

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte MARIE LIN, TOM CHIA,
and CHIU CHIN CHANG

Appeal 2008-4479
Application 10/163,018
Technology Center 1600

Decided: January 5, 2009

Before DEMETRA J. MILLS, RICHARD M. LEBOVITZ, and JEFFREY
N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a homogeneous analytical method to detect binding pair members. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Statement of the Case

Background

“There are a number of occasions on which a sample, particularly a sample of a biological fluid obtained from an individual, is to be screened for the presence of one or more analytes, particularly one or more chemical substances” (Spec. 1:15-17). The Specification notes that “[c]urrently such screening is done by subjecting the sample to a series of individual tests for each substance or family of substances whose presence is sought to be determined. In such tests the predetermined (cutoff) minimum or maximum level may well be different for each substance” (Spec. 2:10-13). According to the Specification, “[i]t would be advantageous to have available a method whereby a sample could be simultaneously screened for the presence of such multiple analytes in a single assay” (Spec. 2:32-33).

The Claims

Claims 1-4, 6-16, and 31 are on appeal. We will focus on claim 1, the only independent claim on appeal, which is representative and reads as follows:

1. A method for detecting the presence of one or more non-serologically cross-reactive analyte types in a sample using a competitive homogeneous assay: where the assay detects a plurality of different analyte types that are non-serologically cross-reactive and, where the assay involves analyte and receptor binding pairs such that the presence of one or more different analyte types is determined by enzyme activity reflecting the concentration of analyte when present in excess of a predetermined concentration of the cutoff said method comprising the steps of:

(I) combining in an aqueous medium:

- (a) glucose-6-phosphate dehydrogenase (G6PDH) analyte binding pair member conjugates, the conjugates comprised of G6PDH covalently linked to a plurality of known analyte binding pair members of which at least two are non-serologically cross-reactive;
- (b) receptors able to bind to each analyte type to be detected and to the G6PDH-analyte binding pair member conjugates; and,
- (c) a sample to be tested for the presence of any of the plurality of analyte types; and,
- (II) detecting increased G6PDH activity in the aqueous medium due to competitive binding of the receptors with the analyte types in the sample where analyte types bind receptors permitting the G6PDH-analyte binding pair member conjugates to exhibit maximal enzyme activity; wherein:
 - (iv) concentrations of G6PDH-analyte binding pair member conjugates and of the receptors are adjusted in the aqueous mixture so that the enzyme rate at the predetermined cutoff concentrations is approximately the same for the different analyte types whose presence is to be detected;
 - (v) wherein the G6PDH is deactivated by from about 20% to about 85% resulting from the covalent linkage to the analyte binding pair member; and
 - (vi) wherein the deactivated G6PDH is inhibited by from about 20% to about 85% when bound to the receptors.

The prior art

The Examiner relies on the following prior art references to show unpatentability:

Rubenstein et al.	U.S. 3,875,011	Apr. 1 1975
Jakobovits et al.	U.S. 6,033,890	Mar. 7, 2000
Jakobovits et al.	U.S. 6,090,567	Jul. 18, 2000

Wei Huang et al, *Homogeneous Bioluminescence Competitive Binding Assay for Folate Based on a Coupled Glucose-6-phosphate Dehydrogenase-Bacterial Luciferase Enzyme System*, 68 ANALYTICAL CHEMISTRY 1646-1650 (1996).

Hallowell et al, *Enzyme-amplified receptor assay screening test for chlorpromazine trifluoperazine and phencyclidine*, 4 J. CLINICAL LABORATORY ANALYSIS 64-73 (1990) – Abstract only.

The issues

- A. The Examiner rejected claims 1, 6-16, and 31 under 35 U.S.C. § 103(a) as being obvious over Jakobovits ‘567, Jakobovits ‘890, and Hallowell (Ans. 4-6).
- B. The Examiner rejected claims 2 and 3 under 35 U.S.C. § 103(a) as being obvious over Jakobovits ‘567, Jakobovits ‘890, Hallowell, and Rubenstein (Ans. 7-8).
- C. The Examiner rejected claim 4 under 35 U.S.C. § 103(a) as being obvious over Jakobovits ‘567, Jakobovits ‘890, Hallowell, and Huang (Ans. 8-9).

