

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte
WILLIAM C. RADER and ALBERT SCHELLER

Appeal 2007-3218
Application 10/282,766
Technology Center 1600

Decided: December 6, 2007

Before ERIC GRIMES, LORA M. GREEN, and NANCY J. LINCK,
Administrative Patent Judges.

GREEN, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a decision on appeal¹ under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1 and 4-13. We have jurisdiction under 35 U.S.C. § 6(b). Claims 1, 4, and 9 are representative of the claims on appeal, and read as follows:

¹ This Appeal was heard on November 12, 2007.

1. A method for aiding in the diagnosis of a human patient comprising the steps of:
labeling stem cells isolated from a human fetus with a biocompatible label;
administering the labeled stem cells to the patient via injection; and
determining whether there are any regions within the patient where the labeled stem cells have accumulated.
4. The method of claim 1 wherein the stem cells isolated from a human fetus comprise hematopoietic stem cells.
9. The method of claim 1 wherein the stem cells isolated from a human fetus comprise neuronal stem cells.

We affirm.

ISSUE

The Examiner rejects claims 1 and 4-13 under 35 U.S.C. § 112, first paragraph, on the grounds that they contain subject matter that was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, contending that the Specification fails to enable the claimed subject matter (Answer 4).

The Examiner also rejects claims 1 and 4-13 under 35 U.S.C. § 112, as containing subject matter that was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, contending that the claims contain new matter, and thus fail to comply with the written description requirement (Answer 12).

Appellants contend that at “the root of the Examiner’s rejections is the Examiner’s insistence on using a different meaning of ‘embryonic stem cell’ than that used by applicant in the specification.” (Br.² 11.)

The issue is thus how should the term “embryonic stem cell” be interpreted when read in light of the Specification as would be interpreted by the ordinary artisan?

FACTS

The Examiner rejects claims 1 and 4-13 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement (Answer 4).

In setting forth the enablement rejection, the Examiner goes through the factors set forth by the Federal Circuit, our reviewing court, in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (Answer 4-12). The factors that should be considered in determining whether a specification would have been enabling, or if it would have required an undue amount of experimentation to practice the invention include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Wands*, 858 F.2d at 737.

In particular, as to the breadth of the claims, the Examiner notes that the claims “broadly encompass using any stem cells (encompassing

² All references to the Brief (Br.) are to the Amended Appeal Brief date stamped November 28, 2006.

embryonic, fetal, and adult) . . . to practice the claimed methods.” (Answer 5.) As to the guidance and the existence of working examples, the Examiner asserts that the Specification teaches that embryonic stem cells, “when placed in [an] environment where they can migrate among other cells, preferentially accumulate near stressed cells, such as cells with damaged membranes, or cancer cells,” with the working example demonstrating *in vitro* migration of embryonic stem cells to stressed or cancer cells (*id.* at 5-6). Thus, according to the Examiner, the Specification “provides no teaching with regard to utilizing stem cells—for the breadth claimed—in aiding the diagnosis of a human patient. The specification provides only guidance with regard to [embryonic stem] cells, and no guidance with regard to utilizing [hematopoietic stem cells] and [neuronal stem cells] in the claimed method.” (*Id.* at 6.)

As to the interpretation of “embryonic stem cells,” the Examiner argues that embryonic stem cells “are art recognized as non-lineage specific cells that can differentiate into cells of all three embryonic germ layers.” (*Id.* at 8.) According the Examiner, the Thomson³ and Shamblo⁴ references, cited by the Specification (Specification 2, ll. 16-26) “teach the common characteristics of an embryonic stem cell, as recognized by the art.” (Answer 8.) The Examiner quotes Thomson as teaching that “[e]mbryonic stem (ES) cells are derived from totipotent cells of the early mammalian

³ Thomson et al., “Embryonic Stem Cell Lines Derived from Human Blastocytes,” *Science*, Vol. 282, pp. 1145-1147 (1998).

