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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SHINYA YAMANAKA, KAZUTOSHI TAKAHASHI, and
KEISUKE OKITA¹

Appeal 2015-005500
Application 13/585,729
Technology Center 1600

Before DEMETRA J. MILLS, TAWEN CHANG, and RACHEL H.
TOWNSEND, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims 1–8 for lack of enablement throughout the claim scope.² We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

¹ Appellants identify the Real Party in Interest as Kyoto University. App. Br. 2.

² We have reviewed a Decision in a related appeal, Appeal No. 2014-006588, Application Serial No. 12/379,564. The present application differs from the related appeal in that Appellant has claimed a much earlier effective filing date for the present application. We also take note of related, undecided, Appeal No. 2015-005533, Application Serial No. 12/289873.

STATEMENT OF CASE

According to the Specification, “[t]he present invention relates to a nuclear reprogramming factor having an action of reprogramming a somatic cell to derive an induced pluripotent stem (iPSC) cell.” Spec. 1.

The pending claims are directed to methods comprising “forcing expression” of certain gene products, including through introducing expression vectors containing genes encoding such gene products encompassing both retroviral vectors or non-retroviral vectors. Spec. 40-41, 50; ¶¶126–127, 152.³

The following claim is representative.

1. A method for preparing a mammalian induced pluripotent stem cell which comprises:
 - a) forcing expression of a group of gene products that comprises at least one of an Oct3/4 gene product, a Klf family gene product, and a Sox family gene product in a mammalian somatic cell, so that the introduced mammalian somatic cell expresses all three of a Oct3/4 gene product, a Klf family gene product and a Sox family gene product,
 - b) culturing the mammalian somatic cell obtained after step (a) under conditions that maintain pluripotency and self-renewal.

Cited References

Matthias Stadtfeld et al., *Induced Pluripotent Stem Cells Generated Without Viral Integration*, Science Vol. 322, p. 945 (November 2008) (“Stadtfeld”).

Keisuke Okita et al., *Generation of Mouse Induced Pluripotent Stem Cells Without Viral Vector*, Science Vol. 322, p. 949 (November 2008) (“Okita”).

³ See also, Appeal Brief, pages 6-7.

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Federico Gonzalez et al., *Generation of mouse-induced pluripotent stem cells by transient expression of a single nonviral polycistronic vector*, PNAS 106(22), p. 8918 (June 2009) (“Gonzales”).

Ryan T. Rodriguez et al., *Manipulation of OCT4 Levels in Human Embryonic Stem Cells Results in Induction of Differential Cell Types*, Exp. Biol. Med (Maywood) (November 2007) (“Rodriguez”).

S. Yamanaka, *Induction of pluripotent stem cells from mouse fibroblasts by four transcription factors*, Cell Prolif. (2008) (“Yamanaka”).

vector (in biotechnology), IUPAC Compendium of Chemical Terminology, 2nd ed. (1997).

Wenbo Zhou et al., *Adenoviral Gene Delivery Can Reprogram Human Fibroblasts to Induced Pluripotent Stem Cells*, Stem Cells 27:2667 (2009) (“Zhou”).

Grounds of Rejection

Claims 1–8 remain rejected under 35 U.S.C. §112, first paragraph for lack of enablement of the full scope of the claim.

FINDINGS OF FACT

The Examiner’s findings of fact are set forth in the Answer at pages 2–29. The following facts are highlighted.

1. The term “vector” is not defined in the Specification. Appellants stipulate that, “‘vectors’ are well known in the art and therefore, need not be disclosed in the specification in detail. In other words, ‘vector’ is a plasmid, virus, bacteriophage, and the originally filed specification discloses introduction of the genes by using such vectors.” Appeal Br. 6-7.
2. The Specification states:

[T]ypes of somatic cells to be reprogrammed are not particularly limited [in the claims], and any kind of somatic cells may be used. For example, matured somatic cells may be used, as well as somatic cells of an embryonic period. Other examples of cells capable of being generated into iPS cells and/or encompassed by the present invention include mammalian cells such as fibroblasts, B cells, T cells, dendritic cells, keratinocytes [sic], adipose cells, epithelial cells, epidermal cells, chondrocytes, cumulus cells, neural cells, glial cells, astrocytes, cardiac cells, esophageal cells, muscle cells, melanocytes, hematopoietic cells, pancreatic cells, hepatocytes, macrophages, monocytes, mononuclear cells, and gastric cells, including gastric epithelial cells.

Spec. 41.

