

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 27

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte JOACHIM ALBRECHT, FRANK HULSTAERT and ROSETTE BECKER

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Appeal No. 2001-1431  
Application 07/968,553

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ON BRIEF

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Before ROBINSON, ADAMS, 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 1-8. Claims 1 and 4 are representative and read as follows:

1. A method for establishing a decision point in order to determine if an unknown sample of cells is positive or negative for a marker comprising the steps of:
  - a) tagging multiple samples of cells which are known to be positive or negative for the presence of the marker with a fluorescent marker that is specific for the marker of interest;

- b) analyzing each of samples of tagged cells by means of flow cytometry and recording the median fluorescence channel for each sample;
- c) setting acceptance criteria for assay sensitivity and specificity;
- d) determining the fluorescence channel number at which the criteria are met; and
- e) utilizing said fluorescence channel number as the decision point such that samples having a median fluorescence channel that exceeds the decision point are classed positive for the marker.

4. The method of claim 1 wherein the marker of interest is HLA-B27.

The examiner relies on the following references:

Schwartz	5,073,497	Dec. 17, 1991
Ellis et al. (Ellis)	4,447,528	May 08, 1984
McKenzie et al. (McKenzie)	5,059,524	Oct. 22, 1991

DAKO Corp. (DAKO Bulletin), "The CD System, Classification of Human Leucocyte Antigen," DAKO Corporation, USA (1990)

Claims 1-3 stand rejected under 35 U.S.C. § 103 as obvious over Schwartz in view of Ellis.<sup>1</sup>

Claims 4 and 5 stand rejected under 35 U.S.C. § 103 as obvious over Schwartz, Ellis, and McKenzie.

Claims 6-8 stand rejected under 35 U.S.C. § 103 as obvious over Schwartz, Ellis, McKenzie, and the DAKO Bulletin.

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<sup>1</sup> The examiner's statement of this rejection in the Examiner's Answer (page 2) does not mention Ellis. It is clear from the examiner's explanation, however, that the rejection is based on the combination of Schwartz and Ellis. See the Examiner's Answer, page 4. This is also the basis on which the claims were finally rejected (Paper No. 18, page 2) and the basis on which Appellants

We reverse all of the rejections.

### Background

The specification discloses

a method for establishing and using a decision point in flow cytometry wherein the decision point defines a point on the axis of a fluorescence histogram for a fluorescent marker of interest such that if the median channel number of cells stained with that fluorescent marker is greater than the decision point then the sample is said to be “positive” for the fluorescence marker used.

Page 1. The specification provides a working example that applies the disclosed method to detecting cells positive for the marker HLA-B27. See pages 8-17.

### Discussion

The examiner rejected all of the claims as obvious based on the combination of Schwartz and Ellis, with McKenzie and the DAKO bulletin cited to meet limitations of the dependent claims. Thus, all of the rejections rely on the combination of Schwartz and Ellis.

The examiner states that “Schwartz teaches a method of calibrating a flow cytometer using fluorescent microbeads, prior to analyzing cell samples.”

Examiner’s Answer, page 3. The examiner states that Schwartz’s calibration method is intended “to achieve reproducible, repeatable results,” but “differs from the instant invention in failing to teach using multiple known positive or negative samples to determine a cut-off point in deciding whether a sample is positive or negative for a marker of interest.” Id. at page 4.

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argued the merits of the rejection. See the Appeal Brief, page 4. Thus, the omission of Ellis from the statement of the rejection appears to have been an oversight and caused no confusion.

The examiner finds this deficiency to be remedied by Ellis, who teaches “an immunoassay method . . . in which positive and negative calibration standards are used to determine the cut-off point between positive and negative samples.” Id. The examiner concludes that “[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to use the cut-off determination of Ellis et al for determining the median channel of the standard microbeads in the method of Schwartz because Ellis et al teach using positive and negative calibrators [to] achieve a rapid, accurate cut-off for qualitative determinations of disease in samples.” Id.

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of going forward with evidence or argument shift to the applicant.” In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). The test of obviousness is “whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention.” In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

Prima facie obviousness based on a combination of references requires that the prior art provide “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).

[E]vidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. . . . The range of sources available, however,

does not diminish the requirement for actual evidence. That is, the showing must be clear and particular.