⁴ Shamblo⁴ et al., “Derivation of pluripotent stem cells from cultured human primordial germ cells,” *Proc. Nat’l Acad. Sci. USA*, Vol. 95, pp. 13726-13731 (1998).

embryo and are capable of unlimited, undifferentiated proliferation *in vitro.*” (Answer 8.)

The Examiner rejects claims 1 and 4-13 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (Answer 12).

According to the Examiner,

the claims are now directed to methods for aiding in the diagnosis of a human patient, using stem cells isolated from a human fetus, and then determining whether there are any regions within the patient where the labeled stem cells have accumulated. The specification fails to provide literal support for the amended claims. The specification does not provide support for the claimed methods as a whole. The specification contemplates distinguishing between stressed and unstressed cells or cancer and non-cancer cells, using *embryonic* stem cells (p. 14, lines 30-35). The specification teaches using *embryonic* stem cells as a diagnostic reagent, to determine sites of accumulated labeled cells (page 15, lines 8-19). However, the specification does not provide support for the instantly claimed embodiments of utilizing any type stem cells isolated from a human fetus in the claimed methods.

(Answer 13.)

Appellants argue that the Specification uses the term embryonic stem cells to include stem cells isolated from a human fetus, including hematopoietic stem cells and neuronal stem cells (Br. 8-9 (citing the Specification 2, ll. 4-5, 8-11; 4, ll. 6-9, 17-26; 9, ll. 21-34; 10, ll. 9-12; 20; ll. 33-35; 23, ll. 12-13; and 24, ll. 33-35)).

According to Appellants:

The basis for virtually all of the Examiner's rejections is the Examiner's express refusal to accept applicant's use of the term "embryonic stem cells." Even though the specification makes

clear that “embryonic stem cells” used in the specification and claims includes hematopoietic and neuronal stem cells isolated from a human fetus . . . , the Examiner insists on using a different, narrower meaning that is not consistent with the specification. Specifically, the Examiner insists on using the . . . dictionary definition of embryo (limited to up to eight weeks of development), which excludes human fetuses (generally referring to the stages of development from eight weeks to birth). The Examiner does so even though the specification expressly states that the embryonic stem cells used in the disclosed methods are obtained from human fetuses. . . . [T]he Examiner’s insistence on using a different definition of “embryonic stem cells” than that used by applicant is the basis for virtually all of the Examiner’s rejections. If the proper definition is used, the Examiner’s rejections can no longer be maintained.

(Br. 11.)

As to the Thompson and Shablott references, Appellants assert that that the narrow definition of embryonic stem cells used in the background section should not be imported into the application and “override the express language to the contrary in the Specification.” (Br. 12.)

The Specification contains language that supports both the Examiner’s and Appellants’ proffered interpretation of the term “embryonic stem cell.”

The Specification teaches:

Shortly after fertilization, a mammalian egg begins to divide into identical, totipotent cells. Each of these cells, if isolated, has the potential to develop into a fetus. Within a very short period of time, however, these cells begin to form into a hollow ball of cells called a blastocyst. The outer layer of the blastocyst will ultimately give rise to the placenta and other tissue necessary to support fetal growth. Inside this outer cell layer is a cluster of cells, the inner cell mass, which will give rise to the cells of the fetus. These cells are pluripotent stem cells, which, although having the potential to develop into many

types of cells, no longer have the potential to develop into a fetus if isolated.

The pluripotent stem cells can further specialize into stem cells committed to develop into particular cell types. For example, hematopoietic stem cells will give rise to red blood cells, white blood cells, and platelets, while neuronal stem cells will give rise to the various types of nerve cells.

(Specification 1.)

Consistent with the Examiner's position, the Specification specifically defines embryonic stem cells as having "the developmental potential to give rise to *any* differentiated cell type." (*Id.* at 9 (emphasis added).)