A. 35 U.S.C. § 103(a) as over Jakobovits ‘567, Jakobovits ‘890, and Hallowell

The Examiner rejected claims 1, 6-16, and 31 under 35 U.S.C. § 103(a) as being obvious over Jakobovits ‘567, Jakobovits ‘890, and Hallowell (Ans. 4-6).

The Examiner finds that the “Jakobovits et al. (U.S. Patent #6,090,567) teach an assay procedure to detect analytes with a glucose-6-phosphate dehydrogenase enzyme” (Ans. 4). The Examiner further finds that Jakobovits differs “from the instant invention in not specifically

teaching an adjustment to the enzyme rate according to a predetermined cutoff concentration for the different analyte types of interest” (*id.* at 5). The Examiner finds that Hallowell teaches “calibration curves (predetermined concentrations) with detection limits at n[a]nomolar levels of drug” (*id.* at 6).

The Examiner also finds that “the reagents and assays were merely combined by Appellant in order to simultaneously access the analyte(s) of interest” (*id.* at 10). The Examiner finds that “the claims read on *single analyte* measurement” (*id.*).

Appellants contend that

Hallowell, like Jakobovits, describes three separate assays for detecting drugs that bind to the acetylcholine receptor but does not suggest combining the three different drug:enzyme conjugates into a single assay mixture . . . None of the cited prior art suggests combining different analyte detecting reagents because such a combination of reagents defeats the essential purpose of the prior art assays, i.e., to inform the user whether a *specific* analyte is present or not in a sample.

(App. Br. 9.)

Appellants contend that their assay “permit[s] the detection of any one of a group of analytes at a predetermined cutoff concentration providing a uniform signal” (Reply Br. 4). Appellants further contend that a “plurality of conjugates with non-serologically cross-reactive analytes clearly requires more than one conjugate type” (Reply Br. 5).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Did the Examiner err in finding that Hallowell and the two Jakobovits patents teach an assay with glucose-6-phosphate dehydrogenase conjugates “linked to a plurality of known analyte binding pair members of which at least two are non-serologically cross-reactive”?

Findings of Fact (FF)

1. Jakobovits ‘567¹ teaches “methods for homogenous immunoassay of an analyte in a sample suspected of containing the analyte” (Jakobovits ‘567, col. 4, ll. 5-7).

2. Jakobovits ‘567 teaches “combining in a liquid medium: (a) the sample to be assayed, (b) a conjugate of (i) an analyte analog and (ii) a mutant NAD⁺ dependent G6PDH [glucose-6-phosphate dehydrogenase]. . . (c) a receptor for the analyte, and (d) substrates for the G6PDH” (Jakobovits ‘567, col. 4, ll. 8-13).

3. Jakobovits ‘567 teaches “determining the enzymatic activity of the G6PDH in the medium; and . . . comparing the enzymatic activity to the enzymatic activity observed with a sample containing the analyte” (Jakobovits ‘567, col. 4, ll. 14-17).

4. Jakobovits ‘567 teaches that “[t]ypically, the mutant G6PDH is conjugated to an sbp [specific binding pair] member analogous to the analyte” (Jakobovits ‘567, col. 9, ll. 66-67).

¹ Jakobovits ‘567 and Jakobovits ‘890 share identical specifications and disclosures since both patents are divisional applications of U.S. patent application 08/044,857 (*see* Jakobovits ‘567, Related U.S. Application Data).

5. The Examiner found that Jakobovits '567 teaches that in “example III, the enzymatic activity was monitored by determining maximum inhibition with a rabbit antidigoxin antiserum . . . [t]he desired end point was 50-70% maximum inhibition . . . [t]he final % of deactivation ranged from 26-40” (Ans. 4).

6. Hallowell teaches a G6PDH immunoassay procedure which “yields calibration curves with detection limits at n[a]nomolar levels of drug, with binding responses dependent on the amounts of receptor and enzyme-labeled drug used” (Hallowell, abstract).

Principles of Law

Claim terms are interpreted using the broadest reasonable interpretation in light of the Specification. *See, e.g., In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000) (“[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification.”). *Also see In re Morris*, 127 F.3d 1048, 1054-56 (Fed. Cir. 1997). (“Absent an express definition in their specification, the fact that appellants can point to definitions or usages that conform to their interpretation does not make the PTO's definition unreasonable when the PTO can point to other sources that support its interpretation.”).

