

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 36

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DONNA BOZYCZKO-COYNE, NICOLA NEFF,
MICHAEL E. LEWIS, and MOHAMED A. IQBAL

Appeal No. 1997-3275
Application No. 07/963,329

ON BRIEF

Before ROBINSON, MILLS, and GRIMES, Administrative Patent Judges.
ROBINSON, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claim 1. Claims 7 - 12, 14 - 39, and 41 - 46, the remaining claims pending in the application, stand withdrawn from consideration by the examiner and are not before us on appeal.

Claim 1 reads as follows:

1. A method for promoting the survival of photoreceptors in a mammal, said photoreceptors being at risk of dying, said method comprising administering to said mammal an effective dose of Insulin-Like Growth Factor-I.

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The references relied upon by the examiner are:

Fryklund et al. (Fryklund)	5,068,224	Nov. 26, 1991
Lewis et al. (Lewis)	5,093,317	Mar. 03, 1992
Sara (European Patent Application)	0227619	July 01, 1987

Fellows et al. (Fellows) "IGF-1 Supports Survival and Differentiation of Fetal Rat Brain Neurons In Serum-Free Hormone-Free Defined Medium," Soc. Neurosci. Abstr., Vol 13, 1615 (1987)

Hansson et al. (Hansson) "Evidence indicating trophic importance of IGF-I in Regenerating peripheral nerves," Acta Physiol. Scand., Vol. 126, pp. 609-614 (1986)

Ocrant et al. (Ocrant) "Localization and Structural Characterization of Insulin-Like Growth Factor Receptors in Mammalian Retina," Endocrinology, Vol. 125, No.5, pp. 2407-2413 (1989)

Leeson "Histology" W.B. Saunders Company Third Edition, Philadelphia, Pa., pp. 554-565 (1976)

Fingl et al. (Fingl) "The Pharmacological Basis of Therapeutics," (L.S. Goodman et al., eds.) Macmillan Publishing Company, pp. 1-46 (1975)

Leschey et al. (Leschey) "Growth Factor Responsiveness of Human Retinal Pigment Epithelial Cells," Investigative Ophthalmology & Visual Science, Vol. 31, No. 5, pp. 839-846 (1988)

Yorek et al. (Yorek) "Amino Acid and Putative Neurotransmitter Transport in Human Y79 Retinoblastoma Cells," The Journal of Biological Chemistry, Vol. 262, No. 23, pp. 10986-10993 (1987)

Grounds of Rejection

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, as being based on a non-enabling disclosure.

Claim 1 stands rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Fryklund, Sara, Fellows, Hansson, Ocrant, Leeson, and Fingl.

Claim 1 stands rejected under the judicially created doctrine of obviousness-type double patenting. As evidence of obviousness, the examiner relies on Lewis, Ocrant, Leschey, Yorek, and Fingl.

Claim 1 stands rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Lewis, Ocrant, Leschey, Yorek, and Fingl.

We reverse these rejections for the reasons set forth herein.

Discussion

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the appellants and the examiner. We make reference to the Examiner's Answer of December 12, 1995 (Paper No. 30) and the Supplemental Examiner's Answer of May 14, 1996 (Paper No. 33) for the examiner's reasoning in support of the rejections and to the appellants' Appeal Brief, filed August 22, 1995 (Paper No. 29), and Reply Brief, filed January 2, 1996 (Paper No. 31) for the appellants' arguments thereagainst.

Background

Applicants describe the claimed invention at page 5 of the Specification as being directed to a method of enhancing the survival of mammalian retinal neuronal cells at risk of dying, by administering to the mammal an effective dose of at least one insulin-like growth factor (IGF) and particularly type 1 insulin-like growth factor (IGF-1)¹. Claim 1, on appeal, is directed to enhancing the survival of photoreceptors in danger of dying.

The rejection under 35 U.S.C. § 112, first paragraph

The examiner has rejected claim 1 under 35 U.S.C. § 112, first paragraph as being based on a disclosure which is not enabling in that it fails to teach how to use the claimed invention. In so doing, the examiner has withdrawn that portion of her arguments in support of this rejection to the extent that they rely on the lack of predictability of IGF-I being able to cross the Brain Blood Barrier (BBB). (Supp. Examiner's Answer, page 1).

