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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

THE FOUNDATION FOR TAXPAYER & CONSUMER RIGHTS
Requester and Appellant

v.

Patent of WISCONSIN ALUMNI RESEARCH FOUNDATION
Patent Owner and Respondent

Appeal 2012-011693
Reexamination Control 95/000,154
Patent 7,029,913
Technology Center 3999

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and
JEFFREY B. ROBERTSON,¹ *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

¹ Jeffrey B. Robertson has replaced Romulo H. Delmendo who participated in the original Board decision.

DECISION ON APPEAL

This is new decision under 37 C.F.R. § 41.77(f) in response to 1) the Patent Owner's Request to Reopen Prosecution after a decision by the Board which instituted new grounds of rejection; and 2) the Examiner's subsequent determination under 37 C.F.R. § 41.77(d) that the new rejections have been overcome.

The Board's jurisdiction for this appeal is under 35 U.S.C. §§ 6(b), 134, and 315. We withdraw the rejections set forth in the Board Decision dated January 29, 2010 and affirm the Examiner decision in the Answer dated July 30, 2009 confirming the patentability of claims 1-3 of US Patent 7,029,913.

STATEMENT OF THE CASE

The patent in dispute in this appeal is U.S. Patent No. 7,029,913 (issued Apr. 18, 2006) ("the '913 patent"), assigned to the Wisconsin Alumni Research Foundation ("WARF"). Dr. James Thomson is listed as the sole inventor. The claims are drawn to human embryonic stem (hES) cells.

The '913 patent is the subject of an inter partes reexamination. After reexamination before the Examiner, the Examiner found all the pending claims allowable. (Action Closing Prosecution (mailed Feb. 25, 2008) & Right of Appeal Notice 80 (mailed Jun. 8, 2008)). The Third Party Requester appealed that determination to the Board.

In the Board decision on the appeal dated April 29, 2010 ("Decision"), we reversed the Examiner's determination not to adopt certain rejections of claims 1-3 of the '913 Patent and designated the new rejections

as new grounds of rejection, entitling Patent Owner to re-open prosecution.

The new rejections are as follows:

1. Claims 1-3 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious based on, Williams² (Examiner's Answer ("Ans") 6);

3. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Robertson '83,³ Robertson '87,⁴ Williams, and Hogan⁵ (Ans. 9);

4. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Piedrahita,⁶ Williams, and Hogan (Ans. 12); and

5. Claims 1-3 under 35 U.S.C. § 103(a) as obvious based on Robertson '83, Robertson '87, Piedrahita, Williams, and Hogan (Ans. 13).

In response to the new grounds of rejection, WARF filed a Request to Reopen Prosecution ("Req. Reopen") accompanied by an amendment and new evidence. The amendment amended Claims 1-3 and added claim 4. The Third Party Requester did not file comments subsequent to the Board decision or subsequent to WARF's Request.

² Robert L. Williams et al., U.S. Patent No. 5,166,065 (issued Nov. 24, 1992).

³ Elizabeth J. Robertson et al., Isolation, Properties, and Karyotype Analysis of Pluripotentiality (EK) Cell Lines from Normal and Parthenogenetic Embryos, in *Teratocarcinoma Stem Cells* (L.M. Silver et al., ed.), 10: 647-663 (1983).

⁴ Elizabeth J. Robertson, Embryo-Derived Stem Cell Lines, in *Teratocarcinomas in Embryonic Stem Cells: A Practical Approach*, Ch. 4: 71-112 (1987), Oxford: IRL Press.

⁵ Brigid L. M. Hogan, U.S. Patent No. 5,690,926 (issued Nov. 25, 1997)

⁶ Piedrahita et al., *On The Isolation of Embryonic Stem Cells: Comparative Behavior of Murine, Porcine, and Ovine Embryos*, 34 *Theriogenology* 879, 879-901 (1990).

The Examiner reviewed all evidence of record anew and determined that claims 1-3 and new claim 4 are patentable over the cited prior art of record as set forth in Rejections 1 and 3-5 (Examiner's Determination under 37 CFR ¶ 41.77(d), p. 17).