In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (citations omitted). The suggestion to combine prior art references must come from the cited references, not from the application's disclosure. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In this case, the examiner has not adequately shown that those skilled in the art would have been motivated to combine the teachings of the cited references. The assay described by Ellis is directed at detecting the presence of "auto blocking" antibodies (autoimmune antibodies that block cellular receptors) by measuring the reduction in binding of a labeled ligand to immobilized receptor, in the presence of serum containing auto blocking antibodies. Ellis describes the use of positive and negative calibrators to aid in determining whether a given assay result is positive for the presence of auto blocking antibodies. Ellis does not suggest the need for such calibrators in other assays.

Schwartz is addressed to ensuring consistency in flow cytometry measurements. See column 3, lines 19-30 ("It is therefore an object of the present invention to provide a method for adjustment of a flow cytometer for analysis of selected samples, . . . in a manner achieving reproduceability [sic] of data which is independent of the specific instrument and time-frame of the data measurement and of the compensation of the instrument."). Schwartz does not discuss use of positive or negative calibrators (i.e., samples corresponding to a positive or negative measurement) in flow cytometry.

The examiner has not adequately explained why a person of skill in the art would have been motivated to combine the positive and negative calibrators, used by Ellis in an immunoassay, with the flow cytometry technique disclosed by Schwartz. The references are directed to different problems encountered when using different techniques. There is simply nothing in the cited references that bridges the gap between their respective teachings. There is no suggestion, for example, that the reproducibility problem addressed by Schwartz could also be solved by the use of Ellis' calibrators.

The examiner asserted that those skilled in the art would have appreciated the applicability of Ellis' calibrators to Schwartz's method because

both radioimmunoassay and flow cytometry are directed toward the detection and/or quantitation of an analyte, both use a labeling system for the detection of said analyte and both use some type of standards or controls to aid in the detection of the analyte, therefore, the principle of negative/positive controls found to be effective in one type of detection assay should also be expected to provide the same function in a similar type of detection assay.

Examiner's Answer, pages 7-8. While this rationale may be enough to establish a reasonable expectation of success, it does not establish adequate motivation to combine the references. First, we disagree that Schwartz "use[s] some type of standards or controls to aid in the detection of the analyte," as the examiner characterizes it. Schwartz's use of standards is not intended to aid in determining whether a given measurement corresponds to a positive result, but only to ensuring that measurements taken at different times, using different machines, are reproducible.

The examiner also states that both Ellis and Schwartz “are directed toward the detection and/or quantitation of an analyte [and] both use a labeling system for the detection of said analyte.” The examiner has not adequately explained, however, how these similarities would have motivated those skilled in the art to apply the positive and negative calibrators of Ellis to the flow cytometry technique of Schwartz.

Finally, the examiner has asserted that “the level of skill for an ordinary artisan in the field of flow cytometry is high, and an ordinary skill artisan in this field would have known that conventional use of positive and negative samples to determine a cut-off point is applicable in a variety of assays.” Examiner’s Answer, page 8. However, a high level of skill in the art cannot be relied on to supply a motivation missing from the prior art. See In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) (“While the skill level is a component of the inquiry for a suggestion to combine, a lofty level of skill alone does not suffice to supply a motivation to combine. . . . Even when the level of skill in the art is high, the [examiner] must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination.”).

Thus, we conclude that the cited references do not provide the required “reason, suggestion, or motivation” to combine their respective teachings. Where the prior art does not provide motivation to combine the teachings of the cited references, rejection for obviousness is improper. Since all of the rejections on appeal rely on the combination of Schwartz and Ellis, we reverse all of the rejections under 35 U.S.C. § 103.

Other Issues

We have to wonder whether the closest prior art has been applied in this case. For example, U.S. Patent 5,369,010 discloses an immunoassay for HLA B27 in which several cell lines, including two cell lines known to express B27 and one known not to express B27, were analyzed by flow cytometry.<sup>2</sup> See column 8, line 57 to column 9, line 12. This patent appears highly relevant to the instant claims but has not previously been considered on the record. Although the ultimate decision on whether the pending claims are patentable rests with the primary examiner, we urge the examiner to thoroughly consider the patentability of the instant claims in view of the '010 patent and any other pertinent prior art. A copy of the '010 patent is attached to this opinion.

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<sup>2</sup> The '010 patent issued November 29, 1994, but has an effective filing date of August 16, 1985.

Summary

We reverse the § 103 rejections because the prior art does not provide adequate motivation to combine the teachings of Schwartz and Ellis.

REVERSED

Douglas W. Robinson	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
Donald E. Adams	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	
Eric Grimes	)	
Administrative Patent Judge	)	

EG/dm

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