Further supporting the Examiner's position, according to the Specification:

Although human embryonic stem cells can be isolated from aborted fetuses and/or embryos produced by in vitro fertilization techniques on an as-needed basis, alternate sources, such as cultured embryonic stem cell lines, are preferred both for ethical and economic reasons. For example, the number of embryonic stem cells used for treating patients according to the practice of the instant invention requires the use of a single fetus per patient as a source of the cells. By contrast, *expanding a population of embryonic stem cells while maintaining the cells in an undifferentiated and pluripotent state would allow several thousand patients to be treated with cells isolated from a single fetus.*

Recently, methods for culturing pluripotent human stem cells in vitro have been developed by James Thomson and Michael Shambloott. James Thomson, et al. (1998) Embryonic stem cell lines derived from human blastocysts, *Science* 282 : 1145-1147; Michael J. Shambloott, et al. (1998) Derivation of pluripotent stem cells from cultured human primordial germ cells, *Proceedings of the National Academy of Sciences* 95: 13726-13731. Thomson isolated pluripotent cells from the inner cell mass of blastocysts, while Shambloott isolated the pluripotent stem cells from fetal tissue obtained from

terminated pregnancies. In both cases, the cells must be grown on a layer of cultured mouse fibroblast feeder cells, a potential source of contamination should these cells be used to treat human (or veterinary) patients.

What is needed, therefore, is *a method for expanding embryonic stem cells in vitro that does not require such feeder cells and which maintains the stem cells in their undifferentiated and pluripotent state*, thereby reducing the number of embryos or fetuses required for stem cell therapy.

(*Id.* at 2 (emphasis added).) Thus, one aspect of the invention disclosed by the instant Specification is an in vitro cell culture system “for expanding *undifferentiated and pluripotent embryonic stem cells* in culture, while maintaining the pluripotent and undifferentiated state of the cells.” (*Id.* at 3 (emphasis added).)

The Specification does, however, blur the distinction between the terms embryonic stem cells, hematopoietic, and neuronal stem cells. For example, the Specification teaches that:

Embryonic stem cells may be isolated from a number of sources. One source of stem cells is an aborted fetus that has been pre-screened for a variety of biological agents and/or genetic conditions. . . .

Once an aborted fetus (or “abortus”) is found to be free from undesirable biological agents, the embryonic stem cells are extracted by standard protocols. In one embodiment, the embryonic stem cells are extracted from the abortus and processed through a series of filtration steps. Typically, between 10^5 and 10^8 human stem cells are isolated from a single abortus. Hematopoietic and neuronal stem cell are isolated separately by manual separation and collection under the microscope. Both cell types are collected at the same time.

An *alternative source of embryonic stem cells* are fresh or frozen cleavage stage embryos, produced by in vitro fertilization for clinical purposes and donated by informed consent. Such embryos are cultured to the *blastocyst stage*,

wherein the inner cell masses (containing the stem cells) are isolated as described in Thomson et al. (1998) Science 282: 1145-1147, and U.S. Patent No. 5,843,780, both hereby incorporated by reference in their entirety.

(*Id.* at 4 (emphasis added).) The reference to harvesting the cells from embryos cultured to the blastocyte stage, however, supports the Examiner's interpretation of "embryonic stem cells."

Examples of language that support Appellants' position may also be found in the Specification. For example, the Specification teaches that:

In the practice of the present invention, both hematopoietic stem cells and neuronal stem cells are administered to a patient in need thereof to treat a wide variety of disorders or diseases. . . . Typically, a patient only requires one dose of each type of stem cell. Alternatively, the embryonic stem cells may be administered intrathecally, by direct injection, as into bone marrow or to the retro bulbar portion of the eye, or intralesionally, as in a cell paste or gel.

(*Id.* at 9 (emphasis added).)

Moreover, the Specification discloses:

In the case of patients suffering from a genetic disorder, embryonic stem cells are administered to the patient by both intravenous injection (hematopoietic cells) and subcutaneous injection (neuronal cells). These embryonic stem cells carry the desired genetic trait and, once administered, differentiate to provide the patient with a population of cells expressing the heretofore lacking gene product.

(*Id.* at 10 (emphasis added).)

