United States Court of Appeals for the Federal Circuit

CELSIS IN VITRO, INC.,

Plaintiff-Appellee,

v.

CELLZDIRECT, INC., AND INVITROGEN CORPORATION,

Defendants-Appellants.

2010-1547

Appeal from the United States District Court for the Northern District of Illinois in Case No. 10-CV-4053, Judge Milton I. Shadur

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Decided: January 9, 2012

ADAM G. KELLY, Loeb & Loeb, LLP, of Chicago, Illinois argued for plaintiff-appellee. With him on the brief was JORDAN A. SIGALE. Of counsel was JULIE L. LANGDON.

FRANCIS M. WIKSTROM, Parsons Behle & Latimer, of Salt Lake City, Utah, argued for defendants-appellants. With him on the brief were DAVID G. MANGUM, C. KEVIN SPEIRS and MICHAEL R. MCCARTHY.

Before RADER, *Chief Judge*, GAJARSA, and PROST, *Circuit Judges*.

Opinion for the court filed by *Chief Judge* RADER. Dissenting opinion filed by *Circuit Judge* GAJARSA.

RADER, *Chief Judge*.

The United States District Court for the Northern District of Illinois granted Celsis In Vitro, Inc.'s ("Celsis") motion for a preliminary injunction against CellzDirect, Inc. and Invitrogen Corporation, now Life Technologies Corporation ("LTC"). Based on the record, the district court did not abuse its discretion. This court affirms.

I.

Celsis is the assignee of U.S. Patent No. 7,604,929 (filed Apr. 21, 2005) ("the '929 patent"), which claims methods for preparing multi-cryopreserved hepatocytes (a type of liver cell). Claims 1 and 10 of the '929 patent are on appeal:

> 1. A method of producing a desired preparation of multi-cryopreserved hepatocytes, said hepatocytes, being capable of being frozen and thawed at least two times, and in which greater than 70% of the hepatocytes of said preparation are viable after the final thaw, said method comprising:
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> (A) subjecting hepatocytes that have been frozen and thawed to density gradient fractionation to separate viable hepatocytes from non-viable hepatocytes,
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> (B) recovering the separated viable hepatocytes, and
>
> (C) cryopreserving the recovered viable hepatocytes to thereby form said desired

> preparation of hepatocytes without requiring a density gradient step after thawing the hepatocytes for the second time, wherein the hepatocytes are not plated between the first and second cryopreservations, and wherein greater than 70% of the hepatocytes of said preparation are viable after the final thaw.
>
> 10. A method of investigating in vitro drug metabolism comprising incubating hepatocytes of a multi-cryopreserved hepatocyte preparation in the presence of a xenobiotic, and determining the metabolic fate of the xenobiotic, or the affect of the xenobiotic on the hepatocytes or on an enzyme or metabolic activity thereof, wherein the hepatocytes have been frozen and thawed at least two times, and wherein greater than 70% of the hepatocytes of said preparation are viable without requiring a density gradient step after thawing the hepatocytes for the second time, wherein the hepatocytes are not plated between the first and second cryopreservations.

'929 patent col.19 l.56 – col.20 l.19, ll.49-59 (emphasis added to the disputed claim terms).

The specification of the '929 patent explains that human hepatocytes are a useful laboratory model for evaluating drug candidates. Two problems, however, have limited their use. First, hepatocytes have a short lifespan which causes an inconsistent and limited supply. Specifically, the only sources of fresh hepatocytes are liver resections or non-transplantable livers of multi-organ donors. Due to this reliance on liver donation, fresh hepatocytes become available at unpredictable times.

Researchers must wait until a liver donation and must often resume or begin research with little advance warning. This unpredictability hinders laboratory studies, which usually require a consistent source of supplies. This supply problem also limits research geographically to the region near the liver donor.

To obtain a more consistent supply, scientists sought techniques for long-term storage of hepatocytes in the laboratory. The option of cryopreservation (freezing) did not work well because freezing extensively damages hepatocyte cells. Hepatocytes are extremely fragile and, once damaged, do not recover. Thus, even a single instance of cryopreservation can jeopardize the need for a sufficient level of viable hepatocytes. For this reason, experts in this field met initial attempts to freeze hepatocytes with skepticism.

