

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 28

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte RICHARD S. KALISH

Appeal No. 2002-1355
Application No. 08/907,783

ON BRIEF

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 1, 3-15, 18-23, 25, 27-44, 47-52, and 54, all of the claims remaining. Claim 1 is representative and reads as follows:

1. A method for screening a test compound for the ability of the test compound to induce a response from human naive T-cells, the method comprising:

obtaining a sample of human blood, wherein the sample of human blood contains human naive T cells and macrophages/monocytes;

admixing the sample of human blood with immortalized B cells lacking class I and class II major histocompatibility antigens

and with a test compound, wherein the B cells act as co-stimulatory molecules; and

determining whether the test compound induces a response from the human naive T cells.

The examiner relies on the following references:

Ho	5,106,746	Apr. 21, 1992
Engleman	WO 94/02156	Feb. 3, 1994

Schwartz, "The Role of Gene Products of the Major Histocompatibility Complex in T Cell activation and Cellular Interactions," Fundamental Immunology, Chp. 15, pp.379-438 (1984)

Del Prete et al. (Del Prete), "Purified Protein Derivative of Mycobacterium tuberculosis and Excretory-Secretory Antigen(s) of Toxocara canis Expand In Vitro Human T Cells with Stable and Opposite (Type 1 T Helper or Type 2 T Helper) Profile of Cytokine Production," J. Clin. Invest., Vol. 88, pp. 346-350 (1991)

ATCC Cell and Hybridoma on-line catalog (ATCC number CRL-1992); (1995)

Mehta-Damani et al. (Mehta-Damani), "Generation of antigen-specific CD4⁺ T cell lines from naive precursors," Eur. J. Immunol., Vol. 25, pp. 1206-1211 (1995)

Yokozeki et al. (Yokozeki), "Experimental Study for the Development of an in vitro Test for Contact Allergens," Int Arch Allergy Immunol, Vol. 106, pp. 394-400 (1995)

Li et al. (Li), "Evaluation of cross-sensitization among dye-intermediate agents using a modified lymphocyte transformation test," Arch Toxicol, Vol. 70, pp. 414-419 (1996)

Krasteva et al. (Krasteva), In vitro primary sensitization of hapten-specific T cells by cultured human epidermal Langerhans cells – a screening predictive assay for contact sensitizers," Clinical and Experimental Allergy, Vol. 26, pp. 563-570 (1996)

Goronzy et al. (Goronzy), "Immunoregulatory Effects of Borrelia burgdorferi on T-B Cell Interactions, Journal of Rheumatology, Vol. 19, No. 4, pp. 573-578 (1992)
Rietschel, "Occupational contact dermatitis," Lancet, Vol. 349, pp. 1093-1095 (1997)

The claims stand rejected under 35 U.S.C. § 103 as obvious in view of the following combinations of references:¹

- Claims 1, 15, 18, 19, 32, 44, 47, and 48 in view of Yokozeki, Goronzy, Schwartz, and the ATCC catalog.
- Claims 3-5 and 33-35 in view of Yokozeki, Goronzy, Schwartz, the ATCC catalog, Krasteva, and Rietschel.
- Claims 6-10, 14, 36-39, and 43 in view of Yokozeki, Goronzy, Schwartz, the ATCC catalog, Engleman, and Ho.
- Claims 11-13 and 40-42 in view of Yokozeki, Goronzy, Schwartz, the ATCC catalog, Krasteva, and Li.
- Claims 20-23, 49-52, and 54 in view of Yokozeki, Goronzy, Schwartz, the ATCC catalog, and Mehta-Damani.
- Claims 27-31 in view of Yokozeki, Goronzy, Schwartz, the ATCC catalog, and Del Prete.

We reverse all of the rejections.

Background

“There is a great need for in vitro methods for testing allergenicity of compounds. . . . In particular, a method is needed to screen for potential allergens in products intended for topical application, such as cosmetics.”

Specification, page 1. “Allergic contact dermatitis is mediated by T-lymphocytes. . . . Allergens thus function as antigens to induce a T-lymphocyte response.” Id., page 2.

“Primary in vitro sensitization is the sensitization of naive T-lymphocytes to antigens which the donor has never encountered. Other investigators have been unable to achieve primary in vitro sensitization without the use of dendritic cells.”

