The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 15

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte FRANCES S. LIGLER,
ANNE W. KUSTERBECK and SINA Y. RABBANY

Appeal No. 1999-1384
Application No. 08/583,912

ON BRIEF

Before SCHEINER, ADAMS and MILLS, Administrative Patent Judges.

ADAMS, 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 claims 1-4, 7-14, 19, 20 and 24-28. Claims 5, 6, 15-18 and 21 are canceled. Pursuant to a Restriction Requirement[1], claims 22 and 23 were withdrawn from consideration as drawn to a non-elected invention.

[1] Paper No. 5, mailed March 6, 1997.

Claims 1, 9 and 25 are illustrative of the subject matter on appeal and are reproduced below:

1. A quantitative assay method for detecting a target analyte, comprising the steps of:
   providing a porous membrane having binding elements immobilized thereon, each of said binding elements having at least one binding site capable of specifically binding to said target analyte;
   exposing said binding sites to a labelled analog of the target analyte to form complexes of membrane-immobilized binding elements and labelled analogs;
   pumping a first aqueous liquid sample, suspected of containing the target analyte, so as to flow said first liquid sample normal to and through said membrane having said complexes thereon, at a flow rate allowing the target analyte to displace the labelled analog from the complexes under non-equilibrium conditions to form downstream of said membrane a flowable liquid effluent including said displaced labelled analog, said flow rate also providing an interaction time between said analyte and said membrane of about 0.1 sec through about 30 sec;
   interrogating said flowable liquid effluent to detect and quantitatively determine the amount of the displaced labelled analog, the amount of said displaced labelled analog being proportional to the concentration of said target analyte in said first sample.

9. A device for the assay of an aqueous sample suspected of containing a target analyte, comprising;
   a porous membrane having binding elements immobilized thereon, each of said binding elements having at least one binding site capable of specifically binding to said target analyte, essentially all of said binding sites on said membrane being occupied by a labelled analog of the target analyte to form complexes of membrane-immobilized binding elements and labelled analogs;
   a pump for flowing an aqueous liquid sample, suspected of containing the target analyte, normal to and through said membrane having said complexes thereon, at a flow rate allowing the target analyte to displace the labelled analog from the complexes under non-equilibrium conditions to form downstream of said membrane a flowable liquid effluent including said displaced labelled analog, said flow rate also providing an interaction time between said analyte and said membrane of about 0.1 sec through about 30 sec; and
   a detector that interrogates said flowable liquid effluent and the presence of said labelled analog therein.

25. The device of claim 9, wherein, after said device has been used to assay a first aqueous sample suspected of containing said liquid analyte by:

flowing said first aqueous liquid sample, suspected of containing the target analyte, normal to and through said membrane having said complexes thereon, at a flow rate allowing the target analyte to displace the labelled analog from the complexes under non-equilibrium conditions to form downstream of said membrane a liquid effluent including said displaced labelled analog, said flow rate also providing an interaction time between said analyte and said membrane of about 0.1 sec through about 30 sec; and

interrogating said liquid effluent for the presence of said labelled analog therein,

said membrane may be rinsed and said device may be reused for the steps of:

flowing a second aqueous liquid sample, suspected of containing target analyte, normal to and through said membrane having said complexes thereon, at a flow rate allowing the target analyte in said second sample to displace the labelled analog from the complexes under non-equilibrium conditions to form downstream of said membrane a liquid effluent including said labelled analog displaced by said target analyte in said second sample, said flow rate also providing an interaction time between said analyte in said second sample and said membrane of about 0.1 sec through about 30 sec; and

interrogating said liquid effluent from said second sample for the presence of said labelled analog displaced by said target analyte in said second sample.

The references relied upon by the examiner are:

Ligler et al. (Ligler)	5,183,740	Feb. 2, 1993
Kidwell	5,369,007	Nov. 29, 1994

GROUNDS OF REJECTION

Claim 25 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite because it is not clear what component of the device is further limited.

Claims 1-4, 7-14, 19-20 and 24-28 stand rejected under 35 U.S.C. § 103 as being unpatentable over Ligler in view of Kidwell.

We reverse.

