IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BioGatekeeper, Inc.
Petitioner

v.

Kyoto University
Patent Owner

U.S. Patent No. 8,058,065 to Yamanaka *et al.*
Issue Date: November 15, 2011
Title: OCT 3/4, KLF4, C-MYC AND SOX2 PRODUCE INDUCED PLURIPOTENT STEM CELLS

Inter Partes Review No.: Unassigned

Petition for *Inter Partes* Review of U.S. Patent No. 8,058,065 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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PETITIONER'S EXHIBIT LIST

BioGatekeeper's Exhibit #	***Description***
EX1001	U.S. Patent No. 8,058,065 to Yamanaka et al.
EX1002	U.S. Pat. No. 7,682,828 to Jaenisch et al., and assigned to Whitehead Institute for Biomedical Research.
EX1003	Benvenisty Paper (Genes Dev. 1992 Dec;6(12B):2513-23)
EX1004	Li Article (Blood. 2005 Jan 15;105(2):635-7. Epub 2004 Sep 9)

I. INTRODUCTION

BioGatekeeper, Inc. ("Petitioner") petitions for *Inter Partes* Review, seeking cancellation of claim 1 ("challenged claim") of U.S. Patent No. 8,058,065 to Yamanaka *et al.* ("the Yamanaka patent") (EX1001), which is owned by Kyoto University ("Kyoto University").

II. STANDING (37 C.F.R. § 42.104(a)); PROCEDURAL STATEMENTS

Petitioner certifies that (1) the Yamanaka patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the Yamanaka patent on the grounds identified herein. This Petition is filed in accordance with 37 CFR § 42.106(a). Concurrently filed herewith are a Power of Attorney and an Exhibit List pursuant to § 42.10(b) and § 42.63(e), respectively. The required fee is paid through online credit card payment.

III. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

A. Each Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real parties in interest are BioGatekeeper, Inc., and Kyoto University.

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

As of the filing date of this petition and to the best knowledge of the Petitioner, the Yamanaka Patent is not involved in any litigation.

C. Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

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D. Notice of Service Information (37 C.F.R. § 42.8(b)(4))

Please direct all correspondence to lead counsel at the above address. Petitioner consents to email service at: aking@ardentlawgroup.com and achang@ardentlawgroup.com.

IV. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

Claim 1 of the Yamanaka Patent is challenged in this petition. Petitioner asks that the Board review the accompanying prior art and analysis, institute a trial for *inter partes* review of Claim 1 of the Yamanaka Patent, and respectfully requests that the Board cancel claim 1 as unpatentable.

V. OVERVIEW

Claim 1 of the Yamanaka patent is unpatentable for failing to satisfy the nonobviousness requirement of 35 U.S.C. § 103. The alleged "invention" involve only the (i) "simple and obvious substitution of one known element for another to obtain predictable results" over what was taught in the prior art; (ii) "choosing from a finite number of identified, predictable solutions," with a reasonable expectation of success; and/or (iii) obvious modification of prior art teachings, with a reasonable expectation of success. Thus, its claim fails to satisfy the requirement for nonobviousness under *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

A. The Yamanaka Patent

The Yamanaka patent is generally directed to "a method of nuclear reprogramming of a somatic cell from a mammalian species, comprising inserting

four genes. Claim 1 of the ‘065 patent (EX1001) reads as follows:

> 1. A method for preparing an induced pluripotent stem cell by nuclear reprogramming of a somatic cell from a mammalian species, comprising:
>
> a) introducing into the somatic cell one or more retroviral vectors comprising a gene encoding Oct3/4, a gene encoding Klf4, a gene encoding c-Myc and a gene encoding Sox2 operably linked to a promoter; and
>
> b) culturing the transduced somatic cell on a fibroblast feeder layer or extracellular matrix in a cell media that supports growth of ES cells of the mammalian species, wherein one or more pluripotent cells are obtained.