3. As set forth in the Answer, the cited references show that, without additional steps not taught in the Specification,

[r]eprogramming attempts with adenovirus have failed. Stadtfeld states initially attempts to reprogram mouse tail-tip fibroblasts through the introduction of Oct4, Sox2, Klf4 and c-Myc failed (Stadtfeld, page 946, col. 1, line 1 to col. 2, line 1, IDS, 11 /14/12, ref. 580).

Ans. 4; *see also* Okita 950, col. 1 (teaching that no iPS cells were generated when Oct3/4 was introduced with adenoviruses and Klf4 and Sox2 with retroviruses, when two factors were introduced by adenoviruses, or when four factors were introduced with separate adenoviral vectors).

4. As the Examiner finds, Stadtfeld shows that

[s]uccessful reprogramming occurred when adenoviral vectors comprising Sox2, Klf4 and c-Myc delivered the factors to mouse fetal liver cells and mouse tail tip fibroblasts . . . expressing Oct4 (Stadtfeld, page 946, col. 2, lines 9–13 and 17–23; and col. 3, parag. 1, lines 1–4 and

9–13). Stadtfeld [also] demonstrated reprogramming in adult mouse hepatocytes, infecting them with adenoviral vectors containing the 4 factors (Stadtfeld, page 946, col. 3, parag. 2, line 8 to page 946, col. 1, line 7). Hepatocytes, as stated by Stadtfeld, were chosen because of their natural compliance to adenovirus infection (Stadtfeld, page 946, col. 3, parag. 2, lines 1–4).

Ans. 4–5.

5. As set forth in the answer, the cited references suggest that, without additional steps not taught in the Specification,

[p]lasmid vectors also failed to provide reprogrammed cells. Okita states the achievement of reprogramming when 3 factors (Oct4, Sox and Klf4) were delivered as a single cistronic sequence with a self-cleaving peptide in an adenoviral vector (Okita, page 950, col. 1, parag. 1, lines 1–3, 5–10 and 15–18, IDS, 11, 14, 12, ref. 513). Plasmid vectors containing the same 3 factors as a polycistron were delivered on days 1 and 3. A separate plasmid vector comprising a c-Myc gene was delivered days 2 and 4 (Okita, page 950, col. 1, parag. 2, lines 1–8).

Ans. 5.

6. As the Examiner finds,

Gonzales describes the delivery of a plasmid comprising Oct4, Sox2, Klf4 and c-Myc 2A-peptide linked ORFS[s] [open reading frames] by nucleofection into mouse embryonic fibroblast cells (Gonzales, page 8921, col. 1, lines 1–8). Gonzales states 2 nucleofections were required to obtain iPSCs (Gonzales, page 8921, col. 1, parag. 2, lines 1–6, IDS, 11 /14/12, ref. 340).

Ans. 5.

7. As the Examiner finds,

Rodriguez supports lentivirus in stating ES cells have a tendency to silence ectopic expression of exogenously introduced nucleic acids (Rodriguez, page 1376, col. 2, parag. 1, lines 6–12, IDS, 11 /14/12, ref. 545).

Ans. 5.

8. As set forth in the Answer,

Yamanaka states a retroviral transfection system is indispensable for iPS cell induction (Yamanaka, page 55, parag. 1, lines 4–5, IDS, 11/14/12, ref. 659.) Yamanaka further states other factors may be able to induce iPSCs without retroviral vectors, but that such factors are yet to be identified (Yamanaka, page 55, parag. 1, lines 7–10.)

Ans. 5.

9. Without additional steps not taught in the Specification, Stadtfeld, Okita and Gonzales failed to produce iPSCs when non-retroviral vectors introduced nuclear reprogramming factor genes into targeted somatic cells.

10. As the Examiner finds,

Zhou used an adenoviral vector to revert a somatic cell to a pluripotent state. While the adenovirus was not materially different from those in the art, the method steps employed by Zhou to obtain pluripotent cells certainly were. Zhou teaches a single infection of fibroblasts with retroviral vectors separately encoding nuclear reprogramming factors did not result in any ES-like cells (Zhou, page 2671, col. 1, parag. 1, lines 9-12). Zhou teaches a protocol with multiple adenoviral vector transductions resulted in iPSC production.

Ans. 25.

11. As the Examiner finds,

The SeV vector taught by Fusaki to successfully induce somatic cells to a pluripotent state is materially different and separate protocol from that disclosed [in Appellants' Specification].

Ans. 28.