¹ None of the rejections set out in the Examiner’s Answer included claim 25. Since claim 25 was rejected in the final Office action (Paper No. 14, mailed Jan. 27, 2000), it is unclear whether or not the rejection of claim 25 was withdrawn. In view of our disposition of the rejections on appeal, however, the issue is moot.

Id. “The ability of dendritic antigen presenting cells to induce a primary immune response to a novel antigen is probably a function of the high expression of co-stimulatory molecules by these cells.” Id. Such co-stimulatory signals are essential for inducing T-cell proliferation. See id., pages 2-3. Dendritic cells, however, “are difficult to isolate in significant numbers, which greatly limits their application to a commercial assay.” Id., page 2.

The specification discloses a method for achieving “primary in vitro sensitization without the use of dendritic cells. This is achieved, in one embodiment, by adding Epstein Barr virus (EBV) transformed human B-cells as a source of co-stimulatory molecules. The human B-cell line used as a source of co-stimulatory molecules lacks the major histocompatibility transplantation antigens HLA-DR, and HLA-A,B,C. This permits the use of these B-cells with lymphocytes from unrelated donors. . . . Culture of these co-stimulatory B-cells lacking transplantation antigens, with human lymphocytes, monocytes, and allergen, induces primary in vitro sensitization of T-lymphocytes to the allergen. Peripheral blood monocytes function as antigen presenting cells in this system, since the co-stimulatory B-cells lack antigen presenting molecules. . . . This culture system . . . can function as an in vitro screen for allergenic compounds.”

Page 9.

Discussion

The claims are directed to a method for screening a test compound (i.e., a potential allergen) for the ability to induce a response in naive T-cells. The claimed method comprises obtaining a sample of human blood that contains

naive T cells and macrophages/monocytes, mixing the blood sample with (1) a test compound and (2) immortalized B cells lacking class I and class II major histocompatibility (MHC) antigens, then determining whether the test compound induces a response from the T-cells. See, e.g., claim 1.

The examiner rejected all of the claims as obvious. The Examiner's Answer sets out fifteen separate § 103 rejections, which are based on six different sets of references. All of the rejections, however, rely (at least in part) in the combination of Yokozeki, Goronzy, Schwartz, and the ATCC catalog. We will start, therefore, with these references.

The examiner characterized Yokozeki as teaching "a method for screening test compounds for the ability to induce a response from mouse naive T cells." Examiner's Answer, page 3. According to the examiner, "[t]he claimed invention differs from the reference only by the recitation of the addition of immortalized B cells which lack class I and class II major histocompatibility complex antigens in place of the keratinocyte cell line" used by Yokozeki. Id., page 4. The examiner cited Goronzy, Schwartz, and the ATCC catalog to make up this difference.

According to the examiner,

- Goronzy "teaches a method of using purified human B cells obtained from peripheral blood that act as antigen presenting cells to stimulate naive T cells in the presence of Borrelia burgdorferi antigen and monocytes,"
- "Schwartz teaches the high frequency of alloreactive T cells that recognize major histocompatibility complex molecules," and
- the ATCC catalog "lists an immortalized human B cell line (T2) which . . . lacks HLA-DR (class II major histocompatibility complex antigens) and does not express class I major histocompatibility complex." Id.

The examiner concluded that it would have been obvious to “use the immortalized B cell line (T2) that lacks major histocompatibility complex antigens taught by [the ATCC catalog], to avoid alloreactivity of T cells taught by [Schwartz], in place of the B cells taught by [Goronzy] in the in vitro allergen system taught by Yokozeki . . . in order to be able to reconstruct in vitro all the necessary components to detect the presence of allergens without having to purify B cells from health donors and to provide a reproducible source of antigen presenting cells.” Examiner’s Answer, pages 4-5.

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness.” In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). “The 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. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure.” In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) (citations omitted).

Appellant argues that the references do not support a prima facie case of obviousness. Among other things, Appellant argues that even if the references were “combined in the manner suggested by the PTO, the method would not work to screen a test compound.” Appeal Brief, page 7. In particular, Appellant argues that, if the references are combined as suggested by the examiner, “one

obtains T2 cells of ATCC as antigen presenting cells, T cells depleted of autoreactivity, and macrophages as co-stimulatory molecules. However, this method could not be used to induce a response from T-cells, because the T2 cells CANNOT present antigen (because they lack MHC I and MHC II).” Id., pages 7-8. Appellant cites Example III from the present specification as supporting this argument.