The second problem is outlier data. If a researcher uses hepatocytes from only one or two donors, the results may not be representative of the larger population. To avoid this, the researcher needs a pool of hepatocytes from a larger group of different liver donors to minimize the effect of outliers. Once again, the unpredictability of liver donations jeopardizes the effort to accumulate a representative pool of hepatocytes. Of course, multiple liver donations are unlikely to occur at the same time. Therefore, the researcher must rely on preserving hepatocytes to accumulate a pool. Specifically, the researcher must combine frozen hepatocytes with fresh hepatocytes to create a pool. Because the pool must be used immediately, any unused cells are discarded; otherwise, refreezing would freeze the thawed cells a second time. Thus, preservation methods severely limit, or even preclude, pooled hepatocyte products.

The '929 patent intends to solve these problems while retaining substantial hepatocyte cell viability through a method of multi-cryopreserving hepatocyte cells. Celsis developed its LiverPool™ pooled multi-cryopreserved hepatocyte products, which it asserts are covered by the '929 patent. LTC also sells pooled multi-cryopreserved hepatocyte products, which Celsis alleges involve performing a process infringing the '929 patent ("the accused process"). For confidentiality reasons, this decision does not give the details of the accused process.

In June 2010, Celsis sued LTC for infringement of the '929 patent. Celsis moved for a preliminary injunction. After a month of discovery, the district court conducted a five-day evidentiary hearing. The district court, upon consideration of the testimony and written submissions, ruled from the bench and granted Celsis a preliminary injunction. LTC moved for a stay pending appeal, which the district court denied.

LTC appealed the district court's grant of a preliminary injunction. It moved for a stay pending appeal, which this court denied in *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, No. 2010-1547, 2010 WL 5080944 (Fed. Cir. Dec. 8, 2010). This court has jurisdiction under 28 U.S.C. § 1292(c)(1).

II.

This court reviews a district court's decision to grant a motion for preliminary injunction for an abuse of discretion. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1345 (Fed. Cir. 2008). To constitute an abuse of discretion, a district court decision must either make a clear error of judgment in weighing relevant factors or exercise discretion based upon an error of law. *Id.*

The district court analyzes four factors when considering a preliminary injunction: (1) likelihood of success on the merits, (2) irreparable harm, (3) balance of hardships, and (4) public interest. *Id.* at 1344.

III.

The district court found that Celsis had shown a likelihood of success on the merits. The district court also considered LTC's defenses: non-infringement, obviousness, written description, and inequitable conduct. LTC has chosen to appeal only the first two.

As to infringement, the district court weighed the testimony of Celsis' expert Dr. Steven C. Strom against the testimony of LTC's marketing director Markus J. Hunkeler. The district court found Dr. Strom's testimony to be helpful in carefully explaining how LTC's accused process meets all the limitations of the asserted claims. In contrast, the district court found that Mr. Hunkeler "really didn't offer anything in the way of opinions to address the proper interpretation of the patent's claims." Preliminary Injunction Hr'g Tr. 4:10-12, Sept. 7, 2010.

Thus, the district court found that Celsis is likely to succeed in proving that LTC's accused process performs all the steps in the asserted claims. First, Dr. Strom gave testimony on the proper reading of the term "density gradient fractionation" in step (A) of claim 1. Then, he applied that term to the accused process. He testified that the accused process performs a density separation that satisfies the "density gradient fractionation" in step (A), because it separates viable from nonviable hepatocytes by density. Though Mr. Hunkeler testified that the accused process performs an "isodensity" separation that does not create a gradient, the district court found Celsis' expert Dr. Strom's testimony more persuasive.

Second, with that claim construction in place, LTC asserted an alternative non-infringement defense based on step (C). LTC presented documents showing that the accused process performs the same density separation after the first thaw (step A) and the second thaw (step C) only in a different medium. In contrast to step (A), step (C) includes the language "without requiring a density gradient step." '929 patent col.20 l.15, ll.57-58 (emphasis added). LTC reads "without requiring" to mean "prohibiting," such that the accused process performs an action "prohibited" by step (C) and therefore does not infringe. LTC made the same argument about claim 10.

