bovine sperm are stained with 38 μM Hoechst 33342 for one hour at 34°C, sorted using a MoFlo® high-speed sorter, and isolated. *Id.,* 25:1-26:2.

Although Seidel does not expressly disclose sorting a frozen-thawed sample of sperm, it would have been both obvious and desirable to do so, particularly for a POSA not wishing to be limited to the bulls in the vicinity of the sorting facility, and desiring the flexibility of being able to preserve sperm for subsequent sorting at a different time or location. Ex. 1003 ¶ 146. A POSA would have been aware of Johnson '94, which had described the advantages of sorting frozen-thawed sperm:

> ***Using cryopreserved semen to begin the sorting process for example would give one access to the best genetics available worldwide....*** Studies have also been initiated to use previously frozen sperm for sorting. This has resulted in fertilized eggs and developed embryos from sperm that had been originally frozen in straws, then thawed, stained and flow sorted.

Ex. 1015, 55 (emphases added); Ex. 1003 ¶ 146.

A POSA practicing Seidel's method but desiring additional flexibility regarding when and where it sorted the sperm would have been motivated by Johnson '94 to freeze the sperm before sorting. Ex. 1003 ¶ 147. Moreover, the POSA would have reasonably expected that frozen-thawed sorted sperm samples

could be used successfully to fertilize eggs and develop embryos given Johnson '94's disclosure that studies had already shown this. *Id.*

This reasonable expectation of success is further evidenced by Lu, which ***in fact*** successfully applied Seidel's general techniques to frozen-thawed sperm, and showed comparable fertilization results with such sperm as compared to sperm that had not been separated and/or frozen. Ex. 1003 ¶ 148.

Claim 16(a): thawing frozen sperm cells;

Both Johnson '94 and Lu expressly disclosed using "previously frozen sperm for sorting." Ex. 1015, 55; Ex. 1005 at 1396-1398. Moreover, it would have been obvious to substitute the frozen-thawed sperm taught in Johnson '94 or Lu for the fresh sperm used in Seidel's method given the advantages of using frozen-thawed sperm ***touted*** by Johnson '94 and ***shown*** by Lu. Ex. 1003 ¶ 151.

Claim 16(b): staining said thawed sperm cells with a concentration of Hoechst 33342 greater than 40 micromolar for a period of time sufficient to achieve uniform staining;

Seidel expressly discloses staining the sperm cells with Hoechst 33342 for a period of time sufficient to uniformly stain the cells. Ex. 1006, 9:25-26 (noting that "each type of sperm cell is stained by the dye"); *id.,* 20:24-25 ("After adding the stain, an incubation period may be used such as incubating at one hour at 34°C to hasten the dye uptake ...."). Seidel also recommends using "***higher amounts***" of

stain for "better results," and claims "***at least about 38*** micro-molar content of stain." *Id.*, 20:19-23 & 35:22-25 (emphases added).

Seidel's disclosed staining concentration of "at least about 38μM" nearly perfectly overlaps with the claimed range of "greater than 40 micromolar." M.P.E.P. 2144.05 ("[W]here the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a prima facie case of obviousness exists.") (citing cases). Moreover, if this were not enough, Seidel's exhortation to use "higher amounts of stain than might to some extent be expected" to achieve "better results" provides explicit motivation to try concentrations higher than 38μM. Ex. 1006, 20:24-25. It would have been trivial optimization for an artisan to have increased the dye concentration a few micromolar. Ex. 1003 ¶ 153; *see also In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990) (increasing concentration was matter of routine optimization); *In re Aller*, 220 F.2d at 456 (stating that it is not inventive to discover the optimum or workable ranges by routine experimentation). Thus, Seidel alone is sufficient to render this limitation obvious.