We agree with Appellant that the references cited by the examiner do not support a prima facie case of obviousness. We note initially that the examiner appears to overstate the similarities between the claimed method and that of Yokozeki. The examiner characterizes the reference as disclosing all of the limitations of the claimed method except that it uses keratinocyte cells instead of B cells lacking MHC class I and class II antigens, but Yokozeki’s method also differs by using purified T cells and macrophages, not a blood sample as in the claimed method. Nonetheless, we can accept the examiner’s characterization of the reference for present purposes, because we agree with Appellant that the relied-upon combination of references has a more fundamental flaw.

The record supports Appellant’s position that cells that lack class I and class II MHC antigens cannot function as antigen-presenting cells. See, e.g., the specification’s Example III, which is headed “In vitro sensitization induced by T2 cells is mediated by T-cells, and is dependent upon non-T cells to present antigen.” Page 14. The portion of the specification states that “T-cells admixed with T2 cells in the absence of non-T cells gave no response, indicating that the T2 cells are not sufficient for antigen presentation, and autologous non-T cells

(e.g. monocytes, macrophages) are required. The T2 cells are not functioning as antigen presenting cells (which is to be expected since the T2 cells lack antigen presenting Major Histocompatibility Complex antigens HLA-DR and HLA-A,B,C), but rather function as accessory cells.” Page 14.

In Yokozeki’s assay system, by contrast, the keratinocytes function as antigen-presenting cells. See Yokozeki, page 394: “We conducted a study on the primary in vitro activation of T cells from non-sensitized mice by using hapten-conjugated Pam 212 cells (keratinocyte cell line). . . . Monolayered Pam 212 cells were incubated with a variety of chemicals exhibiting allergic potential. . . . T cells and macrophages . . . were cocultured for 5 days with those monolayered Pam cells conjugated with chemicals.” See also page 399:

[W]e examined whether or not primary activation of T cells from nonsensitized Balb/c mice can be induced by hapten-conjugated Pam cells and macrophages instead of hapten-conjugated Langerhans [dendritic] cells. . . .

The role of the Pam cells and macrophages in our system remains unclear. . . . Fahr et al. recently suggested that keratinocyte (KC)-derived protein but not 3T3-fibroblast-derived protein can serve as antigenic carriers for hapten. Our data are consistent with those of Fahr et al.

One possibility of the mechanism in our system is that macrophages may play a role as antigen-processing cell and be required as the source of a costimulatory signal (2nd signal) and the Pam cell[s] may serve as antigen carriers for hapten. This possibility is currently under investigation.

(Reference citations omitted.)

The examiner has not adequately explained what would have led those skilled in the art to replace the prior art's antigen-presenting cells with cells that were known to be incapable of functioning as antigen-presenting cells. The examiner's response to Appellant's argument on this point, as we understand it, is that the assay resulting from the combined references would not be inoperable because the sample of human blood used in the assay would contain macrophages, which could function as antigen-presenting cells. See the Examiner's Answer, pages 24-25.

This response is inadequate. The examiner has not rejected the claims under 35 U.S.C. § 101 or otherwise disputed that the assay defined by the claims would be operable. The issue is whether those of skill in the art would have expected that the assay resulting from the combined references would have been operable. If not, there would have been no reason to combine those teachings. The examiner states that "one of ordinary skill in the art at the time the invention was made would have been motivated to use the immortalized B cell line (T2) . . . in order to present antigen (Borrelia burgdorferi antigen) that is present in very low concentrations, as taught by Goronzy." The evidence of record does not support this rationale. The rejection is therefore reversed.

Summary

The disclosures of Yokozeki, Goronzy, Schwartz, and the ATCC catalog would not have made the method of claim 1 prima facie obvious to those of ordinary skill in the art. All of the examiner's other rejections also depend on this

same combination of references, and those rejections therefore fail for the same reasons discussed above. The rejections under 35 U.S.C. § 103 are reversed.

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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