

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 68

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte ROBERT ZIEGELMAIER

Appeal No. 2001-1654
Application No. 08/445,584

ON BRIEF

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 4-8, 13, 14, and 16-24, all of the claims remaining.

Claims 16, 17, and 8 are representative and read as follows:

16. An immunological method for the detection of an antigen specific antibody comprising one or more of the immunoglobulin classes A, M, D or E in a fluid, comprising the simultaneous incubation of:
 - a. A solid phase having bonded thereto antibody specific for said immunoglobulin classes A, M, D, or E;
 - b. A fluid containing an immunoglobulin of class A, M, D, or E;
 - c. A labeled antigen immunologically reactive to the fluid phase immunoglobulin; and

- d. A substance which inhibits the binding of immunoglobulin G to the solid phase and which inhibits the binding of said labeled antigen to immunoglobulin G.
17. An immunological method for the detection of an antigen specific antibody comprising one or more of the immunoglobulin classes A, M, D, or E in a fluid, comprising the simultaneous incubation of:
- a. A solid phase having bonded thereto antibody specific for said immunoglobulin classes A, M, D, or E;
 - b. A fluid containing an immunoglobulin of class A, M, D, or E;
 - c. An unlabeled antigen immunologically reactive to the fluid phase immunoglobulin;
 - d. A labeled antibody, immunologically reactive with said unlabeled antigen; and
 - e. A substance which inhibits the binding of immunoglobulin G to the solid phase and which inhibits the binding of said unlabeled antigen to immunoglobulin G.
8. The method as claimed in claim 16, wherein the labeling means are erythrocytes.

The examiner relies on the following references:

Molinaro et al. (Molinaro)	4,130,634	Dec. 19, 1978
Duermeyer	4,292,403	Sept. 29, 1981
Unger	4,434,227	Feb. 28, 1984
David et al. (David)	4,486,530	Dec. 04, 1984

Schmitz et al. (Schmitz), "Detection of IgM Antibodies to Cytomegalovirus (CMV) Using an Enzyme-labelled Antigen (ELA)", Journal of General Virology, Vol. 50 pp. 59-68 (1980)

Claims 4-7, 13, 14, 16-21, 23, and 24 stand rejected under 35 U.S.C.

§ 103 as obvious in view of Duermeyer, Unger, David, and Schmitz.

Claims 8 and 22 stand rejected under 35 U.S.C. § 103 as obvious in view of Duermeyer, Unger, David, Schmitz, and Molinaro.

We reverse.

Background

The specification discloses a method of detecting antigen-specific antibodies belonging to classes other than IgG, i.e., IgA, IgM, IgD, or IgE.

Detection of these classes of antibodies is important for a variety of reasons.

Immunoglobulins of the IgM class appear very soon after an infection, for which reason their determination is important for the early diagnosis of an infectious disease or for the diagnosis of an acute infection.

The second most abundant immunoglobulins are of the immunoglobulin class IgA and are the most important secretory antibodies.

Immunoglobulins of classes IgD and IgE can be found in elevated concentration in certain pathological processes; for example IgE has properties which sensitize mast cells and it plays a significant part in the pathogenesis of a number of allergic reactions. IgD antibodies are found in autoimmune diseases.

Specification, page 2.

The specification discloses that methods were known for detecting antigen-specific antibodies of a particular class but that these methods suffered from the disadvantage that “the non-antigen-specific immunoglobulin fraction of any particular immunoglobulin class enters into competition with the antigen-specific fraction.” Page 3. The specification discloses a detection method that eliminates this competition and also shortens the time required to perform the assay.

This “one-step method” has become possible after successful elimination of two possible interferences:

In the first place, the effect of antigen-specific IgG antibodies must be eliminated. . . .

In the second place, the activity of rheumatoid factors (RF), that is to say antibodies against IgG which belong to various immunoglobulin classes, has to be suppressed because it can lead to falsification of the result. This falsification is possible because RF are bound to the antibody on the solid phase, and bound over the antigen-specific IgG antigen which is bound by the RF in turn, and thus a false-positive detection reaction is obtained.

