

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 50

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte MARK LEID, PHILIPPE KASTNER and PIERRE CHAMBON

Appeal No. 2001-0531
Application No. 08/216,592

HEARD May 7, 2002

Before WILLIAM F. SMITH, GRIMES, and GREEN, 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 5, 29, 31, 32, 34, 37, and 46-48. Claims 50-82 are also pending and have been allowed.

Claim 5 is representative of the claims on appeal and reads as follows:

5. A method of identifying an agent capable of transactivating a sequence operably linked to a DNA response element comprising the steps of:
 - (a) incubating with the agent, a host cell, organism, or cell-free extract thereof containing a reporter sequence operably linked to the DNA response element; and

(b) assaying for expression of the reporter sequence, wherein the host cell, organism, or cell-free extract has been altered to express one or more dimmers comprising two subunits, wherein one of the subunits is a retinoic acid receptor (RAR) or a thyroid receptor (TR) and the other subunit is a retinoid X receptor (RXR).

The examiner relies on the following references:

Hamada et al. (Hamada), "H-2RIIBP, A Member of the Nuclear Hormone Receptor Superfamily that Binds to Both the Regulatory Element of Major Histocompatibility Class I genes and the Estrogen Response Element," Proc. Natl. Acad. Sci. USA, Vol. 86, pp. 8289-8293 (1989)

Mangelsdorf et al. (Mangelsdorf), "Nuclear Receptor that Identifies a Novel Retinoic Acid Response Pathway," Nature, Vol. 345 pp. 224-229 (1990)

Glass et al. (Glass), "Positive and Negative Regulation of Gene Transcription by a Retinoic Acid-Thyroid Hormone Receptor Heterodimer," Cell, Vol. 59 pp. 697-708 (1989)

Yu et al. (Yu), "RXR β : A Coregulator that Enhances Binding of Retinoic Acid, Thyroid Hormone, and Vitamin D Receptors to Their Cognate Response Elements," Cell, Vol. 67 pp. 1251-1266 (1991)

Claims 5, 29, 32, 34, and 46-48 stand rejected under 35 U.S.C. § 103 as obvious in view of the combined disclosures of Glass and Mangelsdorf.

Claims 5, 32, 46, and 48 stand rejected under 35 U.S.C. § 102(a) as anticipated by Yu.

Claims 5, 29, 34, and 47 stand rejected under 35 U.S.C. § 103 as obvious in view of Yu.

Claims 31 and 37 stand rejected under 35 U.S.C. § 103 as obvious in view of the combined disclosures of Yu and Hamada.

We reverse all of the rejections.

Background

Retinoic acid receptors (RARs), thyroid hormone receptors (TRs), and retinoid X receptors (RXRs) are nuclear receptors. Specification, page 1. These nuclear receptors bind to specific sequences of DNA, known as DNA response elements (REs). Id., page 2. “Retinoic acid (RA) signalling involves at least two classes of proteins, the retinoic acid receptors (RAR α , RAR β , RAR γ) and retinoid X receptors (RXR α , RXR β , RXR γ). RARs and RXRs are members of the steroid/thyroid hormone receptor superfamily, and exhibit the modular protein structure typical to this group, including domains which function in DNA binding, dimerisation, ligand binding and transactivation.” Id., page 81 (citations omitted).

“Ligand binding appears to be required to induce transactivation functions (AFs) which overlap the N-terminal and ligand binding domains of these proteins. It has recently been shown that the affinities of RARs for their target sequences is strongly increased when they are complexed as heterodimers with RXRs.” Id. (citations omitted). “RXRs exhibit promiscuous heterodimerisation properties in vitro, forming complexes with other factors including the thyroid receptor (TR) . . . , which stimulates their cooperative and selective binding to cognate hormone receptor elements in vitro.” Id., page 82.

Discussion

Claim 5 is directed to a method of identifying an agent capable of inducing transactivation of a reporter gene operably linked to a DNA response element. The claimed method begins with cells that contain the reporter gene linked to the response element, and that have also been altered to express heterodimers

composed of a retinoid X receptor (RXR) in combination with either a retinoic acid receptor (RAR) or thyroid hormone receptor (TR). The heterodimer-expressing, reporter gene-containing cells are then incubated with the agent of interest, and an assay is carried out to determine expression of the reporter gene.