B. The Scope and Content of the Prior Art

1. The Whitehead Patent

U.S. Pat. No. 7,682,828 (herein after “the Whitehead patent”) to Jaenisch et al., and assigned to Whitehead Institute for Biomedical Research, discloses reprogramming methods which allows one to genetically engineer animals other

than mouse and human. The Reprogrammed Pluripotent Somatic Cells (RPSCs) produced by the Whitehead patent are embryonic stem (ES) cell-like, and are thus amenable to genetic manipulation. The ES-cell like RPSCs can be manipulated to introduce desired targeted genetic modifications. The resulting engineered RPSCs can then be used to generate a cloned animal with the desired genetic modifications in its germ line, using methods described for ES cells in mouse. The Whitehead patent went on to describe using the disclosed methods to introduce pluripotent genes, including Oct4, Sox2 and Nanog, into a somatic cell.

In contrast, the Yamanaka patent claims a method that introduces 4 pluripotent genes, Oct4, Sox2, Klf4 and C-myc, into a somatic cell.

Although the Whitehead patent discloses a method that introduces only two of the four pluripotent genes as claimed by Yamanaka, as will become clear in this Petition, such claimed method in the Yamanaka patent would have been obvious to one of ordinary skill in the art, because a variety of pluripotent genes were already known in the art, and it would have been obvious for one of ordinary skill in the art to introduce such other known pluripotent genes in the Whitehead method.

VI. TECHNICAL BACKGROUND

A. **Pluripotent Stem Cells in General**

Claim 1 of the Yamanaka patent is about a method for preparing an induced pluripotent stem cell.

Pluripotent stem cells were known to have the potential to differentiate into the full range of daughter cells having distinctly different morphological, cytological or functional phenotypes unique to a specific tissue. By contrast, descendants of pluripotent stem cells are restricted progressively in their differentiation potential, with some cells having only one fate. Pluripotent stem cells have extraordinary scientific and therapeutic potential, as they can be differentiated along the desired differentiation pathway in a precisely controlled manner and used in cell-based therapy.

Two categories of pluripotent stem cells are known to date: embryonic stem cells and embryonic germ cells. Embryonic stem cells are pluripotent stem cells that are derived directly from an embryo. Embryonic germ cells are pluripotent stem cells that are derived directly from the fetal tissue of aborted fetuses.

Prior to Yamanaka patent's filing date, published reports on the isolation and successful culturing of the first human pluripotent stem cell lines have generated

great excitement and have brought biomedical research to the edge of a new frontier. (Stem Cells: A Primer, NIH May 2000, http://www.madrimasd.org/cienciaysociedad/ateneo/dossier/celulasmadre/primer.htm)

B. Known Methods to Produce Pluripotent Stem Cells

Prior to the filing date of the Yamanaka patent, ES cells (lines) were known to be obtained via several methods. In a first method, an ES cell line is derived from the inner cell mass of a normal embryos in the blastocyst stage (See U.S. Pat. No. 6,200,806, Thompson, J. A. et al. Science, 282:1145-7, 1998 and Hogan et al., 2003).

A second method for creating pluripotent ES cells (lines) utilizes the technique of somatic cell nuclear transfer (SCNT). In this technique, the nucleus is removed from a normal egg, thus removing the genetic material. Next, a donor diploid somatic cell is placed next to the enucleated egg and the two cells are fused, or the nucleus is introduced directly into the oocyte by micromanipulation. The fused cell has the potential to develop into a viable embryo, which may then be sacrificed to remove that portion of the embryo containing the stem cell producing inner cell mass.

In a third method, the nucleus of a human cell is transplanted into an entirely enucleated animal oocyte of a species different from the donor cell (referred to herein as animal stem cell nuclear transfer, or "ASCNT"). See U.S. Pat. application Ser. No. 20010012513 (2001). The resultant chimeric cells are used for the production of pluripotent ES cells (lines), in particular human-like pluripotent ES cells (lines). One disadvantage of this technique is that these chimeric cells may contain unknown non-human viruses and still contain the mitochondria of the animal species. Thus, there would be substantial risks of immune rejection if such cells were used in cell transplantation therapies.

In a fourth method, ES cells (lines) can be isolated from the primordial germ cells found in the genital ridges of post-implanted embryos.