The examiner, initially, argues that the specification lacks adequate guidance for the dose of IGF-1 to be used in the claimed method because a dose appropriate for intraorbital administration might not be effective for subcutaneous administration. (Answer, page 5). The examiner, further, urges that the specification lacks adequate guidance for the use of IGF-1 in promoting survival of mammalian photoreceptor cells. The examiner appears to take the position that since the examples of the specification are in

¹ The type 1 insulin-like growth factor is referenced in this record and the references relied on by the examiner as alternatively IGF-1 and IGF-I. For purposes of this appeal, we note that which ever designation is used, the underlying material is the same.

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vitro, and since the cells are not purified, and the label used in the testing is not specific for identifying photoreceptor cells, the results observed relate to all viable cells and not just photoreceptor cells. (Answer, paragraph bridging pages 5-6). The examiner notes that Example 5 is the exception to this observation and acknowledges that the experiment appears to be specific for photoreceptor cells. (Answer, page 6). However, the examiner urges that (id.):

it is unclear how one would conclude that IGF-1 promoted survival of the photoreceptor cells, since an increase in cell number at the end of the experiment may be accounted for by either cell survival, cell proliferation, or both. . . . [t]hus, overall the results appear to simply demonstrate that IGF-I increases the number of retinal cells and photoreceptor cells in vitro. They do not demonstrate an increase in photoreceptor cell survival.

The examiner concludes that (Answer, page 7):

[t]he quantity of experimentation necessary needed [sic] to practice the claimed method is undue because the specification and evidence of record does not support the assertion that IGF-1 promotes survival *per se*. . . . Thus, it would require undue experimentation to determine whether IGF-1 promotes survival of photoreceptor cells in a mammal.

An examiner may reject claims in a patent application on the basis of an alleged failure of the applicants to comply with the enablement requirement of 35 U.S.C. § 112 only if the examiner can establish by a preponderance of the evidence that there is reason to doubt the objective truth of the statements contained in the specification. In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1970). Factors appropriate for

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determining whether undue experimentation is required to practice the claimed invention throughout its full scope are listed in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These factors include:

- (1) the quantity of experimentation necessary,
- (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.

On the record before us, the examiner has failed to provide the factual evidence or reasoning which would reasonably support a conclusion that the present disclosure in support of the claimed invention was not enabling through out the scope of the claimed subject matter. Even if we assume, for purposes of argument, that the area of endeavor is highly unpredictable, the examiner's speculation concerning dosages, routes of administration, and effectiveness are not supported by evidence which would reasonably establish that one skilled in this art could not practice the invention, given the disclosure provided by the specification, without undue experimentation. More is required than merely providing alternative explanations for the results described and direction provided by the specification. The examiner must establish that one skilled in this art would not accept the disclosure as enabling for the claimed invention.

Here, the examiner has not explained why one skilled in this art would not be able to determine the appropriate dose of the claim designated IGF-1 to administer to a mammal given the guidance provided at pages 29 - 30 of the specification. As the examiner has acknowledged (Answer, page 4) "[t]he relative skill of those in the art of neurological treatments is commonly recognized as being high." The examiner has offered no evidence which would reasonably establish that one of "high" skill would not have been able to select and administer the appropriate dose of IGF-1, to a patient in need thereof, without undue experimentation given the guidance provided by the specification.

As to the arguments concerning the evidence of record, including the declaration of Dr. Bozyczko-Coyne filed September 14, 1994, and the examiner's conclusion that appellants have not demonstrated that the administration of IGF-1, as claimed, will result in promoting the survival of photoreceptors in a mammal, we note simply, that the examiner has misplaced the "burden" in this aspect of the rejection. The burden is on the examiner to establish a reasonable basis for questioning whether the claimed method does not provide the benefit or usefulness disclosed by the applicants. Only when the examiner meets this burden, does the burden shift to applicants to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. In re Marzocchi, supra. That some experimentation may be necessary, does not equate to undue experimentation. In re Angstadt, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). Here, the examiner has failed to establish, by a preponderance of the evidence, that the disclosure provided in support of the claimed

invention would not have permitted one skilled in this art to practice the invention without undue experimentation. Therefore, the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, is reversed.

The Prior Art rejections

The appealed claim stands rejected under 35 U.S.C. § 103 as being obvious over the combined teachings of Fryklund, Sara, Fellows, Hansson, Ocrant, Leeson, and Fingl.