In *KSR*, the Supreme Court rejected the rigid application of the teaching, suggestion, and motivation test by the Federal Circuit, stating that

The principles underlying [earlier] cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill

can implement a predictable variation, § 103 likely bars its patentability.

KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007).

Analysis

In analyzing claim 1, our mandate is to give the terms in a claim their broadest reasonable interpretation. *See, e.g., In re Hyatt*, 211 F.3d at 1372.

Claim 1 expressly teaches a method whose first step requires combining in a medium G6PDH analyte binding pair member conjugates which are “covalently linked to a plurality of known analyte binding pair members of which at least two are non-serologically cross-reactive” (Claim 1).

The broadest reasonable interpretation of the word “plurality” is more than one. The claim further clarifies that the claim does not read on multiple molecules of a single type of analyte binding pair members by requiring that “at least two [members] are non-serologically cross-reactive.”

Thus, the broadest reasonable interpretation of claim 1 is that in the medium for detecting the analyte, there are at least two different binding pair members which bind to different analytes. These two different binding pair members must both be conjugated to the same enzymatic label, G6PDH.

While the Examiner has found that the prior art of Jakobovits ‘567, Jakobovits ‘890, and Hallowell teach the remaining limitations of claim 1 (*see* FF 1-6), the Examiner failed to find a teaching or suggestion for two serologically different binding pair members both conjugated to G6PDH and both present in the aqueous medium for analysis (*see* Ans. 4-5).

The Examiner contends that “that “the claims read on *single analyte* measurement” (Ans. 10). The Examiner states that because claim 1 “recites ‘the presence of one or more different analyte types is determined’ . . . the claims read on single analyte determination” (Ans. 11).

While claim 1 may encompass the situation where only a single analyte is detected, claim 1 expressly requires that in the aqueous medium of the assay contains “at least two [members, which] are non-serologically cross-reactive” (Claim 1, step I (a)). None of Jakobovits ‘567, Jakobovits ‘890, and Hallowell teach or suggest putting two different binding pair members simultaneously into an aqueous medium for analyte detection.

The Examiner contends that “a long line of cases have held that the mere use of different starting materials, whether novel or known, in a conventional process to produce the product one would expect therefrom does not render the process unobvious” (Ans. 10). First, the Examiner should reread *Ochiai*, which reversed the rejection of “Ochiai's claims, limited as they are to the use of a particular nonobvious starting material for making a particular nonobvious end product” *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995). The Examiner may also wish to reread 35 U.S.C. § 103(b), which states that “a biotechnological process using or resulting in a composition of matter that is novel under section 102 and nonobvious under subsection (a) of this section shall be considered nonobvious” with two conditions.

Second, even in the cases of known starting materials, the mere use of a conventional process does not necessarily result in a conclusion of obviousness. In the instant case, it is necessary to apply the appropriate test

for obviousness established by *Graham v. John Deere Co.*, 383 U.S. 1 (1966). When comparing the differences between the prior art and claim 1 at issue, the only reasonable conclusion that can be drawn is that Jakobovits '567, Jakobovits '890, and Hallowell do not teach or suggest multiplexing the immunoassay as required by claim 1 to include two non-serologically cross-reactive analyte binding pair members both conjugated to G6PDH. The Examiner has not satisfied the burden of providing evidence that the prior art described a multiplicity of analytes in a single reaction.

KSR teaches that an invention “composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 127 S. Ct. at 1741. There must be “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *Id.* at 1741. The Examiner has provided no such reason to place two non-serologically cross-reactive analyte binding pair members both conjugated to G6PDH in a single aqueous medium in the rejection.

We do not address the obviousness of cutoff concentrations for multiple different analytes in a single aqueous medium, as required by claim 1, because the Examiner has not provided a prima facie case of obviousness regarding the multiplex analysis required by claim 1.

Regarding potential future prosecution, we caution that merely finding an evidentiary reference teaching multiplex analysis of different analytes may not be sufficient to render claim 1 prima facie obvious. The ordinary

multiplex reference either uses different labels² or separates the analyte complexes of the different binding pair members.³ Claim 1 requires that a single G6PDH label is linked to the multiple different binding pair members and that the detection occurs in the aqueous medium without a separation step. The Examiner has failed to provide any evidence which demonstrates these elements of claim 1 in the currently cited prior art and these elements would be required to evidence a proper case of prima facie obviousness.