PRINCIPLES OF LAW

In making our determination, we apply the preponderance of the evidence standard. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office). The Board “determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction ‘in light of the specification as it would be interpreted by one of ordinary skill in the art.’” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (quoting *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004).

The enablement requirement ensures that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims. The scope of the claims must be less than or equal to the scope of the enablement. The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill without undue experimentation.

National Recovery Technols. Inc. v. Magnetic Separation Sys., Inc., 166 F.3d 1228, 1232 (Fed Cir. 1999).

An enablement rejection can be for scope of enablement or for total lack of enablement. *In re Cortright*, 165 F.3d 1353, (Fed. Cir. 1999).

[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

In re Fisher, 427 F.2d 833, 839 (CCPA 1970).

“[A]pplication sufficiency under § 112, first paragraph, must be judged as of its filing date. It is an applicant’s obligation to supply enabling disclosure without reliance on what others may publish after he has filed an application on what is supposed to be a completed invention. If he cannot supply enabling information, he is not yet in a position to file.” *In re Glass*, 492 F.2d 1228, 1232 (CCPA 1974). *See also, Plant Genetic Sys., N.V. v. DeKalb Genetics, Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003).

Alza Corp v. Andrx Pharms., 603 F.3d 935, 938, 943 (Fed. Cir. 2010) (affirming district court’s determination that “claims are invalid for lack of enablement because the specification does not enable the full scope of claim 1, which covers both osmotic and non-osmotic dosage forms”). In *Anza*, “the parties agreed that the specification enables osmotic oral dosage forms, but disputed whether it also enables non-osmotic oral dosage forms.” *Id.* at 938. The Federal Circuit found that “the evidence dictate[d] that a person of ordinary skill in the art would have been required to engage in undue

experimentation to develop non-osmotic oral dosage forms with ascending release rates.” *Id.* at 943.

ISSUE

The Examiner finds that

Claims 1–8 . . . while being enabling for a method for preparing a mammalian induced pluripotent stem cell by nuclear reprogramming of a mammalian somatic cell comprising: a) introducing into the somatic cell one or more retroviral vectors comprising the following four genes: an Oct family gene, a Klf family gene and a Sox family gene operably linked to a promoter; and b) culturing the transduced somatic cell under conditions that maintain pluripotency and self-renewal, does not reasonably provide enablement for a method for preparing an induced pluripotent comprising a) forcing expression of a group of gene products that comprises at least one of an Oct3/4 gene product, a Klf family gene product, and a Sox family gene product in a mammalian somatic cell, so that the introduced mammalian somatic cell expresses all three of a Oct3/4 gene product, a Klf family gene product and a Sox family gene product, b) culturing the mammalian somatic cell obtained after step (a) under conditions that maintain pluripotency and self-renewal for reasons set forth in the office action mailed June 26, 2014. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Ans. 2–3.

Appellants contend that, “In the present case, the only factor weighing against the full scope of enablement of the presently pending claims is that the only working examples present in the application make use of a retroviral vector.” Appeal Br. 6. Appellants further argue that

The specification amply describes the use of vectors generally to express nuclear reprogramming factors. Paragraph [0127] of the specification as filed teaches that “Alternatively, by using a vector containing a gene that is capable of expressing the nuclear reprogramming factor of the present invention, a means of transducing said gene into a somatic cell may be employed.” This phrase is also found in the priority document. Reference to “recombinant vectors[”] generally is found throughout the specification (e.g. [0089], [0106]). Accordingly, the specification as filed is clearly directed to use of vectors generally without limitation to the specific vectors exemplified in the Examples of the specification. Clearly use of vectors other than retroviral vectors for use in the claimed method is well described.

Id. Appellants argue that

“vectors” are well known in the art and therefore, need not be disclosed in the specification in detail. In other words, “vector” is a plasmid, virus, bacteriophage, and the originally filed specification discloses introduction of the genes by using such vectors. Accordingly, the specification as filed duly provides sufficient guidance for the full scope claimed.

Appeal Br. 7. Appellants contend with respect to the references cited for showing lack of enablement at the time of filing of the application that

the references also do not establish that an iPSC could not be prepared by using a suitable vector prepared by one skilled in the art. In fact, Appellant respectfully submits that the references cited by the Examiner actually support the position that retroviral vectors are not required to delivery of reprogramming factors sufficient to reprogram cells which is also indicated by the Examiner in the Final Office Action.

Appeal Br. 8.

