

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 31

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JOSEPH P. HAMMANG and ALBEE MESSING

Appeal No. 1999-1510
Application. 08/447,997

HEARD: October 11, 2001

Before SCHEINER, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 32-43. Claims 32 and 43 are representative and read as follows:

32. An isolated cell transformed with a recombinant DNA molecule comprising:
 - a) a proliferation-promoting gene for inducing cell division when expressed,
 - b) an Mx-1 promoter operably linked to the proliferation-promoting gene,

wherein said isolated cell is induced to proliferate by exposure to an amount of interferon sufficient to result in expression of the proliferation-promoting gene.

43. A method of generating a conditionally immortalized cell, comprising the steps of:
 - a) transforming an isolated cell with a recombinant DNA molecule comprising a proliferation-promoting gene for inducing cell division when expressed and an Mx-1 promoter operably linked to the proliferation-promoting gene, such that said transformed cell is induced to proliferate by exposure to an amount of interferon sufficient to result in expression of the proliferation-promoting gene;
 - b) and culturing said transformed isolated cell.

The examiner relies on the following references:

Robinson et al. (Robinson)	5,489,743	Feb. 06, 1996
McKay et al. (McKay)	5,270,191	Dec. 14, 1993

Mitchell et al. (Mitchell), "Herpes Simplex Virus Pathogenesis in Transgenic Mice is Altered by the Homeodomain Protein Hox 1.3," Journal of Virology, Vol. 67, No. 8, pp. 4484-4491 (1993)

Hug et al. (Hug), "Organization of the Murine Mx Gene and Characterization of Its Interferon- and Virus-Inducible Promoter," Molecular and Cellular Biology, Vol. 8, No. 8, pp. 3065-3079 (1988)

Claims 32-43 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Claims 32-43 also stand rejected under 35 U.S.C. § 103 as obvious over Robinson, either of Hug or Mitchell, and McKay.¹

We reverse both rejections.

¹ In addition to the rejections under 35 U.S.C. §§ 103 and 112, second paragraph, the examiner's Final Rejection (Paper No. 15, mailed February 12, 1997) also contained rejections under 35 U.S.C. §§ 101 and 112, first paragraph. The Examiner's Answer expressly stated that the § 101 rejection was withdrawn. The § 112, first paragraph, rejection was not expressly withdrawn, although the examiner stated that it was no longer an issue on appeal. See id., page 3. Since the rejection under § 112, first paragraph, was not set out in the Examiner's Answer, we will treat

Background

The claims relate to the formation of “bioartificial organs,” or BAOs: “devices which contain living cells and are designed to provide a needed metabolic function to a host.” Specification, page 1. “For example, BAOs containing insulin secreting cells may be used to treat diabetes.” Id.

The specification discloses that BAOs can be made using either differentiated (non-dividing) cells or dividing cells. Use of non-dividing cells in BAOs is preferred, because the number of cells in the BAO does not change over time. Thus, for example, non-dividing cells would provide more predictable results and a more stable dosage of the pharmaceutically active compound secreted by the cells. Specification, page 3. However, the use of non-dividing cells presents several problems: differentiated cells isolated from a donor must be tested to ensure that they are free of pathogens, the cells can be damaged during isolation, the amount of potential source material is limited, and non-dividing tissue is difficult to modify genetically. Id., pages 3-4.

The specification discloses a method that provides the benefits of both dividing and non-dividing cells in BAOs.

According to this method, cell proliferation (i.e., mitosis) can be inhibited or arrested by decreased expression of a proliferation-promoting gene, such as an oncogene (e.g., c-myc, v-mos, v-Ha-ras, SV40 T-antigen, E1-A from adenoviruses). Reduced expression of the oncogene is achieved by downregulation, repression or inactivation of the promoter driving oncogene expression when the BAO is implanted in vivo in a host. Upregulation, activation or derepression of the regulatable promoter

it as having been withdrawn. See MPEP § 1208 (“Grounds of rejection not argued in the examiner’s answer are usually treated as having been dropped.”).

in vitro results in expression of the proliferation-promoting gene, thereby permitting cell proliferation in vitro.

Pages 15-16. Thus, the in vitro culture conditions can be manipulated to “turn on” the regulatable promoter controlling the proliferation-promoting gene, thereby expanding the cell population. When the cells are implanted in vivo, the signal that activates transcription from the regulatable promoter is removed, the proliferation-promoting gene is no longer expressed, and the cells stop dividing.