Conclusions of Law

The Examiner erred in finding that Hallowell and the two Jakobovits patents teach an assay with G6PDH conjugates “linked to a plurality of known analyte binding pair members of which at least two are non-serologically cross-reactive.”

² See, e.g., Nelson et al, U.S. Patent 5,756,709, May 26, 1998, cited in Appellants’ IDS of Sep. 30, 2002 which teaches a multiplex assay with “different chemiluminescent labeling reagents” (Nelson, abstract).

³ See, e.g., Chen, U.S. Patent 5,863,401, Jan. 26, 1999, cited in Appellants’ IDS of Sep. 30, 2002 which teaches a multiplex assay with a single label but requires that “[f]ollowing the competitive binding reaction the antibody –labeled analyte complexes are separated from the labeled analytes by CE [capillary electrophoresis] techniques and detected with laser induced fluorescence” (Chen, col. 8, ll. 17-20).

B. 35 U.S.C. § 103(a) as over Jakobovits '567, Jakobovits '890, Hallowell, and Rubenstein

The Examiner rejected claims 2 and 3 under 35 U.S.C. § 103(a) as being obvious over Jakobovits '567, Jakobovits '890, Hallowell, and Rubenstein (Ans. 7-8).

The Examiner finds that

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use conjugates comprising a plurality of analyte types linked to G6PDH as taught by Rubenstein et al. in the enzyme procedures of Jakobovits et al. (U.S. Patent #6,090,567) or Jakobovits et al. (U.S. Patent #6,033,890) in view of Hallowell et al. because Rubenstein et al. taught that the use of glucose-6-phosphate dehydrogenase as an enzyme conjugate provides selective and sensitive tests for a wide variety of different drugs having widely varying structures.

(Ans. 8.)

Appellants contend that “[c]laims 2-4 depend from claim 1 and are rejected as obvious over Jakobovitz and Hallowell in combination with additional prior art. If claim 1 is deemed patentable, all the pending claims should be considered patentable” (App. Br. 4).

We found that the rejection of claim 1 was in error as discussed above.

Therefore, we frame the obviousness issue before us as follows:

Did the Examiner err in finding that the teaching of Rubenstein, in addition to the teachings of Hallowell and the Jakobovits patents, taught multiple different analyte binding pairs as required by claim 1?

Findings of Fact

7. Rubenstein teaches “[h]aptenic conjugates to glucose-6-phosphate dehydrogenase are provided for employment in homogenous enzyme immunoassays to provide high sensitivity in detecting extremely small amounts of organic materials” (Rubenstein, col. 2, ll. 5-9).

8. Rubenstein teaches in analyzing for the presence of a compound that “the appropriate enzyme conjugate was added which had sufficient enzyme to provide an activity in the absence of antibody” (Rubenstein, col. 21, ll. 16-18).

Analysis

While Rubenstein teaches the analysis of multiple different analytes (FF 7-8), the Examiner does not identify any teaching in Rubenstein for combining in an medium G6PDH analyte binding pair member conjugates which are “covalently linked to a plurality of known analyte binding pair members of which at least two are non-serologically cross-reactive” (Claim 1).

KSR teaches that an invention “composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 127 S. Ct. at 1741. There must be “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *Id.* at 1741. The Examiner has provided no such reason to place two non-serologically cross-reactive analyte binding pair members both conjugated to G6PDH in a single aqueous medium in the rejection further comprising Rubenstein.

Conclusions of Law

The Examiner erred in finding that the teaching of Rubenstein, in addition to the teachings of Hallowell and the Jakobovits patents, taught multiple different analyte binding pairs as required by claim 1.

C. 35 U.S.C. § 103(a) as over Jakobovits '567, Jakobovits '890, Hallowell, and Huang

The Examiner rejected claim 4 under 35 U.S.C. § 103(a) as being obvious over Jakobovits '567, Jakobovits '890, Hallowell, and Huang (Ans. 8-9).

We reversed the rejection of claim 1 over Jakobovits '567, Jakobovits '890, and Hallowell as discussed above. Since Huang does not supplement the deficiencies in that rejection, we are also compelled to reverse the rejection of claim 4 as well.

SUMMARY

In summary, we reverse the rejections of claims 1-4, 6-16, and 31 under 35 U.S.C. § 103(a).

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

REVERSED

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