C. Knowledge About Pluripotency Genes

Prior to the filing date of the Yamanaka patent, "pluripotency genes" were known. Pluripotency gene refers to a gene that is associated with pluripotency. The expression of a pluripotency gene is typically restricted to pluripotent stem cells, and is crucial for the functional identity of pluripotent stem cells. The transcription factor Oct-4 (also called Pou5fl, Oct-3, Oct3/4) is an example of a pluripotency gene. Oct-4 has been shown to be required for establishing and maintaining the undifferentiated phenotype of ES cells and plays a major role in

determining early events in embryogenesis and cellular-differentiation (Nichols et al., 1998, Cell 95:379-391; Niwa et al., 2000, Nature Genet. 24:372-376). Oct-4 is down-regulated as stem cells differentiate into specialized cells. Other exemplary pluripotency genes include Nanog, and Stella (See Chambers et al., 2003, Cell 113: 643-655; Mitsui et al., Cell. 2003, 113(5):631-42; Bortvin et al. Development. 2003, 130(8):1673-80; Saitou et al., Nature. 2002, 418 (6895):293-300.

VII. STATUTORY GROUNDS FOR THE CHALLENGE

This Petition provides a single challenge as follows:

Challenge: Claim 1 is rendered obvious under 35 U.S.C. § 103 by U.S. Patent No. 7,682,828 to Jaenisch *et al*.("Whitehead Patent") (EX1002) in view of The Benvenisty Article ("The Benvenisty Article") (EX1003) and further in view of the Li Article ("the Li Article") (EX1004).

The Whitehead patent issued March 23, 2010, with priority date of November 26, 2003, and is prior art under § 102(a). The Benvenisty Article was Published in 1992. The Li Article was published in January 2005.

VIII. BROADEST REASONABLE CONSTRUCTION

Petitioner bases the instant petition upon the broadest reasonable

interpretation of the claim language in light of the specification. *See* 37 C.F.R. § 42.100(b).

A. "*introducing*" (Claim 1)

One of skill in the art would understand the term ***introducing*** to mean *incorporating by nuclear reprogramming.* This construction is consistent with the specification of the Yamanaka patent. *See* EX1001 at 12:46-57, 15:35-16:66.

Petitioner's position regarding the scope of the claims under their broadest reasonable interpretation is not to be taken as stating any position regarding the appropriate scope to be given the claims in a court or other adjudicative body under the different claim interpretation standards which apply in such proceedings.

IX. ASPECTS OF THE CLAIMS WHICH ARE NOT ENTITLED TO PATENTABLE WEIGHT

Induced Pluripotent "Stem" Cell In The Preamble

The proposed rejections and claim chart set forth below assume, arguendo, that all aspects of the claim are entitled to patentable weight. However, the rule of law prohibits affording patentable weight to the limitations in the preamble of claim 1, more specifically, the intended resulting product (i.e., "induced pluripotent stem cell") from the claimed method, as described in the preamble.

Claim 1 of the Yamanaka patent is directed to a method, not an apparatus. Thus, patentable weight is given to each of the method steps in this method claim. On the other hand, the end-product as recited in the preamble shall have no affect on the qualification of a prior art. Therefore, whether or not the prior art method results in the same end-product as recited in Yamanka patent's claim 1 shall have no effect on the prior art's qualification, so long as the claimed method steps are disclosed and taught in the prior art.

The preamble of the Yamanaka Patent claim 1 states:

> Claim 1: A method for preparing an induced pluripotent stem cell by nuclear reprogramming of a somatic cell from a mammalian species, comprising:

A prior art shall not be disqualified if the prior art references does not explicitly disclose their end products as an induced pluripotent "stem" cell. In fact, the term induced pluripotent "stem" cell" was first coined by inventor of the Yamanaka Patent. Prior to the Yamanaka Patent, such embryonic stem cell-like cells were described by other names in the prior art. For example, the primary reference, the Whitehead Patent, calls such embryonic stem cell-like cells "reprogrammed pluripotent somatic cells (RPSC)."

In addition, although it is generally true that patent applicants are free to be their own lexicographers, see MPEP § 2111.01, it should be especially noted that the recited term induced pluripotent "stem" cell is internally conflicting and scientifically misleading.

The Yamanaka patent explained that its induced pluripotent "stem" cell is sometimes called "embryonic stem cell-like cells" or "ES-like cells." (EX 1001, Yamanaka patent, col. 1, lines 54-65.)