Additionally, a POSA would have been motivated to use higher stain concentrations in any event because it was generally known in the art that, when staining frozen-thawed sperm with Hoechst 33342 for subsequent analysis, higher than normal concentrations of dye may be required. Ex. 1003 ¶ 154. Lu, for

example, taught that the "standard" stain for frozen-thawed samples was 224 μM, but stains as high as 2,224 μM worked at least as well. Ex. 1005, 1398*; see also id.*, Table 3.

Accordingly, a POSA seeking to sort frozen-thawed sperm would have been motivated by Lu to use higher concentrations of dye, such as 224 μM, or even 2,224 μM, and would have reasonably expected from Lu's teachings that such concentrations would be both safe and effective. Ex. 1003 ¶ 155.

Claim 16(c): establishing the staining temperature between about 30°C and about 40 C°;

See Ground 1, Claim 16(c). As discussed above, Seidel recommends incubating the sperm at 34°C for one hour "to hasten the dye uptake." Ex. 1006, 20:24-25; *see also id.,* Example 1 (staining at 34°C).

Claim 16(d): determining a sex characteristic of said sperm cells;

See Ground 1, Claim 16(d). As discussed above, Seidel determines the sex of the sperm samples. Ex. 1006, 25:5-6 ("Sperm were sorted by sex chromosomes on the basis of epifluorescence.").

Claim 16(e): separating said sperm cells according to the determination of their sex characteristic;

See Ground 4, Claim 16(d).

Claim 16(f): ***isolating sperm cells separated according to the determination of their sex characteristic in a collection element;***

See Ground 1, Claim 16(d). Additionally, Seidel claim 18 recites, "collecting cells having the desired sex characteristic while cushioning said cells from impact with a collection container." Ex. 1006, 37:22-23.

Claim 16(g): ***and establishing a frozen-thawed sorted sperm sample from said sperm cells isolated in said collection element, the frozen-thawed sorted sperm sample being capable of fertilizing an egg at success levels of at least about 70% of the success levels with sperm cells that have not been separated and/or frozen.***

See Ground 1, Claim 16(g). As detailed therein, Lu discloses that frozen-thawed bovine sperm sorted under the same conditions as taught by Seidel had fertilization success levels (as measured by blastocyst production) of at least 70% that of bovine sperm that had not been sorted or frozen. Ex. 1005, 1396-1398, Tables 1 & 3; *see also* Ex. 1003 ¶¶ 159-160.

Thus, a POSA using Seidel's conventional sex-sorting method on a frozen-thawed sperm sample stained with 2,224 μM Hoechst 33342 for 60 minutes (as taught by Lu) would have reasonably expected to achieve the same or similar fertilization success levels achieved and reported by Lu. Ex. 1003 ¶ 160. Moreover, as discussed above, the POSA would have been motivated to try this based not only on Lu's teachings, but also on Johnson '94, which described the

various advantages of sorting frozen-thawed sperm, including increased flexibility and availability of better genetics. *Id*.; *see also* Ex. 1015, 55.

2. Ground 5: Claims 1-15 Are Obvious Over Seidel, Lu, and Johnson '94 In Further View Of Rens.

As detailed below, each of these recitations added by claims 1-15 was described in the prior art.

Claim 1 (preamble): A method of producing a frozen-thawed sorted artificial insemination sample comprising:

See Ground 4, Claim 16 (preamble). Additionally, Seidel expressly discloses using the sorted sperm sample for AI. Ex. 1006, 25:16-18 ("Sexed semen and liquid control semen were inseminated using side-opening blue sheaths (IMV), one half of each straw into each uterine horn (3 x 10^5 live sperm/heifer).").

Claim 1(a): thawing frozen sperm cells;

See Ground 4, Claim 16(a).

Claim 1(b): staining said thawed sperm cells with a concentration of a Hoechst 33342 greater than 40 micromolar;

See Ground 4, Claim 16(b).

Claim 1(c): establishing the staining temperature between about 30°C and about 40 C°;

See Ground 4, Claim 16(c).

Claim 1(d): determining a sex characteristic of said sperm cells;

See Ground 4, Claim 16(d).