DISCUSSION

In reaching our decision in this appeal, we considered appellants' specification and claims, in addition to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer[2] for the examiner's reasoning in support of the rejections. We further reference appellants' Brief[3], and appellants' Reply Brief[4] for the appellants' arguments in favor of patentability. We note that the examiner entered and considered appellants' Reply Brief[5].

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH:

As set forth in Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed. Cir. 1991):

> The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. See Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits.").

Furthermore, claim language must be analyzed "not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary skill in the

[2] Paper No. 12, mailed June 8, 1998.
[3] Paper No. 9, received February 18, 1998.
[4] Paper No. 13, received August 5, 1998.
[5] Paper No. 14, mailed August 17, 1998.

pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

According to the examiner (Answer, page 4) "the recitation [in claim 25] that the membrane may be rinsed and said device may be reused does not provide any positive limitation that the membrane and device are reused." Therefore, the examiner finds (Answer, page 4) that "the intended use, rather than any device component, is being further limited."

According to appellants' specification (page 6) "the use of a non-absorbent membrane allows the membrane, once used, to be readily rinsed of sample and reused." Appellants' specification (page 3) contrasts the claim invention with that of Kidwell, disclosing that in Kidwell "[a]nalyte from the sample displaces the labelled analyte, causing the labelled analyte and the remainder of the sample to pass into a superabsorbent layer. The superabsorbent layer contains a substrate for the enzymatic label and any needed indicator…. Additionally, the Kidwell microassay card is not reusable."

Appellant argues (Brief, page 4) that "[c]laim 25 further limits claim 9 by requiring that the device be constructed so as to be reusable. … Reusability in the recited manner is not merely a matter of intended use, but must be engineered into the apparatus itself."

We agree with appellants. When claim 25 is viewed in the context of appellants' specification, and the prior art, the limitation that "the membrane may be rinsed and said device may be reused" further limits the device of claim 9, so that it is to be reusable.

Accordingly we reverse the rejection of claim 25 under 35 U.S.C. § 112, second paragraph.

THE REJECTION UNDER 35 U.S.C. § 103:

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). In meeting this burden, we note that it is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion or motivation to lead an inventor to combine those references. Pro-Mold and Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). Furthermore, as set forth in Ecolochem Inc. v. Southern California Edison, 227, F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000) the:

> "[S]uggestion to combine may be found in explicit or implicit teachings within the references themselves, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved." … However, there still must be 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." … "[A] rejection cannot be predicated on the mere identification … of individual components of claimed limitations. Rather particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed."…. [Citations omitted].

According to the examiner (Answer, page 4) Ligler "teach a device and method for a displacement assay essentially as claimed…." In addition, the examiner finds (Answer, page 5) that "[l]imitations regarding … optimization of

flow rates to provide optimal reactions times can also be found in Ligler et al. ('740)(columns 5-10)." Ligler discloses (column 6, lines 48-54) that:

> The flow rate of the liquid stream in the method of this invention should be between 0.1 and 2.0 milliliters per minute, preferably between 0.3 and 0.8 milliliters per minute. The optimum flow rate is such that the residence time of the target on the exchanger is sufficient to generate displacement of measurable quantities of labelled antigen in the shortest possible time.

Ligler discloses (column 9, lines 53-54) that "[t]ypical flow rates used with the system are 0.3-0.8 ml/min, and that "picomoles of antigen can be detected under continuous flow rates as fast as 0.8 ml/min" (column 10, lines 28-29). However, the examiner recognizes (Answer, bridging paragraph, pages 4-5) that Ligler's exemplified support medium is a sepharose bead. While Ligler discloses other alternative support media (column 9, lines 6-16), Ligler does not teach a porous membrane as claimed.

To make up for this deficiency the examiner applies Kidwell. According to the examiner (Answer, page 5) "Kidwell teaches a displacement assay device and method wherein the binding elements having labelled analogs of a target analyte are immobilized on a porous [supporting] membrane." According to Kidwell (column 6, lines 22-38):

> The semipermeable membrane can be any membrane that, together with the supporting membrane, regulates the fluid flow rate so that the proper reactions take place. Preferably, this interaction time is between about one to about five minutes, with two minutes being most preferred. Hence, one can vary the pore size and the area of the supporting and semipermeable membranes to achieve the proper interaction time. The smaller the pore size and the smaller the surface area of the membranes, the longer the interaction time and the greater the sensitivity. Also, depending upon the pore size of the supporting membrane, an additional semipermeable membrane may not be required. In the displacement mode using a nitrocellose [sic] membrane, optimum performance in both time and sensitivity results from 0.45 μm pore size, with a three-sixteenth inch diameter membrane and

> application of 40 µl test solution to obtain a two minute draw-through time.