It has been possible to eliminate both possibilities of interference by, for example, addition of anti-human IgG, gamma chain (“RF adsorbent” of Behringwerke AG) to the sample (for example serum).

Specification, pages 4-5.

Thus, the disclosed method involves simultaneous incubation of all the components of the immunoassay: a solid phase that will bind antibodies of a particular class (IgA, IgM, IgD, or IgE), a sample, an antigen-specific label,¹ and “a substance which inhibits binding of immunoglobulin G to the solid phase and inhibits binding of [the] . . . antigen to immunoglobulin G.”

Discussion

The examiner rejected claims 4-7, 13, 14, 16-21, 23, and 24 as obvious in view of Duermeyer, Unger, David, and Schmitz. The examiner also rejected claims 8 and 22 over these same references, combined with Molinaro.

¹ The antigen-specific label can be supplied in the form of labeled antigen or in the form of unlabeled antigen combined with a labeled, antigen-specific antibody. The first embodiment is disclosed in the specification at page 6, lines 14-15, and recited in claim 16; the second embodiment is disclosed in the specification at page 6, lines 17-19, and recited in claim 17.

The examiner characterized Duermeyer as teaching a method of detecting an antigen-specific antibody of class IgM, IgA, IgD, or IgE. According to the examiner, Duermeyer differs from instant claim 17 only “in failing to exemplify the use of an additional substance to inhibit the binding of IgG to the antigen and to the antibody on the solid phase.” Examiner’s Answer, page 4. The examiner states that Duermeyer teaches “an immunological reagent composition” comprising three components, and teaches that “the immunological reagent composition may be combined to form a single reagent.” Examiner’s Answer, page 4.

We agree with Appellants that this characterization of Duermeyer somewhat overstates the relevance of the reference. Specifically, we agree with Appellants that Duermeyer also fails to teach the “simultaneous incubation” limitation of the claims. Duermeyer states that the assay is performed in at least two steps: first, “serum . . . is brought into contact with an insolubilized antibody against the antigen specific IgX concerned,” then “[a]n incubation is subsequently performed with an antigen . . . , after which a further incubation takes place with a labelled antigen binding fragment of an antibody” against the antigen. Column 2, lines 28-39. Duermeyer’s working example makes clear that these steps are separated by washings. See column 4, line 51 to column 5, line 30. Although Duermeyer states that the antigen and labeled antibody fragment can be complexed beforehand (see column 2, lines 61-66), this embodiment would still involve two incubation steps separated by a wash. Therefore, we do not agree

that Duermeyer discloses the claim limitation requiring simultaneous incubation of all reaction components.

Thus, the method disclosed by Duermeyer differs in two respects from the method recited in claim 17: first, it includes a washing step between binding of the sample and addition of a labeled reagent, and second, it does not include an IgG-binding inhibitor in the incubation. The examiner cited Unger, David, and Schmitz to make up these deficiencies.

Like Duermeyer, Unger discloses a method for detecting an antigen-specific antibody of class IgA, IgM, IgD, or IgE. Unger discloses the problem of false-positives resulting from RF interacting with antigen-specific IgG in the sample, giving the appearance of an antigen-specific IgM. See column 2, lines 22-33. Unger discloses that this problem can be avoided by pretreating the sample with anti-IgG, which prevents RF from binding to IgG in the sample. See column 3, lines 5-11. Thus, Unger's assay comprises the steps of (1) treating the sample with anti-IgG, (2) contacting the treated sample with a solid support having antigen bound to it, (3) washing to remove unbound sample, and (4) treating the sample bound to the solid support with labeled anti-IgX antibody to detect bound (antigen-specific) antibody of the IgX class. Column 3, lines 11-26.