The claims are directed to compositions and methods representing a specific embodiment of this general approach. In all of the claims on appeal, the proliferation-promoting gene is under the control of the Mx-1 interferon-inducible promoter.

Discussion

1. The indefiniteness rejection

The examiner rejected all of the claims under 35 U.S.C. § 112, second paragraph, as indefinite. The examiner stated that

[n]one of claims 32-43 indicate any characteristic phenotype for the cells nor the transgenic non-human animals. Induction to proliferate is not a phenotype nor is it apparent that induction to proliferate is a genotype nor does the application as filed define induction to proliferate as a phenotype or genotype. . . . None of claims 32-43 indicate any characteristic phenotype and therefore of the genotype for the cells nor the transgenic nonhuman mammals.

Examiner’s Answer, page 4.

Appellants argue that

it is not necessary for patentability that the cells or transgenic mammals differ in phenotype – it is sufficient that they differ in genotype from the cells or mammals found in nature. . . . Here, the claimed cells or transgenics clearly require a genotypic change –

the genome of the claimed cells or transgenics must contain a recombinant DNA molecule having an Mx-1 promoter operably linked to a proliferation promoting gene. Such a recombinant DNA molecule . . . simply does not naturally exist in wild type cells or mammals.

Appeal Brief, page 14.

“The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification.” Miles Laboratories Inc. v. Shandon Inc., 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993). Claims are in compliance with 35 U.S.C. § 112, second paragraph, if “the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits.” Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1987).

We agree with Appellants that a person of ordinary skill in the art would understand the meaning and scope of the claims. The claims are directed to isolated cells and transgenic animals having a proliferation-promoting gene under the control of an Mx-1 promoter. The examiner has not alleged that those skilled in the art would be unable to recognize a particular gene as a proliferation-promoting gene or a particular promoter as an Mx-1 promoter. Thus, we cannot agree that the claims are indefinite.

Whether the claimed cells and transgenic animals display a “characteristic phenotype” is simply not germane. “The purpose of claims is . . . to state the legal boundaries of the patent grant.” S3 Incorporated v. NVidia Corp., 259 F.3d 1364, 1369, 59 USPQ2d 1745, 1748 (Fed. Cir. 2001). The claims on appeal do

so in a manner that can be understood by those skilled in the art. No more is required.

The examiner's concern may be that those skilled in the art would not be able to determine easily (i.e., based on phenotype) whether a given cell or transgenic mammal was within the scope of the instant claims. However, "the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite." Exxon Research & Eng'g Co. v. United States, No. 00-5077, 2001 U.S. App. LEXIS 20590, at *20 (Fed. Cir. Sept. 19, 2001).

2. The obviousness rejections

The examiner rejected all of the claims as obvious over the disclosures of Robinson and McKay, combined with either of Hug or Mitchell. The examiner characterizes Robinson as disclosing DNA encoding SV40 large T antigen "under control of a promoter that is highly regulated with respect to activity, both temporally and spatially," and characterizes McKay as "one of many references that disclosed expression of DNA encoding SV40 large T antigen and that T-antigen has the function of growth or cell proliferation." Examiner's Answer, page 5. The examiner cites Hug and Mitchell, alternatively, as disclosing the Mx-1 promoter. See id., page 5 (Hug "disclosed that expression of DNA under the control of the Mx promoter is regulated by the presence/absence of interferon.") and page 6 (Mitchell disclosed that "the Mx gene promoter had been used to express heterologous DNA in transgenic mice.").

The examiner also pointed out Robinson's disclosure that "DNA encoding SV40 large T antigen had previously been expressed under control of a promoter that was responsive to interferon." Id., page 5. This, he argues, "would have motivated one of ordinary skill in the art to have considered and put the DNA encoding SV40 large T antigen disclosed in the Robinson et al. reference under the control of the mouse Mx promoter," which was known to be induced by interferon. Id. The examiner concluded that "[i]t would have been obvious to one of ordinary skill in the art to have used the DNA disclosed in the combined cited references to effect cellular immortalization that was highly regulated such as by a promoter subject to induction control such as by interferon in the case of the Mx promoter." Id.