We agree with the Examiner's determination.

1. ANTICIPATION BY WILLIAMS

Initially, we reversed the Examiner's determination that Williams did not anticipate the claims to human embryonic stem cells. First, we found that Williams disclosed human embryos in a list of animal embryos that could be used as a source of embryonic stem cells (FF5) (Decision 10). Second, we determined that Williams was enabling to make human embryo stem cells (Decision 11-14). WARF had argued that Williams was not enabling, but we found that WARF did not provide persuasive evidence that the Williams' method would not work when applied to human embryos (*id.* at 12).

To address the new grounds of rejection, WARF provided a second declaration by Colin Stewart, D. Phil. (Second Stewart Declaration (2nd Stewart Decl.), filed June 29, 2010). Dr. Stewart states in his declaration that he obtained a doctorate in Mouse Embryology and that his "research career has centered on the development and application of genetic manipulation techniques to studying embryogenesis, stem cells and disease formation in mammals using the mouse as a model organism." (2nd Stewart Decl. ¶ 1.) Dr. Stewart is therefore qualified as an expert in the subject matter of this appeal.

Dr. Stewart testified in his written declaration that the Williams patent is not enabled to produce human embryonic stem cells. Dr. Stewart stated that Williams' method of isolating stem cells without feeder cells did not work when applied to human embryo cells (2nd Stewart Decl. ¶¶7-11). Dr. Stewart testified:

8. Williams discloses two methods for isolating murine embryonic stem (ES) cells from a blastocyst. The first requires the direct plating of a murine blastocyst onto a plastic tissue culture dish in the presence of the cytokine (growth factor) LIF. The second involves performing immunosurgery on a murine blastocyst and then subsequently plating the resulting inner cell mass (ICM) on a plastic tissue culture dish in the presence of LIF. While these methods are suitable for murine ES cells, they do not work when applied to human blastocysts or human ICMs.

10. The reason that neither Williams method will work to isolate hES [human embryonic stem] cells is that hES cells can only be isolated by plating a human post-immunosurgery ICM on a feeder layer of cells. The addition of LIF to the culture will have no effect on helping to isolate hES cells.

As evidence of this, Dr. Stewart cited the Bongso publication, published after the filing date of the '913 patent:

13. My position is supported by the report of Bongso who followed the Williams ICM [inner cell mass from human blastocysts] method and plated human post-immunosurgery derived ICM onto a tissue culture dish that contained LIF, but the dish did not contain a feeder layer of cells. Bongso noted that this method failed to isolate a replicating in vitro cell culture of pluripotent hES cells. This failure was reported by Bongso et al. in 1994 (Human Reproduction 9: 2110-2117; "Bongso"). This supports my position that hES cells can only be isolated by plating a post-immunosurgery derived ICM on a feeder layer of cells.

WARF's evidence is persuasive (Req. Reopen 7-10).

First, the evidence supports WARF's position that Williams does not describe using feeder cells to isolate embryonic stem cells. As argued by WARF, the instances in which feeder cells are utilized by Williams, the feeder cells were used to maintain ES cells, but not to derive them (Williams, col. 2, ll. 54-59; 2nd Stewart Decl. ¶ 11).

In addition, we agree with WARF that Bongso reported negative results without feeder cells. Bongso wrote:

Our preliminary studies prior to this report demonstrated clearly that, in the absence of an initial feeder layer and subsequent HLIF, the ICM cells were difficult to sustain or always differentiated into fibroblast-like cells.

Bongso, pp. 2115-2116.

As WARF has provided persuasive evidence that Williams did not enable one of ordinary skill in the art, at the time the invention was made, to make human embryonic stem cells as claimed, we withdraw the anticipation rejection of claims 1-3 over the Williams patent.