It is conflicting and misleading because "embryonic stem cell-like cells" or "ES-like cells" were known in the art at the time of the Yamanaka patent, and it was known that although such cells are "like" embryonic stem cells, they are NOT synonymous with the term "stem" cells.

The Whitehead patent (EX 1002) describes the same process of nuclear reprogramming a somatic cell by introducing pluripotent genes into a someatic cell (by integrating gene coded vector into a somatic cell's genome and transfect it and convert it into a pluripotent cell). Just like the Yamanaka patent, the Whitehead patent starts out with somatic cells, and ends up with pluripotent cells that are "ES-like cells." (See EX1002, col. 13, lines 12-13). The difference is that the Whitehead patent does not call its end product a type of "stem cell," rather, the

Whitehead patent calls its end product a "reprogrammed pluripotent somatic cell (RPSC)."

Therefore, although the Yamanaka Patent contends to have created an induced pluripotent "stem" cell, the claimed method in the Yamanaka Patent, if truly successful, would have merely and essentially reprogrammed a patient's own somatic cells to have pluripotency and growth ability similar to those of ES cells. (EX1001, col. 13, lines 20-30).

Therefore, whether the end product in the Yamanaka patent is really just "reprogrammed pluripotent somatic cells," "ES-like cells," or "pluripotent cells," the recited term induced pluripotent "stem" cell shall have no patentable weight.

X. REPRESENTATIVE PROPOSED REJECTIONS AND SHOWING THAT PETITIONER IS LIKELY TO PREVAIL

The references addressed below each provide the teaching believed to be missing from the prior art and variously render obvious the claimed subject matter. It should be understood that rejections may be premised on alternative combinations of these same references. Under the broadest reasonable construction, the independent claim 1 may be organized into the following two

basic steps: (a) inserting four genes into a somatic cell, (b) culturing the somatic cell.

A. Claim 1 is obvious under 35 U.S.C. § 103 by the Whitehead Patent in view of the Benvenisty Article and further in view of the Li Article

Claim 1 of the Yamanaka patent is renderd obvious under 35 U.S.C. § 103 by the Whitehead patent in view of the Benvenisty article and further in view of the Li article.

The claim chart below sets forth the correspondence between the combined teachings of Whitehead Patent, Benvenisty article, and Li Article, and claim 1 of the Yamanaka patent. As demonstrated therein, claim 1 is rendered obvious by this combination of references.

Claim 1 of the '065 Patent	**Disclosures and Teachings of the Whitehead Patent, Benvenisty article, and the Li Article**
1. A method for preparing an induced pluripotent stem cell by nuclear reprogramming of a somatic cell from a mammalian species, comprising:	The Whitehead patent discloses a method of nuclear reprogramming of a somatic cell from mammalian species, the method disclosed are:
a) introducing into the somatic cell one or more retroviral vectors comprising	Introducing into the somatic cell one or more retroviral vectors comprising the following pluripotent genes:
a gene encoding Oct3/4, a gene encoding Klf4, a gene encoding c-Myc and a gene encoding Sox2	a gene encoding Oct4, a gene encoding Sox2, and a gene encoding Nanog.
operably linked to a promoter; and	The Whitehead patent is silent as to introducing the pluripotent genes c-Myc and Klf4. The Benvenisty article teaches c-Myc as a pluripotent gene. The Li article teaches Klf4 as a pluripotent

	gene. Therefore, it would have been obvious at the time the Yamanaka invention was made, to modify the method disclosed in the Whitehead patent, by inserting the c-Myc and Klf4 genes instead of inserting Nanog gene, because these genes were known to be pluripotent genes, and the Whitehead patent clearly disclosed that its method includes introducing any and all suitable pluripotent genes into a somatic cell.
b) culturing the transduced somatic cell on a fibroblast feeder layer or extracellular matrix in a cell media that supports growth of ES cells of the mammalian species, wherein one or more pluripotent cells are obtained.	The culturing step is commonly known and disclosed in the Whitehead Patent (EX 1002, col. 13, lines 18-22; col.13, lines 25-30; col. 14, lines 3-4)

The Whitehead patent was issued March 23, 2010, having earliest priority date of November 26, 2003 and qualifies as prior art to the challenged claim under 35 U.S.C. § 102(1). (EX1002). Whitehead describes a method of nuclear

reprogramming of a somatic cell from mammalian species, by first introducing into the somatic cell one or more retroviral vectors comprising the following pluripotent genes: a gene encoding Oct4, a gene encoding Sox2, and a gene encoding Nanog. EX1002 at 4: 50-68, 6:1-2, 6:60-67, 18:65, claim 9.