The issue is: Has the Examiner established a prima facie case of lack of enablement throughout the pending claim scope on the evidence of

record? If so, have Appellants rebutted any prima facie case with argument or evidence?

ANALYSIS

We agree with the Examiner's fact finding, statement of the rejection and responses to Appellants' arguments as set forth in the Answer. We find that the Examiner has provided evidence to support a prima facie case of lack of enablement commensurate with the claim scope. We provide the following additional comment to the Examiner's argument set forth in the Final Rejection and Answer. Appellants do not argue individual claims separately, therefore we select claim 1 as representative claim. There appears to be no dispute that the production of iPSC was nascent technology at the time of filing of the present application.

The Examiner argues that the cited references (Stadtfeld, Okita, Gonzalez, Rodriguez and Yamanaka) show that

at the time of filing non-retroviral vectors, or factors eliminating the need for retroviral vectors that caused the induction of pluripotency in somatic cells were not known in the art. Those methodologies that may produce iPSCs without retroviral vector delivery of nuclear reprogramming factor genes employed protocols not disclosed by the present specification.

Ans. 5–6, 16-28. These references are extensively and creditably discussed by the Examiner in the Final Action and Answer, and we will not discuss them further here.

Appellants insist that the Specification, as filed, discloses the full scope of the claim because it “describes use of vectors generally,” i.e., “discloses a non-limited ‘vector’”, “a large number of vectors and their use for delivery of a wide variety of genes was well known at the time the

invention was made”, and “[t]hose having ordinary skill were well-versed in delivery of genes at the time the invention was made.” App. Br. 6–7, 11.

The only mention of vectors other than retroviral vectors in Appellants’ Specification is paragraph 127. This Specification paragraph states:

Alternatively, by using a vector containing a gene that is capable of expressing the nuclear reprogramming factor of the present invention, a means of transducing said gene into a somatic cell may be employed. When such vector is used, two or more kinds of genes may be incorporated into the vector, and each of the gene products may be simultaneously expressed in a somatic cell.

There is no specific indication in the Specification that the non-retroviral vector can be a plasmid, or a description of a specific type of plasmid, or how to prepare the plasmid. There is no indication in the Specification as to which and how the nuclear reprogramming factors are oriented in the plasmid. Nor does the Specification describe a specific transduction protocol for successful non-retroviral plasmid expression to obtain transformation of a somatic cell to a pluripotent stem cell. Thus, there is a lack of disclosure in Specification of how to effect the pluripotency of the modified somatic cell using non retroviral vectors, in combination with the evidence of record of the failure of some others to achieve pluripotent cells from non-viral vector modified somatic cells after the effective filing date of the application. *See, Alza Corp v. Andrx Pharms.*, 603 F.3d 935, 941-943 (Fed. Cir. 2010).

Appellants do not specifically respond to the Examiner’s comments concerning the cited references (Ans. 19–24), which show that it was not until after the effective filing date of the present application (December 13,

2005)⁴ that attempts at using non-retroviral vectors for preparing a mammalian induced pluripotent stem cell were successful.

Importantly, Appellants have not shown that one of ordinary skill in the art at the time of the invention, following the disclosure of Appellants' Specification would have been able to prepare a pluripotent stem cell from a somatic cell using a non-retroviral vector, without undue experimentation.

In particular, Appellants allege that

Zhou et al., (Cell 27:2667-2674, 2009, IDS March 3, 2014) disclose that iPSCs were successfully produced by using an adenoviral vector. The procedure taught by Zhou did not employ any surprising technique. Rather, the procedure could be achieved with expenditure of no more effort than is normally required in the art.

App. Br. 10. Fusaki⁵ was submitted by Appellants as evidence to show that vectors other than retroviral vectors could have been used for producing iPSCs. *Id.*

We are not persuaded by Appellants' citations to Zhou and Fusaki. "Zhou used an adenoviral vector to revert a somatic cell to a pluripotent state." Final Act. 10. The method steps employed by Zhou to obtain pluripotent cells were different from those in the prior art. *Id.* Zhou does not disclose the use of a non-retroviral vector to create pluripotent cells. Ans. 25–26. The Examiner further found that, "The SeV vector taught by Fusaki to successfully induce somatic cells to a pluripotent state is materially

⁴ Appellants have not contested that December 13, 2005 as the effective filing date of the instant application. App. Br. 7.

⁵ Fusaki, N., et al., *Efficient induction of transgene-free human pluripotent stem cells using a vector based on Sendai virus, an RNA virus that does not integrate into the host genome*, Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 85:348-362, 2009.

different and separate protocol from that disclosed [in the Specification].”