Claim 1(e): ***separating said sperm cells according to the determination of their sex characteristic;***

See Ground 4, Claim 16(e).

Claim 1(f): ***isolating sperm cells separated according to the determination of their sex characteristic in a collection element at a rate of greater than 1000 sperm per second for either X-chromosome bearing sperm or Y-chromosome bearing sperm;***

See Ground 4, Claim 16(f). Additionally, it would have been obvious and desirable to modify Seidel's method to improve the sort speed. Indeed, Seidel provides explicit motivation to do so:

> ***[S]horter and shorter sorting times have been desired for several reasons....*** Thus, the time critical nature of the sperm cells and of the process has made ***speed an essential element*** in achieving high efficacy and success rates.

Ex. 1006, 3:2-8 (emphases added); *see also id.,* 7:15-17 ("Sorting in a manner which affords both ***high speed*** and low stress sorting, and which is especially adapted for sperm cell sorting in a low dose context is an ***important goal*** as well.") (emphases added).

Accordingly, a POSA would have sought ways to increase the sort speed. Ex. 1003 ¶ 177. One way to do so is expressly disclosed in Rens, which, like Seidel, also emphasizes the importance of sorting speed. Ex. 1007, 1:10-39, 1:51-2:20. Moreover, as detailed in Ground 2, claim 1(f), Rens provided both additional

motivation to sort sperm at speeds at or greater than 1,000 sorts/second, as well as the reasonable expectation of success in doing so. Ex. 1003 ¶¶ 118-127, 178.

Claim 1(g): ***establishing a frozen-thawed sorted artificial insemination sample from said sperm cells isolated in said collection element;***

See Ground 4, Claim 1 (preamble).

Claim 1(h): ***and fertilizing an egg with said frozen-thawed sorted artificial insemination sample at success levels of at least about 70% of the success levels with sperm cells that have not been separated and/or frozen.***

This claim limitation is substantially similar to the limitation discussed in Ground 4, Claim 16(g), except that it requires ***actual*** fertilization at the recited success level. Seidel expressly discloses using the sorted sperm sample for AI. Ex. 1006, 25:16-18. Moreover, as discussed above in Ground 1, Claim 16(g), the recited fertilization success level would have been obvious in view of at least Lu, which discloses that a frozen-thawed sorted sperm sample has the recited fertilization success rate. Ex. 1003 ¶ 181. Moreover, a POSA would not expect that increasing the speed at which the sperm is sorted, as taught by Rens 1999, to affect this. *Id*.

Claim 2: ***The method according to claim 1 wherein the sperm cells isolated in said collection element comprise spermatozoa sorted into separate populations, wherein the spermatozoa of one of the populations comprises a purity greater than 85% Y chromosome bearing sperm cells.***

As discussed above, Seidel describes sorting purities of about 90% for each of X- and Y-bearing sperm cells. Ex. 1006 at 26:35-36 ("Sorting rates of up to 2 x 10^6 sperm of each sex per 5-6 h at ~ 90% purity were achieved.").

Claim 3: ***The method according to claim 1 wherein the sperm cells isolated in said collection element comprise spermatozoa sorted into separate populations, wherein the spermatozoa of one of the populations comprises a purity greater than 85% X chromosome bearing sperm cells.***

See Ground 5, Claim 2.

Claim 4: ***The method according to claim 1 wherein the frozen sperm cells comprise bovine sperm cells.***

As discussed above, Seidel teaches sorting bovine sperm (Ex. 1006, 25:1-18), and Johnson '94 teaches sorting frozen-thawed bovine sperm (Ex. 1015, 55).