The examiner relies on Fryklund, Sara, Fellows, Hansson as teaching (Answer, page 8) "the important role of IGF-1 in stimulating various types of neurons *in vivo* and *in vitro*, to promote their regeneration, growth, differentiation, and survival." The examiner acknowledges that the teachings of these references differ from the claimed invention in that they (*id.*) "do not teach the use of IGF-1 to promote survival of photoreceptor cells in particular." However, the examiner relies on Ocrant as teaching (Answer, paragraph bridging pages 8-9):

that IGF-I and IGF-II (i.e., IGF-1 and IGF-2) are polypeptide mitogens which are structurally homologous to insulin, are produced in the central nervous systems (CNS) of both adult and fetal animals, participate in growth and differentiation of fetal CNS, participate in the regulation of growth hormone secretion and satiety, are found in the vitreous humor of the eye, and act by binding to specific receptors (e.g., abstract and p. 2407, cols. 1 and 2). Ocrant *et al.* also teach the use of radiolabeled, iodinated IGF-I (125I-IGF-I, p. 2408, col. 1) to identify the distribution of IGF-I receptors in mammalian retina (p. 2408, col. 2), in order to study the function of IGF-I in the CNS (paragraph bridging pp. 2407-2408). Using tissue sections of rat and bovine retina, the labeled IGF-I localized to

the neural retina and to the retinal pigment epithelium (e.g., Figures 1-4, pp. 2409-2410 and p. 2411). Specifically, IGF-I [is] localized to the chorioid, ganglion cell layer, inner nuclear layer, inner plexiform layer, outer nuclear layer, inner plexiform layer, outer rod segment, pigment cell epithelium, and to the sclera (e.g., Figure 1, C and F). In addition, receptors for IGF-I and IGF-II were found in membrane preparations of retina (e.g., p. 2411, Figures 5 and 6 and cols. 1 and 2).

The examiner relied on Leeson as providing (Answer, page 9):

evidence that photoreceptor cells (i.e., rods and cones) are present in the outer nuclear layer of the retina and extend to the pigment epithelium (pp. 556-564 and Figure 20-17, p. 556 in particular).

The examiner combines the teaching of Leeson with that of Ocrant and concludes that (id.)

"it logically may be inferred that the photoreceptor cells, which are present in the outer nuclear layer, express receptors for IGF-1."

The examiner relies on Fingl as teaching the general manner of using pharmacological agents in vivo and the determination of the parameters for administering such agents.

The examiner concludes that (Answer, paragraph bridging pages 9-10):

it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of treating neurons with IGF-1 in a mammal as taught by U.S. Patent No. 5,068,224 and Hansson et al. to treat photoreceptor neurons in particular to promote their survival, because: (i) U.S. Patent No. 5,068,224 [Fryklund], Hansson et al., EP 0227619 [Sara], and Fellows et al. collectively teach that IGF-1 was known to simulate and to have a beneficial effect on various types of neurons in general, and to promote their regeneration, growth, differentiation, and survival; (ii) a specific receptor that binds IGF-1 was known to be present in the region of the retina where photoreceptor cells are present, as taught by Ocrant et al. and Leeson et al.; and, (iii) photoreceptors are a type of neuron, as taught by Leeson et al.

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Since the art teaches that IGF-1 generally produces a beneficial effect and stimulates or enhances a number of positive activities (including survival) in various types of neurons, there is a reasonable expectation that IGF-1 will produce the same effect in a particular type of neuron, namely, photoreceptor cells. Fingl et al. teach that the determination of effective dosage for treatment in humans was known and routine. It is further noted that all living cells are at risk of dying. Accordingly, claim 1 is *prima facie* obvious over the prior art, absent sufficient objective factual evidence to the contrary.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicants. Id. In order to meet that burden the examiner must provide a reason, based on the prior art, or knowledge generally available in the art as to why it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297, n.24, 227 USPQ 657, 667, n.24 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). Moreover, the prior art must also establish that one would have had a reasonable expectation of achieving the present invention, i.e., a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in appellants' disclosure. In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