2. OBVIOUSNESS REJECTIONS

In the Decision, we reversed the Examiner's determination that claims 1-3 were not obvious under 35 U.S.C. § 103(a) over 1) Williams; 2) Robertson '83, Robertson '87, Williams and Hogan; 3) Piedrahita, Williams and Hogan; 4) Robertson '83, Robertson '87, Piedrahita, Williams and Hogan. In reaching this conclusion, we grouped all the rejections together, since they involved the same set of facts and issues (Decision 20). After considering all the evidence of record, we stated that "it would have been *obvious to have tried* the known mouse protocols on human embryos, and

because such protocols would have resulted in human stem cells, we conclude that the claimed human embryonic stems would have been obvious to persons of ordinary skill in the art” (Decision 38 (emphasis added)).

The so-called “obvious to try” standard is applicable when there is a finite number of identified, predictable solutions” available to one of ordinary skill in the art that would have routinely led to the claimed invention.

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 has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was *obvious to try* might show that it was obvious under §103.

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Whether an invention is “obvious to try” is just another factor to be considered in making an obviousness determination. As made clear by the Supreme Court, and subsequently by the Federal Circuit, there is no one test or single standard for determining obviousness. Rather, all the evidence of record must be considered:

This court cannot, in the face of *KSR*, cling to formalistic rules for obviousness, customize its legal tests for specific scientific fields in ways that deem entire classes of prior art teachings irrelevant, or discount the significant abilities of artisans of ordinary skill in an advanced area of art.

In re Kubin, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

While we acknowledged in the original Decision that there was uncertainty as to whether the prior art stem cell technology would work in

human embryos, we found this outweighed by the strong reason to make human embryonic stem cells (“obvious to try”) and the prior art technology to do so (Decision 36). However, WARF has now cited evidence that identifying human embryonic stem cells was not routine because human stem cells do not have the same morphology as mouse embryonic stem cells and thus it would not have been known which cells to select during the stem cell derivation process.

Dr. Stewart testified that Dr. Thomson “succeeded in part” in isolating hES cells “because he was the first to identify the particular morphology of primate ES cells” (2nd Stewart Decl. 34).

35. As noted in my previous Declaration dated May 29, 2007 at paragraph 19, the primate ES cell colonies that Dr. Thomson selected for further study were compact and flatter than mouse ES cell colonies. Mouse ES cell colonies are distinctly different in that they are compact, often tear-drop shaped mounds. Flat, compact colonies of hES cells had not been described at any time before Dr. Thomson's invention. It should be remembered that at this stage in the process, the culture dish contains a heterogeneous mixture of cells and debris, a plethora of colonies, and it would not have been apparent what cells/colonies to choose for further study without the insight exhibited by Dr. Thomson.

Dr. Stewart’s testimony is consistent with the disclosure in the ‘913 Patent. The ‘913 Patent described the isolation of primate ES cells:

The colony morphology of primate embryonic stem cell lines is similar to, but distinct from, mouse embryonic stem cells. Both mouse and primate ES cells have the characteristic features of undifferentiated stem cells, with high nuclear/cytoplasmic ratios, prominent nucleoli, and compact colony formation. The colonies of primate ES cells are flatter than mouse ES cell colonies and individual primate ES cells can be easily distinguished.

'913 Patent, col. 9, ll. 57-64. Thus, a preponderance of the evidence supports WARF's argument that Dr. Thomson, in deriving embryonic stem cells from human embryos, did more than just follow the path that had already been taken in the mouse (Decision 34). Rather, the invention took innovation by Dr. Thomson.

As discussed above, whether an invention is obvious because it is "obvious to try," must be weighed against other evidence of nonobviousness in the record. In this case, WARF provided new rebuttal evidence of repeated failures to make rat embryonic stem cells using the available stem cell technology. The Buehr⁷ publication was cited by WARF as

. . . conclusive evidence that the path was not so definite [for isolating human embryonic stem cells], the landmarks not so explicit, and the solutions not so predictable. Buehr discloses, for the first time, in 2008, twenty-seven years after the first isolation of murine ES cells, the isolation of rat ES cells. All of the attempts to make rat ES cells that occurred before Buehr failed.

Req. Reopen 20. The failure, until 2008, to make rat stem cells using the available stem cell technology is another factor which militates against a finding of obviousness.