The district court found this argument to be "hokum" and an improper attempt to insert a limitation not in the claims. Hr'g Tr. 5:13. In finding for Celsis, the district court adopted Dr. Strom's expert testimony by reference to Celsis' post-hearing briefing. The district court concluded: "In sum, it is an understatement to say that Celsis has shown substantially more than a reasonable likelihood of success on the subject of infringement." Hr'g Tr. 7:3-5.

This record shows that the district court did not abuse its discretion in finding a likelihood of success on infringement. LTC errs in reading "without requiring" to mean "prohibiting." The claim language is not susceptible to this unnatural reading. Instead, "without requiring" means simply that the claim does not require the density gradient step. Thus, performance of that step does not preclude a finding of infringement. For that reason, this court need not reach LTC's subsequent argument concerning performance of the "density gradient step" in step (C). This court also declines to reach the joint infringement issue that LTC raised for the first time at oral argument. *See Henry v. DOJ*, 157 F.3d 863, 865 (Fed. Cir. 1998) (not considering an argument raised for the first time at oral

argument); *Darwin Constr. Co. v. United States*, 811 F.2d 593, 596 n.1 (Fed. Cir. 1987) (same).

As to non-obviousness, the district court reviewed the testimony and submissions of Celsis and LTC's fact and expert witnesses. It noted the "vast proliferation of authors and articles dealing with hepatocytes and use of cryopreservation." Hr'g Tr. 7:15-17. But, the district court found: "[N]ot a single one of that astonishingly large body of literature was devoted to the subject of multi-cryopreservation of hepatocytes." Hr'g Tr. 7:19-22 ("I have properly laid stress on 'multi.'").

The district court rejected LTC's attempt to fill that gap. LTC's expert Dr. Sanjeev Gupta opined that the only reference to multi-cryopreservation in the prior art is an article in 2002 that he co-authored ("the Malhi article"). *See* Harmeet Malhi et al., *Isolation of human progenitor liver epithelial cells with extensive replication capacity and differentiation into mature hepatocytes*, 115 (13) Journal of Cell Science 2679 (2002). The Malhi article discusses fetal hepatocytes as experiment models because they can replicate in laboratory conditions (unlike mature or adult hepatocytes). The essence of the article was not to introduce a new method or advance in cryopreservation but instead to focus on the advantages of using fetal hepatocytes due to their replication abilities. The Malhi article does report on the "poor viability of hepatocytes after cryopreservation."

The district court found Dr. Gupta's testimony unpersuasive and, as to the Malhi article, found that "nothing in that skeletal reference suggests or even hints at the advance conceived of by the inventor here." Hr'g Tr. 8:14-15. The district court instead credited Celsis' expert Dr. Strom who testified that due to the independent replication of the fetal hepatocytes, it could not be definitively

determined whether the same cells were cryopreserved more than once. Dr. Gupta also conceded this same point. The district court found that LTC was attempting to make much of "a wisp of a term that is buried in the Malhi article." Hr'g Tr. 8:2-3. It deemed LTC's arguments to be nothing more than "second guessing and hindsight." Hr'g Tr. 8:17-18. The district court concluded that "again Celsis has demonstrated more than a substantial likelihood of success on the issue." Hr'g Tr. 10:8-9.

The issue on appeal is whether the district court erred in finding Celsis likely to succeed on non-obviousness in view of G. de Sousa et al., *Increase of cytochrome P-450 1A and glutathione transferase transcripts in cultured hepatocytes from dogs, monkeys, and humans after cryopreservation*, 12 Cell Biology and Toxicology 351 (1996) ("the de Sousa article"). On appeal, LTC does not assert its obviousness argument based on the Malhi article, despite LTC's own expert Dr. Gupta opining that Malhi was the only reference in the prior art that allegedly disclosed multi-cryopreservation. Instead of disclosing multi-cryopreservation, the de Sousa article analyzes whether single-cryopreserved hepatocytes can replace fresh hepatocytes as laboratory models, by comparing fresh versus (single) cryopreserved human, monkey, and dog hepatocytes. Specifically, while previous studies determined the effect of single cryopreservation on fresh hepatocytes by evaluating differences in cell viability, cell attachment, and protein synthesis, the aim of this article was to evaluate whether three different chemicals could induce (*i.e.* increase activity of) two different enzymes.

Under 35 U.S.C. § 103, a patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time

the invention was made to a person having ordinary skill in the art." The obviousness analysis is based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1336 (Fed. Cir. 2010).