Unger does not disclose incubating all the reactants simultaneously. The examiner cited David as disclosing this limitation. See the Examiner's Answer, page 5: "David teaches a simultaneous assay involving a single incubation step as the antibody bound to the solid support and the labeled antibody are both added to the sample being tested at the same time." Finally, apparently in

reference to claim 16, the examiner also cited Schmitz as teaching an immunoassay using “an enzyme-labelled antigen.” Examiner’s Answer, page 5.

The examiner concluded that it would have been obvious to add the anti-IgG taught by Unger to the assay method disclosed by Duermeyer, in order to prevent RF-induced false positives. The examiner also concluded that “[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the assay by simultaneously adding all necessary reagents because such optimization procedure involves a single incubation step and eliminates washing steps which serve to shorten the length of time required for an assay,” Examiner’s Answer, page 6, and that it would have been obvious to use a labeled antigen for detection, as disclosed by Schmitz.

“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.” Ecolochem, 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)).

In this case, although the references suggest most of the limitations of the claims, they are not adequate to support a prima facie case under § 103. On the one hand, the combination of Duermeyer and Unger appears to be reasonable. Both references disclose assays to detect an antigen-specific antibody of class IgA, IgM, IgD, or IgE, and both refer to the problem of RF-induced false positives. See Duermeyer, column 2, lines 10-19, and Unger, column 2, lines 22-33. Duermeyer discloses avoiding false positives by using “a labelled antigen binding fragment of an antibody” for detection (column 2, lines 56-61), while Unger addresses the same problem by pretreating the sample with anti-IgG (column 3, lines 5-11). Thus, Unger and Duermeyer teach complementary methods of addressing the problem of RF-induced false positives. A person skilled in the art would have found it obvious to include Unger’s anti-IgG pretreatment step in Duermeyer’s assay, in order to further reduce the incidence of RF-induced false positives. We agree with this much of the examiner’s analysis.

However, we do not agree that the references would have suggested conducting the claimed assay in a “simultaneous incubation” of all the recited components, as required by both claims 16 and 17. The examiner relies on David to meet this limitation, but we find David’s disclosure to be more limited than the examiner characterizes it.

David teaches that a sandwich immunoassay can be conducted by simultaneously incubating an immobilized antibody, the antigen, and a labeled antibody. See column 4, lines 50-61. David's assay comprised only these three components. See column 8, lines 6-25. David teaches that simultaneous incubation is possible if both the immobilized antibody and the labeled antibody are monoclonal antibodies, directed to different epitopes of the same antigen. See id.

David does not provide guidance with respect to immunoassays in general, nor does it suggest that all immunoassays can or should be conducted by simultaneously incubating all the components in a single incubation. In particular, David does not suggest converting Unger's pretreatment with anti-IgG into a simultaneous incubation of anti-IgG with the other assay components.

Schmitz also fails to suggest this limitation of the claimed method. The examiner cited Schmitz simply to meet the limitation requiring use of a labeled antigen. See the Examiner's Answer, page 6 ("It would have been obvious . . . to use the labeled antigen of Schmitz in the assay of Duermeyer."). Schmitz does not suggest simultaneous incubation of all the recited reagents.

We therefore conclude that the references cited by the examiner do not teach or suggest all of the limitations of the instant claims. In particular, the references do not suggest the limitation requiring simultaneous incubation of "a substance which inhibits binding of immunoglobulin G to the solid phase and inhibits binding of [the] . . . antigen to immunoglobulin G" with an immobilized anti-IgX antibody, a sample, and an antigen-specific label.

With respect to the rejection of claims 8 and 22, the examiner additionally cited Molinaro for teaching the limitation that “the labeling means are erythrocytes.” Molinaro does not remedy the deficiency discussed above. The rejection of claims 8 and 22 is also reversed.

Summary

The cited references do not teach or suggest simultaneous incubation of all the reagents recited in claims 16 and 17, and therefore do not render the claimed methods prima facie obvious. The rejections under 35 U.S.C. § 103 are reversed.

REVERSED

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