Ans. 27. Thus, that Fusaki and Zhou may exemplify post-filing successes, does not demonstrate Appellants’ specification enables the claimed invention. *Accord, Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1376 (1999) (“We also agree with Calgene that Enzo’s evidence of enablement was inconclusive, as Enzo did not prove that the alleged post-filing successes were accomplished by following the teachings of the specifications.”) *See also, In re Wright*, 999 F.2d 1557, 1563-1564 (Fed. Cir. 1993) (holding that demonstration using one retrovirus is inadequate to enable claims to all retroviruses or even all avian RNA viruses and that undue experimentation would be required, despite the routine nature of the experimentation involved); *MagSil Corp. v. Hitachi Global Storage Technologies Inc.*, 687 F.3d 1377, 1384 (Fed. Cir. 2012) (“The record contains no showing that the knowledge of that artisan would permit, at the time of filing, achievement of the modern values above 600% without undue experimentation, indeed without the nearly twelve years of experimentation necessary to actually reach those values. . . . This court holds that the asserted claims are invalid for lack of enablement because their broad scope is not reasonably supported by the scope of enablement in the specification.”)

We find that *Wyeth and Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380 (2013) is also instructive here. *Wyeth*, as in the present case, involved a question of enablement throughout the claim scope of a method claim where only a single embodiment (use of sirolimus), of a broad claim (encompassing multiple rapamycin compounds), was disclosed in the specification. The district court below had relied “on the unpredictability of

the chemical arts, the complexity of the invention, and the limited knowledge of treatment of restenosis using sirolimus at the time of the invention” in invalidating the claims at issue. *Id.* at 1384. The Federal Circuit affirmed the district court below and held in *Wyeth* that

Here, the specification . . . discloses only a starting point for further iterative research in an unpredictable and poorly understood field. Synthesizing candidate compounds derived from sirolimus could, itself, require a complicated and lengthy series of experiments in synthetic organic chemistry.

. . .

The specification offers no guidance or predictions about particular substitutions that might preserve the immunosuppressive and antirestenotic effects observed in sirolimus. The resulting need to engage in a systematic screening process for each of the many rapamycin candidate compounds is excessive experimentation. We thus hold that there is no genuine dispute that practicing the full scope of the claims, measured at the filing date, required undue experimentation.

Id. at 1386. The present case, as in *Wyeth*, similarly involves the unpredictable technology of a method of converting somatic cells to induce pluripotent stem cells, despite the “art [knowing] that the nucleus of a somatic cell can be reprogrammed,” that particular “nuclear reprogramming factors . . . are responsible for reprogramming a somatic cell” (Reply Br. 4), that “‘vectors’ are well known in the art,” and that, in general, “gene transfer techniques that use vectors were well-known, common techniques in the art” (Appeal Br. 7). The Specification only enables performance of the method with retroviral vectors and provides no guidance as to manipulations required to achieve induced pluripotent stem cells with other, non-retroviral

vectors within the broad scope of the claims. We agree with the Examiner that

[s]ilence in the prior art on a particular invention or a particular aspect of an invention renders it incumbent on the disclosure to provide the necessary guidance to the skilled artisan to make and use the claimed invention. The present specification does not suggest any particular non-retroviral vector constructs, nor does the specification suggest modifications to non-retroviral vectors to enhance delivery and/or expression of nuclear reprogramming factor nucleic acids in somatic cells. Each successful implementation of the claimed method by the post-filing art using a nonretroviral vector, used a vector and/or method not disclosed by or supported by the specification. From this, reprogramming somatic cells to an earlier undifferentiated, pluripotent states ranks among nascent inventions. MPEP states “The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art.”

Ans. 11. The Examiner further finds that even if the skilled artisan would have known how to optimize the particular non-viral vector to use in the claimed method, at the time of the invention it would have required undue experimentation to produce a non-retroviral vector capable of inducing pluripotency from in a somatic cell. Final Act. 11. We conclude that practicing the full scope of the claims, measured at the filing date, required undue experimentation.

We agree with the Examiner that claims 1–8 do not enable the full scope of the claim, and the 35 USC § 112, first paragraph rejection of the claims for lack of enablement is affirmed for the reasons of record.

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DECISION

We affirm the lack of enablement rejection of claims 1–8 for the reasons of record. The cited references, and preponderance of the evidence, support the Examiner’s lack of enablement rejection.

AFFIRMED