This preliminary record shows that the district court did not abuse its discretion in finding that Celsis has shown a likelihood of success on nonobviousness. LTC will have an opportunity at the merits stage to expand upon the arguments it made at the preliminary injunction stage. The record as it now stands, however, reveals no clear error by the district court. And this court does not opine on the final determination, which lays in the realm of the district court in the first instance.

As an initial matter, this court acknowledges that the present invention is in an art well-known for its unpredictability. As to the scope and content of the prior art, the district court correctly emphasized and found based on the preliminary record that the art was a crowded field for many years and yet there was not one reference to multi-cryopreservation. Moreover, the record shows that the prior art taught away from multiple freezings. A single round of freezing severely damages hepatocyte cells and results in lower cell viability. Celsis provided a sufficient showing at this preliminary injunction stage that, at the time of the invention, a person of ordinary skill would expect a second freezing on those damaged cells to kill even more cells than the first freezing. Celsis provides a helpful analogy. Imagine a runner who finishes one marathon and then immediately begins a second marathon. One would not expect the runner to perform the second in the same time as the first. More

likely, the runner would not even finish the second marathon. Similarly, as Celsis' expert Dr. Strom testified, one would expect lower cell viability and a greater loss of cells after the second cryopreservation than after the first, thus teaching away from multi-cryopreservation.

With respect to the de Sousa article, this court sees no error in the district court's reliance on Dr. Strom's testimony that de Sousa does not describe or suggest more than one round of freezing, nor does it describe or suggest pooling. Instead, de Sousa only discloses a single cryopreservation. Even LTC's expert Dr. Gupta did not testify that de Sousa discloses multi-cryopreservation. This court has not seen LTC identify any teaching, suggestion, or motivation in the de Sousa article that multiple rounds of freezing would somehow increase rather than decrease cell viability. Instead, to make this leap, LTC makes vague references to "market need" and testimony from its witnesses Dr. Gupta and Dr. Albert Li. Without more, this reference to "market need," properly linked to the claimed invention, is actually probative of long felt need under objective criteria analysis and supportive of non-obviousness.

Dr. Gupta opined on a "more resistance" theory, and Dr. Li opined on a "mathematical calculation" theory. Specifically, Dr. Gupta (opining specifically on the de Sousa article) claimed that cells that survived the first freeze would be "more resistant" and therefore more likely to survive a second freeze. Dr. Li (opining generally, not specifically on the de Sousa article) claimed that the same number of cells that survived the first freeze would survive the second freeze. The de Sousa article does not disclose either of these hindsight theories.

The district court did not find the testimony of LTC's experts Dr. Gupta and Dr. Li credible. The district court

has wide discretion to weigh expert credibility. *Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1362-63 (Fed. Cir. 2006) ("As for the relative weight given to the testimony of both sides' expert witnesses, we accord the trial court broad discretion in determining credibility because the court saw the witnesses and heard their testimony.") (quoting *Energy Capital Corp. v. United States*, 302 F.3d 1314, 1329 (Fed. Cir. 2002)); *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1236 (Fed. Cir. 2003) ("Moreover, the district court did not find convincing or credible the opinion of RPR's expert . . . . [T]he district court is best suited to make credibility determinations, and we accord such determinations deference.") (citing *Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1582 (Fed. Cir. 1996)). This court defers to such credibility determinations. *Nilssen v. Osram Sylvania, Inc.*, 504 F.3d 1223, 1231-32 (Fed. Cir. 2007) ("While an opposite conclusion could have been reached, it is not the function of a court of appeals to override district court judgments on close issues, where credibility findings have been made."); *Agfa Corp. v. Creo Prods. Inc.*, 451 F.3d 1366, 1379 (Fed. Cir. 2006) ("This court must defer heavily to the trial court's credibility determinations. . . . Credibility determinations by the trial judge can virtually never be clear error.") (quoting *JVW Enters., Inc. v. Interact Accessories, Inc.*, 424 F.3d 1324, 1334 (Fed. Cir. 2005)). Thus, these determinations of credibility also buttress the record for nonobviousness.