On the record before us, the examiner has not met the initial burden of establishing why the prior art relied on would have led one of ordinary skill in this art to arrive at the claimed method of promoting the survival of photoreceptors in a mammal by administering thereto an effective dose of Insulin-Like Growth Factor-1. Critical to the examiner's case is the consideration of Ocrant. While Ocrant may be said to establish the likelihood that there are receptors capable of binding IGF-1 in the area of the eye where the photoreceptors are located, the reference does not describe any benefit or pharmacological effect resulting from this binding. Appellants do not dispute that such receptors are present in the photoreceptors; but urge that this "does not in any way suggest that such binding will provide the claimed result." (Brief, page 16). We agree. The examiner relies on the remaining references, which are not explicitly related to photoreceptors, to demonstrate that the IGF-1 type compounds have growth and regeneration effects on neurons. The examiner, thus, urges that one would have expected to observe the same effect when IGF-1 is administered to photoreceptors which are also neurons. (Answer, page 10). However, the examiner's principal reference would suggest otherwise.

We read Ocrant to suggest a detectable or noticeable difference in the photoreceptors when compared to other neurons found elsewhere in the body. Specifically, Ocrant begins his analysis by noting that "Insulin-like growth factors (IGFs) are peptide mitogens, structurally related to insulin, whose biological actions in the CNS are

incompletely known." (page 2407, first sentence of the abstract) (Emphasis added.).

Ocrant, further, notes that "[a]ffinity labeling disclosed differences in the apparent mol. wt. of IGF-I and IGF-II receptors from bovine eye tissue and those from liver and brain."

(Abstract, col. 2). In stating his conclusion, Ocrant states "[w]e conclude that mammalian retina contains both IGF-I and -II receptors, which differ from those found in other tissues and have a characteristic spatial distribution within the retina." (Abstract, last sentence). At page 2411, column 1, first full paragraph, Ocrant observes that "the retina expresses unique forms of both type 1 and 2 receptors on the basis of apparent M_r in polyacrylamide gels. . . . The meaning of these differences, in functional terms, is not understood." This discussion, taken as a whole, would bring into question whether one of ordinary skill in this art, noting the difference in the nature of the neurons located in different tissues of the mammal, would reasonably expect the IGFs to act pharmacologically in the photoreceptors of the mammal in the same manner as they would act on other neurons found at the other sites within the mammal. This conclusion is reinforced by the concluding remarks of Ocrant which state (page 2412, col. 1, last sentence of the first paragraph):

Since our data indicate that the mammalian retina contains unique forms of both type 1 and 2 receptors, each of which

has a characteristic spatial distribution within the retina, these studies imply that the retina may be valuable in identifying potentially new and unique actions of IGFs in the CNS. (Emphasis added.)

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The examiner has provided no facts or evidence which would reasonably establish that administration of IGF-1 to a mammal would have any particular pharmacological effect on the photoreceptors. In our opinion, the references relied upon, taken in combination, would not have suggested to one of ordinary skill in this art at the time of the invention, that the administration of IGF-1 would have likely resulted in promoting the survival of photoreceptors as presently claimed. Only appellants' specification provides any suggestion that administering IGF-1 to a mammal would serve to promote the survival of photoreceptors at risk of dying. However, use of this information as a basis for establishing a prima facie case of obviousness, within the meaning of 35 U.S.C. § 103, would constitute impermissible hindsight.

Thus, in our opinion, the examiner has failed to provide those facts or evidence which would reasonably support a conclusion that the claimed subject matter would have been prima facie obvious within the meaning of 35 U.S.C. § 103. Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir.1988). Therefore, this rejection of claim 1 under 35 U.S.C. § 103 is reversed.

In rejecting the claims under the judicially created doctrine of obviousness-type double patenting, the examiner initially focuses on claim 1 of U.S. Patent 5,093,317 to Lewis and states that the patent is (Answer, page 10):

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drawn to a method of enhancing the survival of non-mitotic cholinergic neuronal cells in a mammal, using IGF-I. . . . The '317 patent does not claim the method for photoreceptor neurons in particular.

Ocrant is relied on as discussed in the previous rejection. The examiner relies on Leschey as teaching that "an understanding of the factors that control retinal pigment epithelium (RPE) cell proliferation may provide information that is relevant to normal and abnormal ocular wound [sic, wound] healing (p. 839, col. 1), and that several different growth factors, including IGF-I, increase DNA synthesis and cell proliferation of human RPE cells *in vitro*." (Answer, page 11). The examiner relies on Yorek as teaching that "IGF-I increases the uptake of the neurotransmitter glycine in human Y79 retinoblastoma cells *in vitro* (e.g., abstract, p. 10986)." (Id.)