In addition, the Specification notes:

Alternatively, embryonic stem cells may be injected directly into sites of tissue or organ damage, where the microenvironment of the surrounding tissue will induce

differentiation of the injected cells. For example, mesenchymal stem cells injected into cardiac muscle will differentiate into cardiac muscle cells. Thus, these cells can be used to treat heart damage following, for example, a myocardial infarction.

(*Id.* at 14 (emphasis added).)

In an example of treatment of a patient with AIDS, the Specification states that “[e]mbryonic stem cells (hematopoietic and neuronal) were isolated from an aborted fetus,” wherein “[a]pproximately 40 million hematopoietic stem cells . . . were given to [the] Patient.” (*Id.* at 20-21 (emphasis added).)

As to the method of claim 1, the Specification teaches:

It has been found that embryonic stem cells, when placed in an environment where they can migrate among other cells, preferentially accumulate near stressed cells, such as cells with damaged membranes, or cancer cells. This characteristic suggests that embryonic stem cells, injected intravenously or subcutaneously, may target sites of cell damage, allowing the injected embryonic stem cells to accumulate at and repair damaged tissue.

It is not completely clear how embryonic stem cells detect and distinguish between stressed and unstressed cells, or between cancer and noncancer cells, but the reduced membrane potential of the cancer cells and cells with damaged membranes from other traumatic, hypoxic or diseased states may play a role. It is known, for example, that cancer cells have a lower membrane potential, typically from about -40 mV to about 0 mV, than noncancer cells. Embryonic stem cells, administered to a patient having a tumor or other site of cell damage, detect the lower membrane potential of the cancer and/or damaged cells, preferentially migrating and accumulating at the site of the tumor or other cell damage.

Whatever the exact mechanism, this characteristic of embryonic stem cells also makes them useful as a diagnostic reagent. For example, embryonic stem cells may be labeled

with a biocompatible agent such as technetium, indium, iodine and the like, then administered to a patient displaying symptoms of an unknown etiology or to detect an asymptomatic underlying or latent disease process. After allowing sufficient time for the administered cells to circulate through the body, the patient may be examined to detect the specific label used on the cells and to thereby determine sites of accumulated labeled cells. Such sites should be considered potential areas of tissue damage, tumor growth, or undiscovered potential disease processes.

(*Id.* at 14-15.)

The Specification then describes an *in vitro* experiment conducted in a Petri dish, wherein “[e]mbryonic stem cells labeled with ethidium bromide were found to migrate preferentially to human cells that had been stressed, causing damage to the cell membrane, or to human cancer cells, or, most preferentially, to stressed human cancer cells.” (*Id.* at 18-19, Example 2.)

As noted by the Examiner in the rejection, the Specification cites both Thomson and Shambloot as disclosing methods for culturing pluripotent stem cells (Specification 2, quoted above). Thomson is also cited for teaching a method of collecting cells from embryos cultured to the blastocyte stage (Specification 4, also quoted above). Thus, Thomson and Shambloot provide evidence of the understanding of the ordinary artisan at the time of filing of the instant application.

Thomson teaches that “[e]mbryonic stem (ES) cells are derived from totipotent cells of the early mammalian embryo and are capable of unlimited, undifferentiated proliferation *in vitro*.” (Thomson, p. 1145, first column.) Thomson specifically refers to embryonic stem cells as being pluripotent (*id.* (“The term ‘ES cell’ was introduced to distinguish these

embryo-derived pluripotent cells from teratocarcinoma-derived pluripotent embryonal carcinoma (EC) cells.”).

Consistent with Thomson’s definition of embryonic stem cells as being pluripotent, Shablott also teaches that embryonic stem cells are pluripotent (Shablott, p. 13726, first column) (“Embryonic stem (ES) cells are derived from the inner cell mass of preimplantation embryos, and embryonic germ (EG) cells are derived from primordial germ cells (PGCs). Both ES and EG cells are pluripotent and demonstrate germ-line transmission in experimentally produced chimeras.”).