Here, the district court found that the LTC expert's "revisionist history is unpersuasive." Hr'g Tr. 10:7-8; *see also* Hr'g Tr. 7:11-13 ("Instead of a more candid 'Why didn't I think of that,' we get [LTC arguing] 'Anybody reasonably skilled in the art would have thought of that.'"). Not one of LTC's experts testified to actually performing the claimed process or documenting their

alleged understanding before the time of the invention, despite having the financial, scientific, and professional incentive to do so. The district court found that LTC's experts did not predict the results of the claimed methods at the time of the invention, nor could they find any reference in the prior art suggesting that any other scientist had. Hr'g Tr. 7:23-8:1 ("That was not the subject of numerous articles authored or assembled by Dr. Li or Dr. Gupta or by any of the other scientists who participated in the consortium about which Dr. Li testified, or for that matter by anybody else."). Accordingly, in this preliminary injunction context, this court determines that the district court did not clearly err in finding a person of ordinary skill in the art likely would not have found the invention obvious either.

In sum, the record supports the district court's conclusion that Celsis has shown a likelihood of success that a person of ordinary skill in the art would not have considered the claimed methods obvious at the time of the invention.

IV.

The district court found that Celsis would suffer irreparable harm absent a preliminary injunction. As the district court recognized, the simple fact that one could, if pressed, compute a money damages award does not always preclude a finding of irreparable harm. As its name implies, the irreparable harm inquiry seeks to measure harms that no damages payment, however great, could address. *See Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1010 (Fed. Cir. 2009); *see also Sampson v. Murray*, 415 U.S. 61, 90 (1974) ("The key word in this consideration is *irreparable*. Mere injuries, however substantial, in terms of money, time and energy necessarily expended in the absence of a stay, are not

enough.") (quoting *Va. Petroleum Jobbers Ass'n v. Fed. Power Comm'n*, 259 F.2d 921, 925 (D.C. Cir. 1958)). The district court found that the permanent, irreparable harm to Celsis would include price erosion, damage to ongoing customer relationships, loss of customer goodwill (*e.g.*, when an effort is later made to restore the original price), and loss of business opportunities. As the district court explained: "There is no effective way to measure the loss of sales or potential growth – to ascertain the people who do not knock on the door or to identify the specific persons who do not reorder because of the existence of the infringer." Hr'g Tr. 16:25-17:4.

Based on the record before the district court, this court sees no error in the district court's finding that Celsis would suffer irreparable harm absent a preliminary injunction. Price erosion, loss of goodwill, damage to reputation, and loss of business opportunities are all valid grounds for finding irreparable harm. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362 (Fed. Cir. 2008); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382-83 (Fed. Cir. 2006). Thus, contrary to LTC's assertions, the district court did not err as a matter of law in relying on such evidence. Further, the mere possibility of future monetary damages does not defeat a motion for preliminary injunction. *See Abbott Labs.*, 544 F.3d at 1361-62; *Sanofi-Synthelabo*, 470 F.3d at 1382.

Celsis offered testimony from its expert Mark Peterson on irreparable harm. In contrast, LTC did not offer expert testimony in rebuttal. This court sees no error in the district court's reliance on Celsis' unrebutted expert testimony. To substantiate its claims, Celsis presented fact and expert testimony as well as specific financial records. Celsis presented evidence of LTC's significantly discounted prices as well as specific instances when customers purchased from LTC instead of Celsis. The

record also shows that Celsis had a general no-discount policy to maintain its premium product pricing that it was forced to break in order to compete with LTC. The record included evidence that the LiverPool™ products are Celsis' flagship products and that the products are in their growth phase and will soon be entering the mature phase with the highest revenues and strongest market position. The record also included testimony that this market was particularly sensitive because customers buy in bulk and at irregular times, such that the loss of a single sale in this market may be more harmful than for products purchased daily.

Then, Celsis proffered expert testimony on the damage to Celsis' price, reputation, and business opportunities. Mr. Peterson testified to the irreversible price erosion. He also testified to the difficulty in quantifying the effect on reputation and business due to Celsis being precluded from marketing to potential and existing customers that it is the exclusive market leader. During the growth stage of a product, it is particularly crucial to be able to distinguish oneself from competitors. This includes building the brand, expanding the customer base, and establishing one's reputation and leadership in the market.