The examiner finds (Answer, page 6) that "[i]t would have been obvious to the ordinarily skilled artisan at the time the instant invention was made to have substituted the solid phase support of the displacement assay device and method of Ligler et al. with a porous membrane such as is taught by Kidwell." According to the examiner (id.):

> The limitation as to the amount of interaction time being no more than about 15 seconds appears to be a result effective variable which depends upon pore size of the membrane, the surface area of the membrane, and the analyte to be detected ([s]ee Kidwell[,] column 6, lines 22-34), as well as the flow rate of the system (Ligler et al.) and it would have been obvious to one having ordinary skill in the art at the time the invention was made to have designed the system and method so as to achieve a rapid interaction time and obtain displacement as desired by Ligler et al. (e.g. column 6, lines 51-54) since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

In response, appellants argue (Brief, pages 5-6) that:

> To achieve the proper flow rate through the membrane and thus (in a passive flow system) the correct interaction time of one to five minutes, Kidwell must use a small pore size for the supporting membrane or provide a flow-control membrane of a specified pore size beneath the supporting membrane (col. 6, lines 3 through 44). The obvious implication of Kidwell's teaching is that unless sample flow is significantly restricted, even gravity-assisted flow through a transversely positioned antibody-supporting membrane is too fast to allow an adequate interaction times [sic] for immunoassays. Therefore Kidwell also teaches against actively pumping a sample through a transversely positioned antibody-supporting membrane.

Appellants find (Brief, page 6) that "[t]his teaching against is particularly pertinent where, as in the claims, the resulting interaction time are [sic] no more

than half the interaction times described by Kidwell (col. 6, lines 26 and 27)." In response, the examiner argues (Answer, page 8-9) that:

> Appellant [sic] and Ligler et al[.] ('740) both teach flow control for regulation of adequate interaction times and, notwithstanding [a]ppellant's [sic] apparent assertions to the contrary, there is nothing in evidence that the desired flow rates in the closed pump system of [a]ppellant [sic] or Ligler et al[.] ('740) exceed that which would be expected in an open gravity-mediated flow system.

In our opinion, the examiner's response misses appellants' point. While the examiner's response focuses on flow rate, appellants' argument is directed at analyte-membrane interaction time. In other words, appellants argue that according to Kidwell the flow through an open gravity-mediated flow system is too fast to allow for adequate analyte-membrane interaction times. To solve this problem Kidwell restricts the flow rate by using a second semi-permeable membrane or alternatively modifying the pore size and/or surface area of the membrane (column 6, lines 22-43), to allow for an analyte-membrane interaction time of one to five minutes. According to appellants (Brief, pages 5-6) if gravity-mediated flow is too fast for adequate analyte-membrane interaction time, actively pumping a sample through the system, as claimed, would also be expected to be too fast, absent something to enhance the analyte-membrane interaction time to, according to Kidwell, one to five minutes.

On this record we do not disagree with the examiner that the membrane support taught by Kidwell could be substituted in place of the support media taught by Ligler. Answer, page 6. We are not persuaded by appellants' argument (Reply Brief, page 2) that "[n]o motivation exists to combine Kidwell et al.'s teaching with those of Ligler et al. to result in a flow-immunoassay system

that includes a membrane positioned perpendicular to sample flow in addition to a pump" [emphasis removed]. In this case, the support media of Ligler and the membrane of Kidwell both serve as support media. See Ligler, Fig. 2, #33 and column 8, line 54 through column 9, line 40; and Kidwell, Fig. 2, #223, column 4, line 41 through column 6, line 44. Where, as here, the prior art recognizes two components to be equivalent, an express suggestion to substitute one for another need not be present in order to render such substitution obvious. In re Fout, 675 F.2d 297, 301, 213 USPQ 532, 536 (CCPA 1982).