Claim 5: ***The method according to claim 4 wherein said frozen-thawed sorted artificial insemination sample has a number of isolated sperm cells between about one hundred and fifty thousand to about one million.***

See Ground 2, Claim 5. Additionally, Seidel describes "a bovine insemination sample of no more than two hundred fifty thousand sperm cells" and "a bovine insemination sample of no more than three hundred thousand sperm cells." Ex. 1006, 33:5-14 (claim 5). Ex. 1003 ¶ 186. Thus, a POSA would have known from Seidel that some sorted AI samples contain no more than 250,000

bovine sperm and, further, would have known from Lu that some frozen-thawed sorted AI samples contain less than 1.5 million isolated sperm cells. *Id*. ¶ 187. As such, it would have been obvious to produce a frozen-thawed sorted AI sample containing between 150,000 and 1 million isolated sperm cells. *Id*.

> ***Claims 6 & 13:*** ***The method according to claim 1 wherein the frozen sperm cells comprise equine sperm cells and wherein said frozen-thawed sorted artificial insemination sample has a number of isolated sperm cells between about forty million and one hundred million.***

See Ground 5, Claim 1. Additionally, Seidel discloses sorted equine sperm samples comprising from about one-tenth to one-half of "hundreds of millions" of cells. Ex. 1006, 7:4-6, 19:6-10. Seidel also provides explicit motivation for sorting equine sperm. *Id.,* 1:12-14.

> ***Claim 7:*** ***The method according to claim 1 wherein the step of fertilizing an egg further comprises: fertilizing an egg in vitro.***

See Ground 5, Claim 1. Additionally, Seidel discloses using the sorted sperm in IVF. Ex. 1006, 20:1-2 ("Naturally, the sexed sperm can be utilized not just in an artificial insemination mode, but in other techniques such as *in vitro* fertilization and the like."); *id.,* 23:30-24:2 ("Sexed semen would be useful for *in vitro* fertilization and to inseminate cows superovulated for embryo transfer.").

> ***Claim 8:*** ***A method of producing an embryo in vitro in vitro [sic] comprising sorting sperm by the method of claim 1, and fertilizing an egg with said sorted sperm to produce an embryo in vitro.***

See Ground 5, Claim 7.

Claim 9: ***The method according to claim 1 wherein the sperm cells isolated in said collection element comprise spermatozoa sorted into separate populations, wherein the spermatozoa of one of the populations comprises at least about 85% Y chromosome bearing sperm cells.***

See Ground 5, Claim 2.

Claim 10: ***The method according to claim 1 wherein the sperm cells isolated in said collection element comprise spermatozoa sorted into separate populations, wherein the spermatozoa of one of the populations comprises at least about 85% X chromosome bearing sperm cells.***

See Ground 5, Claim 2.

Claim 11: ***The method according to claim 1 wherein the frozen sperm cells comprise bovine sperm cells and wherein said frozen-thawed sorted artificial insemination sample has a number of isolated sperm cells between about one million to about three million.***

See Ground 5, Claims 4 and 5; *see also* Ground 2, Claim 11.

Claim 12: ***The method according to claim 1 wherein the frozen sperm cells comprise bovine sperm cells and wherein said frozen-thawed sorted artificial insemination sample has a number of isolated sperm cells between about one hundred and fifty thousand to about one million.***

See Ground 5, Claims 4 and 5.

Claim 14: ***The method according to claim 1 wherein the frozen-thawed sorted artificial insemination sample is capable of fertilizing an egg in vitro.***

See Ground 5, Claim 7.

Claim 15: ***A method of producing an embryo in vitro comprising sorting sperm by the method of claim 1, and fertilizing an egg with said sorted sperm to produce an embryo in vitro.***

See Ground 5, Claim 8.

IX. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that trial be instituted and that claims 1-16 of the '769 patent be cancelled.

Dated: December 1, 2017

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. § 42.24, I certify that the foregoing **PETITION FOR *INTER PARTES* REVIEW** contains 13,373 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: December 1, 2017

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CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I hereby certify that on this 1st day of December, 2017, true and correct copies of this PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto**,** were served by overnight courier service at the following address for the Patent Owner:

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