This court declines to reach LTC's new argument that these effects can be quantifiable in this case because this is supposedly a two-competitor market and such harms are allegedly not irreparable in such a market. LTC chose not to properly raise this before the district court. The general rule is that this court does not consider arguments not raised below. *See Singleton v. Wulff*, 428 U.S. 106, 120 (1976). This court finds no reason to disregard that rule here.

In light of the unrebutted expert testimony, this court finds no reason to reverse the district court's weighing of evidence and fact finding that Celsis would suffer irreparable harm absent a preliminary injunction.

V.

The district court concluded that "plainly the balancing of harms tilts heavily in Celsis's favor." Hr'g Tr. 17:11-12. This preliminary injunction factor is also affected by LTC's decision not to present expert testimony to rebut Celsis' expert testimony. The district court found that any asserted harm to LTC was "of lesser scope" than the harm to Celsis and also "protectable by a bond." Hr'g Tr. 17:9-11 (citing *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558 (Fed. Cir. 1996)).

The district court did not clearly err in finding the balancing of harms favors Celsis. Absent a preliminary injunction, Celsis would lose the value of its patent as well as suffer the irreparable harms opined on by its expert. The losses alleged by LTC *upon* a preliminary injunction (loss of goodwill and reputation) would also be incurred by Celsis *absent* a preliminary injunction. Moreover, the record shows that the district court properly considered LTC's interest in fulfilling its current contract obligations. *See PPG Indus., Inc.*, 75 F.3d at 1567. In fact, the district court allowed LTC to complete some sales. This court sees no clear error in the district court rejecting the LTC witness Mr. Hunkeler's claims that it would have to shut down operations upon a preliminary injunction. Further, the preliminary record suggests that LTC's losses were the result of its own calculated risk in selling a product with knowledge of Celsis' patent. *See Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006).

As to the bond, this court sees no abuse of discretion in the district court's bond amount. *See Sanofi-Synthelabo*, 470 F.3d at 1386 ("The amount of a bond is a determination that rests within the sound discretion of a trial court."). LTC argues that the bond is inadequate. But, the district court invited LTC to present additional evidence to substantiate a higher bond. LTC presented no such evidence.

VI.

The district court found that Celsis had carried its burden to prove that the public interest would favor a preliminary injunction. This court sees no error in the district court's conclusion. The public interest favors the enforcement of Celsis' patent rights here. *See Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006) ("We have long acknowledged the importance of the patent system in encouraging innovation."). Such investment in drug research and development must be encouraged and protected by the exclusionary rights conveyed in valid patents. *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362-63 (Fed. Cir. 2008). That incentive would be adversely affected by taking market benefits away from the patentee and giving them to the accused infringer in this case. *See id.* Though LTC argues that it sells products for drug research and development such that the public interest would disfavor enjoining LTC, both LTC and Celsis sell the same products and are in direct competition. In other words, the public can obtain the products from Celsis. The record shows that the district court has considered and properly addressed the public's interest in obtaining an adequate supply of pooled multi-cryopreserved hepatocyte products. *See PPG Indus., Inc.*, 75 F.3d at 1567.

VII.

The district court found that all four preliminary injunction factors favor Celsis. This court sees no reversible error in the district court's findings. Based on this record, the district court did not abuse its discretion in granting the motion for preliminary injunction. This court therefore affirms.

VIII.

This court declines to review LTC's new argument that the scope of the preliminary injunction is overbroad, in terms of geography and time. *See Singleton v. Wulff*, 428 U.S. 106, 120 (1976). LTC did not raise this objection before the district court. Nor did it offer alternative forms to the injunction before the district court.

AFFIRMED.

United States Court of Appeals for the Federal Circuit

CELSIS IN VITRO, INC.,
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Defendants-Appellants.

2010-1547

Appeal from the United States District Court for the Northern District of Illinois in Case No. 10-CV-4053, Judge Milton I. Shadur.

GAJARSA, *Circuit Judge*, dissenting.