The examiner concludes that (id.):

it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of enhancing survival of nonmitotic, cholinergic neurons with IGF-I in a mammal as taught by U.S. Patent No. 5,093,317 to treat photoreceptor neurons in particular to promote their survival, because (i) Ocrant et al., Leschey et al., and Yorek et al. collectively teach that IGF-1 was known to stimulate and bind the retina and to bind to the region of the retina where photoreceptor cells are present in particular; (ii) a specific receptor that binds IGF-1 was known to be present in the region of the retina where photoreceptor cells are present, as taught by Ocrant et al.; and, (iii) photoreceptors are a type of neuron.

The examiner, further, urges that (id.):

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[s]ince the art teaches that IGF-1 generally produces a beneficial effect and stimulates or enhances a number of positive activities retinal neurons, and binds to photoreceptor regions in particular, there is logically a reasonable expectation that IGF-1 will produce the same effect in photoreceptor neurons.

The examiner's rejection of claim 1 under 35 U.S.C. § 103 as unpatentable over Lewis Ocrant, Leschey, Yorek, and Fingl is based on the same reasoning.

We have already discussed the relevance of the teaching of Ocrant to the claimed invention. Consideration of these two rejections requires only that we determine whether the additional references, relied on by the examiner, provide that which we found missing from Ocrant. In our opinion, they do not.

We note, initially, that both the claims and disclosure of Lewis are limited to enhancing the survival of non-mitotic cholinergic neuronal cells in a mammal. However, appellants have argued that the photoreceptors are not cholinergic (Brief, page 21) and at page 18 of the response filed September 19, 1994 provided evidence in support of this proposition. We find nothing in Lewis which would reasonably suggest that photoreceptors fall within the scope of the invention claimed in that patent or described in the specification of the patent.

The Leschey reference would appear relevant to the presently claimed invention since it describes the stimulation of retinal pigment epithelium with IGF-1. However, in the Abstract, Leschey states that "insulinlike growth factor-1, and insulin were weak or modest

stimulators when used alone." To the extent the Leschey would be regarded as relevant to the presently claimed invention, this statement would appear to teach away from the use of IGF-1 in the treatment of retinal related disorders. However, more relevant is the fact that Leschey is limited to describing the effect of IGF-1 on the retinal pigment epithelium. As evidenced by Figure 20-17, page 556 of Leeson, the retinal pigment epithelium is a distinctly different layer of cells in relation to the rods and cones which make up the photoreceptors of the eye. (See the description which accompanies the figure.).

Yorek is even more remote from the claimed invention. At best it can be said to describe the effect of IGF-I in stimulating of amino acid (glycine) uptake in retinoblastoma cells. Yorek provides no information which would reasonably suggest the use of IGF-I for enhancing the survival rate of photoreceptors in danger of dying.

Thus, we conclude that the combination of Lewis, whether under the doctrine of obviousness-type double patenting or 35 U.S.C. § 103, with Ocrant, Leschey, Yorek, and Fingl, fail to provide the evidence which would reasonably have led one of ordinary skill in this art to arrive at the presently claimed invention. Therefore, we reverse both rejections.

Summary

The rejection of claim 1 under 35 U.S.C. § 112, first paragraph, is reversed. The rejections of claims 1 under 35 U.S.C. § 103 as unpatentable over the combined teachings of Fryklund, Sara, Fellows, Hansson, Ocrant, Leeson, and Fingl or, alternatively, over the combined teachings of Lewis, Ocrant, Leschey, Yorek, and Fingl are reversed. The

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rejection of claim 1 under the judicially created doctrine of obviousness-type double patenting is reversed.

REVERSED

Douglas W. Robinson)	
Administrative Patent Judge)	
)	
)	
)	BOARD OF PATENT
Demetra J. Mills)	
Administrative Patent Judge)	APPEALS AND
)	
)	INTERFERENCES
)	
Eric Grimes)	
Administrative Patent Judge)	

Paul T. Clark
Fish & Richardson
225 Franklin St.
Boston, MA 02110-2804

DR/dym