However, while we recognize that Ligler discloses (column 10, lines 29-30) that "picomoles of antigen can be detected under continuous flow rates as fast as 0.8ml/min," Ligler does not disclose the flow rate, interaction time or expected sensitivity of a system with a membrane support. While the membrane support of Kidwell, can be substituted for the Ligler support, sensitivity, flow rate and analyte-support interaction time are expected to be different than Ligler's. On this record, the only prior art disclosure of appropriate analyte-support media interaction times for a membrane based support media is found in Kidwell.

The examiner is correct in that the "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art," In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) (citations omitted). However, in Boesch 617 F.2d at 206, 205 USPQ at 219:

> appellants' specification [disclosed] that certain precipitate-hardened nickel base alloys, after being exponsed to elevated temperatures for prolonged periods of time, suffered "from a marked and catastrophic decrease in room temperature ductility and a marked increase in the rate of creep deformation." It was

> observed that other nickel base alloys having the same percentage ranges of components did not suffer such deleterious changes.

The court in Boesch found (id.) that "considering … that the composition requirements of the claims and the cited references overlap, we agree with the Solicitor that the prior art would have suggested 'the kind of experimentation necessary to achieve the claimed composition…'" [emphasis added].

We do not disagree with the examiner's position (Answer, page 6) that the "result effective variable" relating to the interaction time between the analyte and the membrane "depends upon [the] pore size of the membrane, the surface area of the membrane, and the analyte to be detected." Appellants' specification (page 6) discloses membrane thickness, surface area and porosity are important in obtaining interaction times within the claimed range:

> [M]embranes useful in the present invention have thicknesses, exposed surface areas, and porosities that allow detection of the analyte with an interaction time of about 0.1 sec to about 30 seconds, and typically about 1 sec to about 15 seconds, between a sample suspected of containing of the analyte and the membrane having a labelled analyte of the analyte thereon. Generally, the pore sizes in the membrane are about 0.2-1.0 microns, and are typically about 0.45 microns. Of course, other pore sizes may be used to achieve the desired interaction time. Likewise, the thickness and surface area of the membrane can be adjusted to provide the desired interaction time.

Similarly, Kidwell (column 6, lines 28-33) discloses that "one can vary the pore size and the area of the supporting and semipermeable membranes to achieve the proper interaction time. The smaller the pore size and the smaller the surface area of the membranes, the longer the interaction time and the greater the sensitivity."

However, while both appellants and Kidwell recognize the result effective variables, the object of appellants' invention (appellants' specification, bridging paragraph, pages 3-4) is "to perform bioassays capable of detecting minute quantities of an analyte in under one minute." In contrast, Kidwell prefers (column 6, lines 26-28) an interaction time "between about one to about five minutes, with two minutes being most preferred." Kidwell further discloses (column 6, lines 32-33) that the longer the interaction time, the greater the sensitivity.

The examiner is reminded that "[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." In re Dow Chemical Co. 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). On this record, the examiner has not provided, and we do not find, a suggestion in the prior art, that the interaction times of one to about five minutes, as disclosed by Kidwell, could be reduced, with a reasonable likelihood of success, to "about 0.1 sec through about 30 sec" as required by the claimed invention. Instead, we agree with appellants that Kidwell teaches away from analyte-membrane interaction times of about 0.1 through about 30 seconds. On this record, there is no suggestion to reduce the analyte-membrane interaction time below one minute as taught by Kidwell. Therefore, in our opinion, in contrast to the facts of Boesch, the prior art relied on by the examiner would not have suggested the kind of experimentation necessary to obtain appellants' claimed invention.

While a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the protocols taught by Ligler and Kidwell, the modification is not obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 211 USPQ 1125, 1127 (Fed. Cir. 1984). Here we see no such reason to modify the references as applied. On this record, the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness. 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).

Accordingly, we reverse the rejection of claims 1-4, 7-14, 19-20 and 24-28 under 35 U.S.C. § 103 as being unpatentable over Ligler in view of Kidwell.

REVERSED

TONI R. SCHEINER Administrative Patent Judge	))))) BOARD OF PATENT
DONALD E. ADAMS Administrative Patent Judge	)) APPEALS AND)) INTERFERENCES
DEMETRA J. MILLS Administrative Patent Judge	)))

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