The purpose of the Whitehead method was to generate a "reprogrammed pluripotent somatic cell (RPSC)" which allows one, for the first time, to genetically engineer animals other than mouse and human. EX1002 at 17:8-11. The Whitehead patent described that these "RPSCs are embryonic stem (ES) cell-like cells, and are thus amenable to genetic manipulation. To date, no ES cells are available, for animals other than mouse and human. As a result, for these animals, it is currently practically impossible to create genetically modified animals having targeted mutations. The ES-cell like RPSCs can be manipulated to introduce desired targeted genetic modifications. The resulting engineered RPSCs can then be used to generate a cloned animal with the desired genetic modifications in its germ line, using methods described for ES cells in mouse. See Capecchi and Thomas, U.S. Pat. Nos. 5,487,992, 5,627,059, 5,631,153, and 6,204,061. Genetic engineering in animals has potentially great applications in a variety of animals, especially farm animals." (EX1002, col. 17, lines 8-23).

As presented in the above claim chart, the Whitehead Patent discloses a method of generating "reprogrammed pluripotent somatic cells" by introducing at

least two pluripotent genes (i.e., Oct-4 and Sox2, see claim 9). The Whitehead Patent further explained that "somatic cells may be reprogrammed to gain either a complete set of the pluripotency characteristics and are thus pluripotent. Alternatively, somatic cells may be reprogrammed to gain only a subset of the pluripotency characteristics. In another alternative, somatic cells may be reprogrammed to be multipotent." (EX1002, Col 9, lines 4-8). "A reprogramming agent may belong to any one of many different categories. For example, a reprogramming agent may be a chromatin remodeling agent….a pluripotency protein, including, for example, Nanog, Oct-4, and Stella. Such an agent may also be a gene essential for pluripotency, including, for example, Sox2, FoxD3, and LIF, and Stat3." (EX1002, col. 12, lines 26-39). The Whitehead patent defines its pluripotent genes as "a gene that is associated with pluripotency."

The Whitehead patent, however, does not explicitly disclose also using the Klf4 gene and the c-Myc gene to reprogram a somatic cell.

The Benvenisty Article, dated 1992, teaches c-Myc as a gene involved in a significant role in the physiology of cell division and differentiation. EX1003 at 2513, left column.

The Li Article, dated 2005, teaches Klf4 gene as a pluripotent gene associated with increased capacity in cell self-renewal. EX1004, abstract.

B. Reason to Combine

As discussed above, the Whitehead patent, Benvenisty article, and the Li article are within the same field – each describing genes with pluripotent properties and potential uses of creating ES-like cells expressing such genes. Therefore, it would have been obvious to one or ordinary skill in the art at the time the Yamanaka patent was made, to modify the Whitehead Patent by additionally introducing the c-Myc gene and the Klf4 gene, because these two genes qualifies as pluripotency genes as required and defined by the Whitehead patent, in order to reprogram a somatic cell to achieve either a complete set or a subset of pluripotent characteristics.

Although the Benvenisty article and the Li article do not specifically call the c-Myc gene and the Klf4 gene pluripotency genes,

XI. CONCLUSION

Substantial, new and noncumulative technical teachings have been presented for claim 1 of the Yamanaka patent, which is rendered obvious for the reasons set forth above. There is a reasonable likelihood that Petitioner will prevail as to claim 1. *Inter Partes* Review of claim 1 is accordingly requested.

Respectfully submitted,

ARDENT LAW GROUP, PC

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CERTIFICATE OF SERVICE

The undersigned certifies, in accordance with 37 C.F.R. § 42.205, that service was made on official correspondence address and patent counsel of the Patent Owner as detailed below.

Date of service	August 12, 2014
Manner of service	By Carrier
Documents served	Petition for *Inter Partes* Review; Power of Attorney Petitioner's Exhibit List; Exhibits EX1001 through EX1004
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