Claims 29, 31, 32, 34, 37, and 46-48 depend directly or indirectly on claim 5. For the reasons discussed below, we need not separately address the limitations of the dependent claims.

1. The rejection based on Glass and Mangelsdorf

The examiner rejected claim 5, together with claims 29, 32, 34, and 46-48 as obvious in view of the combined teachings of Glass and Mangelsdorf. The examiner characterized Glass as teaching an expression assay similar to that of claim 5 but involving heterodimers of RAR and TR. Examiner's Answer, pages 4-5. She cited Mangelsdorf as teaching an expression plasmid encoding RXR which, when co-transfected into host cells along with a reporter plasmid, causes transactivation of the reporter gene in the presence of retinoic acid. Id., page 5.

The examiner concluded that it would have been obvious to a person skilled in the art to modify the assay system disclosed by Glass by replacing either the RAR or TR used by Glass with the RXR taught by Mangelsdorf, "because Glass et al. suggest that other steroid hormone receptors also form dimers for more elaborate control of transcription." Id., page 6.

"[T]o 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.” In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000). That is, “the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.” Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984).

We agree with Appellants that Glass and Mangelsdorf do not support a prima facie case of obviousness. Although Glass and Mangelsdorf together disclose all the elements of the claimed assay method, the examiner has not established that those skilled in the art would have been led to combine those elements in the manner claimed.

The examiner’s position is that those skilled in the art would have been led to combine RXR with Glass’ assay system because Glass states that their “results suggest that by forming heterodimers, more elaborate [sic] control of transcription can be achieved.” Page 697 (abstract). The examiner also points to page 706 of the reference, which she characterizes as stating that dimerizations may occur between other members of the steroid hormone receptor family. The passage relied on states:

We speculate that interactions of the type described between the thyroid hormone and retinoic acid receptors may occur between other members of the ligand-dependent transcription factor gene family. Such interactions may be required to achieve the necessary complexity of transcriptional control that serves to regulate the processes of growth, development, and homeostasis.

Glass, page 706.

We do not agree that these statements would have led those skilled in the art to combine the RXR taught by Mangelsdorf with Glass' assay system. The examiner has not adequately explained why those skilled in the art would have found it desirable to achieve more elaborate control of transcription in an assay like that disclosed by Glass. Taken in context, the reference in Glass to "elaborate control of transcription" should be read to refer to "the necessary complexity of transcriptional control that serves to regulate the processes of growth, development, and homeostasis."

The examiner has not adequately explained why this "complexity of transcriptional control," while "necessary . . . to regulate the processes of growth, development, and homeostasis," would be desirable in an in vitro assay to identify agents that induce transactivation by heterodimers including RXR and either RAR or TR. Thus, the examiner has not shown that the cited references would have led those skilled in the art to combine their respective teachings.

In the absence of an adequate motivation to combine, the references do not support a prima facie case under 35 U.S.C. § 103. The rejection is reversed.

2. The rejections based on Yu

The examiner rejected all of the claims as anticipated by Yu or obvious in view of Yu, either alone or in combination with Hamada. Appellants do not appear to dispute the substance of these rejections, but argue that they have removed Yu as prior art via a declaration filed under 37 CFR § 1.131.

The examiner concedes that "the affidavits show that a manuscript describing the claimed invention was sent to the United States prior to the

publication of Yu et al.” Examiner’s Answer, page 15. She concluded, however, that the 131 declaration was insufficient to remove Yu as prior art because

the evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the Yu et al. reference . . . [because] the actual research was done in France. Therefore, the claimed invention was not reduced to practice in this country prior to the publication of Yu et al. because the manuscript is considered to be conceptual and not a reduction to practice.

Id. The examiner stated that “[i]f the recipient of the manuscript had repeated the experiments set forth in the manuscript before December 20, 1991, then the invention would be considered to be reduced to practice in this country.” Id.

Thus, the examiner’s position appears to be that Appellants’ evidence must show that the invention was reduced to practice in this country prior to the effective date of Yu, in order to antedate the reference. This position is not supported by Rule 131.

Rule 131 provides three alternative ways of showing prior invention. See 37 CFR § 1.131(b):

The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference, coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application.