I respectfully dissent from the majority's decision to uphold the "extraordinary and drastic remedy" of a preliminary injunction because, in my judgment, Cellzdirect, Inc. and Invitrogen Corporation (collectively, "LTC") raised a substantial question as to the validity of U.S. Patent No. 7,604,929 (the "'929 patent"). The grant or denial of a preliminary injunction is within the broad discretion of the district court. In this case, however, the district court committed legal error in granting the preliminary injunction. The district court's obviousness analysis was legally deficient, and it erroneously held

LTC to a clear and convincing standard of proof regarding the '929 patent's invalidity. By affirming the injunction, the majority perpetuates these errors and reinvigorates the pre-*KSR* standard for obviousness, rigidly requiring an explicit teaching, suggestion, or motivation for multi-cryopreserving hepatocytes. *Majority Op.* at 11.

I.

Claim 1 of the '929 patent reads as follows:

> A method of producing a desired preparation of multi-cryopreserved hepatocytes, said hepatocytes, being capable of being frozen and thawed at least two times, and in which greater than 70% of the hepatocytes of said preparation are viable after the final thaw, said method comprising: (A) subjecting hepatocytes that have been frozen and thawed to density gradient fractionation to separate viable hepatocytes from non-viable hepatocytes, (B) recovering the separated viable hepatocytes, and (C) cryopreserving the recovered viable hepatocytes to thereby form said desired preparation of hepatocytes without requiring a density gradient step after thawing the hepatocytes for the second time, wherein the hepatocytes are not plated between the first and second cryopreservations, and wherein greater than 70% of the hepatocytes of said preparation are viable after the final thaw.

'929 patent col.19 l.56-col.20 l.20. The district court held that LTC had not proven that its obviousness defense had substantial merit because two limitations of the claimed invention were not present in the prior art: freezing and thawing hepatocytes a second time and making the density gradient fractionation optional after the second thaw.

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Yet obviousness does not require that each element of the claimed invention must be present in the prior art. Indeed, the Patent Act precludes such a requirement by stating that obviousness depends on whether the "*differences between the subject matter sought to be patented and the prior art* are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art . . . ." 35 U.S.C. § 103(a) (2006) (emphasis added). Furthermore, this court has recognized that proof of obviousness does not require that every element be present in the prior art. *See Tegal Corp. v. Tokyo Electron Am., Inc.*, 257 F.3d 1331, 1349 (Fed. Cir. 2001) (acknowledging that the claimed invention could be obvious even if prior art did not teach one of its elements).

Moreover, all of the claimed elements were present in the prior art. Properly interpreted, the claimed invention requires three steps: (1) thawing cryopreserved hepatocytes; (2) using density gradient fractionation to separate viable and non-viable cells; and (3) refreezing and rethawing the hepatocytes. Both cryopreservation and density gradient fractionation were well known in the art at the time of the invention. *See* '929 patent col.2 ll.41-54 (listing prior art references relating to cryopreservation); J.A. 2981 (Celsis Invitro, Inc.'s ("Celsis") expert Dr. Strom testified that use of density gradient fractionation to "enhance viability" of cells is "well-established to everyone in th[e] field."). The last "step" of the claimed invention requires nothing more than measuring the viability of cells thawed for a second time. If the cells have more than 70% viability, they meet this limitation; if they do not have 70% viability, they do not meet this limitation.

In other words, Celsis' invention uses two known techniques, repeats them, and happens to obtain 70 percent viability of hepatocytes. This "invention" is a "patent for a combination which only unites old elements with no change in their respective functions [and] obviously withdraws what already is known into the field of its monopoly," *Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 152-153 (1950), which is a "principal reason" for finding a patent obvious. *KSR Int'l. Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). Repeating known steps to obtain a desired result is not inventive. *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1330-31 (Fed. Cir. 2009) (finding obvious a claimed invention that required performance of three steps known in the prior art, followed by repetition of those steps until a desired result was obtained).

The majority attempts to complicate the simplicity of the claimed invention by asserting that the art was unpredictable while simultaneously asserting that a person of ordinary skill in the art would have predicted low viability of hepatocytes that had been frozen and thawed twice. *See Majority Op.* at 10-11. The majority cannot have it both ways. To the extent the art was unpredictable—an issue on which the district court was silent—this alone does not require a holding that the invention is not obvious. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.").

The majority also faults LTC for failing to point out an explicit teaching, suggestion, or motivation to multi-

cryopreserve hepatocytes.[1] *Majority Op.* at 11. This is directly contrary to the Supreme Court's opinion in *KSR*, which the majority fails to recognize. *KSR* explicitly rejected the rigid application of the teaching-suggestion-motivation test, explaining that "the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." 550 U.S. at 418. The majority fails to follow *KSR*'s mandate in deciding that LTC's obviousness defense lacked substantial merit.