Consistently, in a post-filing date publication on stem cell science that appeared in the *Harvard Magazine*, July-August 106(6):36-45, 37 (2004), it was stated:

Nevertheless, harvesting and maintaining a line of stem cells from any animal is "not routine at all," explains Andrew McMahon, professor of molecular and cellular biology. No one has been able to derive stem cells from rats, for example, even

⁷ Buehr et al., "Capture of Authentic Embryonic Stem Cells from Rat Blastocysts," *Cell*, 135: 1287-1298, 2008.

though mice and rats are closely related. So it was an astounding breakthrough when, in 1998, University of Wisconsin researcher James Thomson successfully established and sustained several human stem-cell lines in culture.

Dr. Thomson's isolation of hES was characterized as a "breakthrough" in the *Harvard Magazine* article. To further support this statement, WARF cited numerous examples of recognition and accolades by the lay and scientific community of Dr. Thomson's work with human embryonic stem cells (Req. Reopen 28-29). Thus, the invention of human embryonic stem cells by Dr. Thomson was highly praised by scientists.

In the original Decision, we had recognized the shortcomings in the prior art for making stem cells of certain animal species, including rat, but we had found this offset by the evidence of record, including a declaration by Dr. Douglas Melton that that human ES cells were successfully isolated "by simply following those methods taught for deriving mouse, rat, pig and sheep ES cells" (Decision 37).

WARF provided new evidence in the Request to Reopen Prosecution that Dr. Melton's declaration should be given less weight. We agree. WARF noted that Dr. Melton had said in his declaration that "we have successfully isolated human ES cells in our lab by simply following these methods taught for deriving mouse, rat, pig and sheep ES cells. We did so without recourse to Dr. Thomson's publications or patents" (Melton Decl. 13). However, WARF provided Dr. Melton's own scientific publication in *The New England Journal of Medicine* in which he described the isolation of hES cell lines (Cowan et al. 2004, *New Eng. J. Med.* 350 (13) 1353-1356; Req. Reopen 25). WARF states:

In that paper, Dr. Melton refers to Dr. Thomson's seminal paper in *Science* in 1998 . . . as guiding the isolation of their (Cowan and Melton's) hES cells. For example, . . . the authors state that "97 inner cell masses were isolated, and 17 individual human embryonic stem-cell lines . . . were derived according to published protocols that we modified in terms of medium composition, enzymatic disassociation, and procedures for freezing and thawing . . .," citing to Thomson et al. *supra*.

Even more probative is the fact that in this very same publication, Dr. Melton nowhere credits Robertson '83 or Robertson '87, or Piedrahita, references that according to Dr. Melton in his Declaration submitted in the present proceedings, informed him as to how to isolate his hES cells "without recourse to Dr. Thomson's publications or patents." Declaration of Melton, paragraph 13.

Req. Reopen 26.

Thus, despite Dr. Melton's statements to the contrary, in his own research in making human embryonic stem cells, Dr. Melton credited Dr. Thomas's published work.

In sum, while there was a strong reason to have made human embryonic stem cells, the closest prior art cited in this proceeding – the Williams patent – did not make them or enable making them because it did not describe utilizing feeder cells to derive them or describe which cells in the derivation culture were the human embryonic stem cells.

There was reason to try other available prior art methods for making human embryonic stem cells. However, strong evidence of non-obviousness outweighs the countervailing evidence of obviousness. This nonobviousness evidence includes:

- The isolation of human embryonic stem cells required innovation;

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- The failure to make stem cells from closely related species, particularly rat;
- Those (Melton) making human embryonic stem cells followed Thomson's work; and
- Acclaim by both the lay and scientific community.

CONCLUSION

Upon reconsideration of the new evidence provided by WARF, the rejections set forth in the Board Decision dated January 29, 2010 are withdrawn and we affirm the Examiner decision in the Answer dated July 30, 2009 confirming the patentability of claims 1-3 of US Patent 7,029,913.

AFFIRMED

ack

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