(Emphasis added.) The MPEP also makes clear that

37 CFR 1.131(b) provides three ways in which an applicant can establish prior invention of the claimed subject matter. The showing of facts must be sufficient to show:

(A) reduction to practice of the invention prior to the effective date of the reference; or

(B) conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice; or

(C) conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to the filing date of the application (constructive reduction to practice).

MPEP § 715.07.

The examiner focuses entirely on the first alternative provided by the rule: reduction to practice prior to the effective filing date of the reference. Appellants' 131 declarations, however, are addressed to the third alternative provided by the rule: prior conception coupled with due diligence to a constructive reduction to practice.

Appellants' 131 declaration includes declarations showing that a manuscript was received in this country on December 19, 1991, one day before the publication date of Yu.¹ See Paper No. 22, filed November 5, 1996, pages 3-4. The examiner appears to concede that this manuscript shows conception of the method now claimed. See the Examiner's Answer, page 15 ("[T]he affidavits show that a manuscript describing the claimed invention was sent to the United States prior to the publication of Yu et al. . . . If the recipient of the manuscript

¹ We note that, as it arrived at the Board, the application file contained only the 131 declaration signed by inventor Kastner. It did not contain copies of the 131 declaration signed by inventors Leid and Chambon. The record indicates that the Leid declaration had been submitted together with the Kastner declaration. See Paper No. 22 (filed Nov. 5, 1996), transmittal page. Paper No. 22 also indicated that the "Declaration executed by Dr. Chambon will be filed in a Supplemental Response as soon as it is received by Applicants' . . . attorney." Id., page 3 of the Supplemental Response. However, the administrative record contained no evidence that the Chambon declaration had ever been submitted. At oral argument, Appellants' attorney indicated that the Leid and Chambon declarations had been submitted, and agreed to file new copies of the declarations, together with evidence that they had previously been received by the PTO. The newly submitted copies and evidence were submitted and have been entered into the file as

had repeated the experiments set forth in the manuscript before December 20, 1991, then the invention would be considered to be reduced to practice.”) and page 16 (“[D]elivery of the manuscript from France into the United States is knowledge of the invention that was brought into this country and disclosed to others.”).

The examiner also concedes that the invention was constructively reduced to practice on January 24, 1992. See the Examiner’s Answer, page 16 (“Reduction to practice occurred with the filing of application SN 07/825667 on January 24, 1992.”). The only issue, therefore, is whether Appellants have provided evidence of diligence, to link the prior conception to the later constructive reduction to practice.

Appellants’ 131 declaration includes evidence intended to show diligence for the time period between reception of the manuscript in this country and the filing of the ‘667 application five weeks later. Appellants assert that the evidence shows that from December 19, 1991, to January 9, 1992, the manuscript was under review by the assignee to determine whether to file a patent application; that on January 13, 1992, the assignee requested outside patent counsel to prepare a patent application based on the manuscript; and that an attorney worked on drafting the application almost daily from January 14, 1992, until the application was filed on January 24, 1992. The examiner has not alleged that Appellants’ showing of diligence is in any way deficient.

Thus, the examiner has not disputed the evidence submitted by Appellants to show conception of the claimed method prior to the effective date of the reference, coupled with due diligence to the filing of the application five weeks later. Since Rule 131 expressly allows an applicant to antedate a reference by showing prior conception coupled with diligence to a later constructive reduction to practice, the examiner has not carried her burden of explaining why Appellants' 131 declarations are insufficient to overcome the rejections based on Yu. Since Appellants have apparently complied with the requirements of Rule 131 and effectively removed Yu as prior art with respect to the instant claims, the rejections based on Yu are reversed.

Summary

The examiner has not shown that a person of ordinary skill in the art would have been led to combine the teachings of Glass and Mangelsdorf and thereby produce the claimed method. In addition, Appellants have effectively antedated Yu by showing prior conception of the claimed method, coupled with diligence to a constructive reduction to practice. We therefore reverse all of the rejections on appeal.

REVERSED

William F. Smith)	
Administrative Patent Judge)	
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)	BOARD OF PATENT
Eric Grimes)	
Administrative Patent Judge)	APPEALS AND
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)	INTERFERENCES
)	
Lora M. Green)	
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