Under the flexible approach of *KSR*, there is a substantial question of obviousness concerning the '929 patent. The patent spells out clearly—as does Celsis' brief—that there was a need in the art to multi-cryopreserve hepatocytes. The basic approach to determine whether hepatocytes could be frozen multiple times and remain viable was simply to pursue it. Celsis did and found that the hepatocytes were viable. This process is not entitled to be deemed an invention. *See KSR*, 550 U.S. at 421 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp," the invention is likely obvious.); *see also Wyers v. Master Lock Co.*, 616 F.3d 1231, 1239 (Fed. Cir. 2010) ("*KSR* and our later cases establish that the legal determination of obviousness may include recourse to logic, judgment, and com-

[1] The majority also claims that the failure of LTC's experts to practice the claimed invention weighs against obviousness. Of course, had LTC's experts actually practiced the claimed invention, it would be anticipated, not obvious. By failing to appreciate this distinction the majority continues to compound the error.

mon sense, in lieu of expert testimony." (citations omitted)). I would thus vacate the district court's grant of a preliminary injunction.

II.

The district court also erred in failing to appreciate that to avoid a preliminary injunction, LTC needed only to offer proof that the '929 patent was vulnerable, as opposed to clear and convincing evidence of its invalidity. As the patentee, Celsis bears the burden of proving that "in light of the presumptions and burdens that will inhere at trial on the merits," the '929 patent will withstand LTC's challenges to its validity. *See Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350 (Fed. Cir. 2001). Thus, if LTC raises a substantial question as to the '929 patent's validity, the preliminary injunction should not issue. *Id.* at 1350-51. *See also Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1364 (Fed. Cir. 1997) ("[W]ith regard to [the alleged infringer's] validity defenses, the question on appeal is whether there is substantial merit to [its] assertion that the . . . patent claim [is invalid]."); *Kimberly-Clark Worldwide, Inc. v. First Quality Baby Products, LLC*, 431 Fed.Appx. 884, 886-7 (Fed. Cir. 2011) (Prost, J.) (nonprecedential opinion) (stating the same and that "[v]ulnerability is the issue at the preliminary injunction stage, while validity is the issue at trial") (citations omitted).

Importantly, it is unnecessary to prove a substantial question of invalidity by clear and convincing evidence. Rather, the party challenging the patent's validity must show that the patent is vulnerable, which "requires less proof than the clear and convincing showing necessary to establish invalidity itself." *Amazon*, 239 F.3d at 1359. Here, the district court found that because LTC had not shown that every element of the claimed invention was

present in the prior art, its obviousness defense lacked substantial merit. But as explained *supra*, this is not the standard for obviousness. Moreover, requiring the defendant to prove obviousness improperly shifts the burden to the defendant. Instead, the district court must simply decide whether it is more likely than not that the patent will be proven invalid at trial. *See Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1379-80 (Fed. Cir. 2009) ("The fact that, at trial on the merits, the proof of invalidity will require clear and convincing evidence is a consideration for the judge to take into account in assessing the challenger's case at the preliminary injunction stage; it is not an evidentiary burden to be met preliminarily by the challenger.")

The majority affirms the district court's erroneous analysis, stating that "LTC will have an opportunity at the merits stage to expand upon the arguments it made at the preliminary injunction stage." *Majority Op.* at 10. While the present record may not present a clear and convincing case for obviousness, it certainly raises a substantial question on that issue, which the majority implicitly recognizes. By relying on the patent and admissions from Celsis' expert, LTC demonstrated that all of the claim elements were present in the prior art. From there, based on the need for multi-cryopreserved hepatocytes, Celsis repeats the well-known steps to obtain its desired result.

CONCLUSION

In my judgment, the district court abused its discretion in finding that Celsis had demonstrated a likelihood of success on the merits because the claimed invention is nothing more than a repetition of steps already known in the art. Moreover, the majority perpetuates this error, and in so doing applies the wrong standard for obvious-

ness and rationalizes the issuance of the preliminary injunction because it would prevent competition with a patented process which may be proven to be invalid. For these reasons, I dissent.