PRINCIPLES OF LAW

During prosecution before the Office, claims are to be given their broadest reasonable interpretation consistent with the Specification as it would be interpreted by one of ordinary skill in the art. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1364 (Fed. Cir. 2004). It is “the general rule that words in patent claims are given their ordinary meaning in the usage of the field of the invention, unless the text of the patent makes clear that a word was used with a special meaning.” *Toro Co. v. White Consol. Indus.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999). “An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.” *In re Zletz*, 893 F.2d 319, 322 (Fed. Cir. 1989). Moreover, it is during prosecution that applicants have “the opportunity to amend the claims to obtain more precise claim coverage.” *American Academy*, 367 F.3d at 1364.

ANALYSIS

The issues in this Appeal stand or fall with the interpretation of the term “embryonic stem cell.” If the term is interpreted as by the Examiner, wherein “embryonic stem cell” is a pluripotent cell that has the developmental potential to give rise to any differentiated cell type, then the rejections under 35 U.S.C. § 112, first paragraph, are both affirmed. If the term is interpreted as urged by Appellants, such that the term embryonic stem cell includes stem cells isolated from a human fetus, including hematopoietic stem cells and neuronal stem cells, then the rejections under 35 U.S.C. § 112, first paragraph, are both reversed.

We admit that the Specification is not always precise in its use of the term “embryonic stem cells,” and at times appears to use it almost interchangeably with “hematopoietic” and “neuronal” stem cells. But as noted above, prosecution before the Office is the time when such ambiguities should be resolved.

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); *In re Kollar*, 286 F.3d 1326, 1329 (Fed. Cir. 2002) (“The PTO bears the initial burden of demonstrating that the preponderance of the evidence establishes *prima facie*, facts supporting the conclusion that the claimed invention was on sale within the meaning of § 102(b).”). We conclude that the preponderance of the evidence supports the Examiner’s interpretation of “embryonic stem cells,” that is, stem cells that are pluripotent, having the developmental potential to give rise to any differentiated cell type. That interpretation is consistent with the majority of

the teachings in the Specification, and also consistent with the only clear and unambiguous definition of the term provided by the Specification (p. 9), that is embryonic stem cells have “the developmental potential to give rise to any differentiated cell type.”

We have also considered the portions of the Specification relied upon by Appellants, such as “[e]mbryonic stem cells (hematopoietic and neuronal) were isolated from an aborted fetus.” (Specification 20.) Those passages, however, at best appear to use the terms almost interchangeably. But none of the passages cited by Appellants unambiguously state that the term embryonic stem cell includes the terms hematopoietic stem cells and neuronal stem cells.

Our conclusion that the term “embryonic stem cell” should be interpreted as stem cells that are pluripotent, having the developmental potential to give rise to any differentiated cell type, is also consistent with the understanding of that term as used by the ordinary artisan at the time of filing of the instant application. As noted above, both Thompson and Shablott teach that embryonic stem cells are pluripotent.

Using the interpretation of “embryonic stem cell” as being stem cells that are pluripotent, having the developmental potential to give rise to any differentiated cell type, the term “embryonic stem cell” does not include hematopoietic stem cells and neuronal stem cells, as those stem cell types are not pluripotent. As taught by the Specification, “[t]he pluripotent stem cells [*i.e.*, the embryonic stem cells] can further specialize into stem cells committed to develop into particular cell types. For example, hematopoietic stem cells will give rise to red blood cells, white blood cells, and platelets,

while neuronal stem cells will give rise to the various types of nerve cells.”
(Specification 1.)

CONCLUSIONS OF LAW

Thus, we conclude that the preponderance of the evidence supports the interpretation of “embryonic stem cell” as used by the Examiner, that is, an “embryonic stem cell” is pluripotent, having the developmental potential to give rise to any differentiated cell type. Using that interpretation, the term “embryonic stem cell” does not include hematopoietic stem cells and neuronal stem cells, as those stem cells are not pluripotent.

As Appellants’ only response to the rejection of claims 1 and 4-13 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, and under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement was to argue that the Examiner failed to use the correct interpretation for the term “embryonic stem cell,” in view of our conclusion that the term should be interpreted as used by the Examiner, both rejections of record are affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc:

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