Appellants argue that the cited reference would not have led those skilled in the art to combine the Mx-1 promoter with a proliferation-promoting gene such as the SV40 large T antigen gene. Appeal Brief, pages 17-22. Appellants also argue that they have presented evidence demonstrating the "unexpected advantages" of the claimed combination, if any was needed to overcome a prima facie case of obviousness. Appeal Brief, pages 22-24.

"In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. [The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant

teachings of the references.” In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citations omitted).

An adequate showing of motivation to combine requires “evidence that ‘a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.’” Ecolchem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000) (quoting In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998)). See also In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000):

[I]dentification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

Thus, in this case, the references will support a prima facie case of obviousness only if their disclosures would have led a person of ordinary skill in the art to combine the Mx-1 promoter with a proliferation-promoting gene. After reviewing cited references and the arguments of the examiner and Appellants, we agree with Appellants that the examiner has not made out a prima facie case.

The examiner argues that those skilled in the art would have been led to combine the Mx-1 promoter with the SV40 large T antigen gene by Robinson’s disclosure that the same gene had previously been cloned under the control of a different promoter that was regulated by interferon. Examiner’s Answer, page 5.

We disagree. The relevant passage is found in the “Background of the Invention” section of the Robinson patent, and reads as follows:

Jar et al. . . . teach production of mice with a DNA construct that contains a mutant SV40 large T antigen gene (the SV40 tsA58 mutant) linked to a major histocompatibility complex I promoter (H-2Kb). The specific promoter is used to facilitate expression of the transgene in a wide variety of tissues, and is induced by certain interferons. These mice are used as a source for generating transformed cell lines.

Robinson, column 1, lines 50-58.

However, the mere fact that the SV40 large T antigen gene had been expressed under the control of an interferon-regulated promoter would not necessarily have led those skilled in the art to combine it with another interferon-inducible promoter, unless the prior art provided some reason to do so. As Appellants point out (Appeal Brief, pages 17-18), Robinson does not suggest combining the SV40 large T antigen gene with an interferon-inducible promoter. Rather, Robinson suggests use of “promoters primarily active in platelet precursor cells, megakaryocytes, and/or megakaryocyte precursor cells such as, for example, the PF4 promoter.” Column 4, lines 10-15.

The examiner has pointed to nothing in the remaining references that would have led those skilled in the art to make the required combination. We have reviewed the cited references but we find nothing in them that would have suggested the claimed invention to those of ordinary skill in the art. McKay discloses conditionally immortalized cells that express the SV40 large T antigen but does not suggest expressing the T antigen gene under the control of an inducible promoter, much less an interferon-inducible promoter such as the Mx-1

promoter. Hug discloses the cloning of the mouse Mx gene,² including its promoter, but does not suggest expressing a heterologous gene, much less the SV40 large T antigen gene, under the control of the promoter. Mitchell discloses cells and transgenic mice comprising the mouse Hox 1.3 protein under the control of the Mx-1 promoter. The construct's purpose was to test whether the Hox 1.3 protein (which binds the regulatory region of some herpes simplex virus genes) would affect HSV pathogenesis when "the Hox 1.3 protein is expressed under the control of a virus-inducible regulatory element," i.e., the Mx-1 promoter. Page 4484, right-hand column. Mitchell does not suggest combining the Mx-1 promoter with a gene that promotes cell growth or proliferation.

Thus, we conclude that the cited references, although they disclose the SV40 large T antigen gene and the Mx-1 promoter, do not provide the requisite motivation to combine those elements. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (citations omitted).

Since we conclude that the references do not support a prima facie case under 35 U.S.C. § 103, we need not address Appellants' evidence of unexpected results.

² Appellants do not dispute that Hug's Mx gene is the same as the Mx-1 gene referred to in the instant specification.

Summary

We reverse the rejection under 35 U.S.C. § 112, second paragraph, because the claims are not indefinite. We reverse the rejections under 35 U.S.C. § 103 because the references cited by the examiner provide no motivation to combine the elements of the claimed invention.

REVERSED

Toni R. Scheiner)	
Administrative Patent Judge)	
)	
)	
)	BOARD OF PATENT
Demetra J. Mills)	
Administrative Patent Judge)	APPEALS AND
)	
)	INTERFERENCES
)	
Eric Grimes)	
Administrative Patent Judge)	

EG/dym

Appeal No. 1999-1510
Application No. 08/447,997

Mintz, Levin, Cohn, Ferris,
Glovsky, and Popeo, PC
One Financial Center
Boston, MA 02111