

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

Paper No. 13

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte MICHAEL G. ROSENBLUM and NICHOLAS J. DONATO

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Appeal No. 1997-3542  
Application No. 08/192,507

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ON BRIEF

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Before WILLIAM F. SMITH, SPIEGEL and MILLS Administrative Patent Judges.

MILLS, 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 appealed claims 1-7 and 11-17. Claims 8-10 and 18-20, the only other claims pending in the application, have been withdrawn from consideration by the examiner.

We affirm-in-part.

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Claims 1, 3 and 14 are illustrative of the claims on appeal and reads as follows:

1. An anti-IgM antibody conjugate comprising:  
a monoclonal antibody which binds selectively to IgM antibody, does not bind to IgG<sub>1</sub> or IgG<sub>2</sub> antibody, has a G isotype; and a cytotoxic moiety conjugated to aid monoclonal antibody.

3. The conjugate of claim 1, wherein said monoclonal antibody is produced by a hybridoma named 2G10.

14. The conjugate of claim 11, wherein said monoclonal antibody is either produced by the 1C2 hybridoma.

The prior art references of record relied upon by the examiner in rejecting the appealed claims are:

Julius et al. (Julius), "Induction of resting B cells to DNA synthesis by soluble monoclonal anti-immunoglobulin," Eur. J. Immunol. Vol. 14, pp. 753-757 (1984).

Kung et al. (Kung), "A Mouse IgM Allotypic Determinant (Igh-6.5) Recognized by A Monoclonal Rat Antibody," The Journal of Immunology, Vol. 127, No. 3, pp. 873-876 (1981).

Lambert et al. (Lambert), "Purified Immunotoxins That Are Reactive with Human Lymphoid Cells," The Journal of Biological Chemistry, Vol. 260, No. 22, pp.12035-12041 (1985).

Taylor et al. (Taylor), "Redistribution and Pinocytosis of Lymphocyte Surface Immunoglobulin Molecules Induced by Anti-Immunoglobulin Antibody," Nature New Biology, Vol. 233, pp.225-229 (1971).

DeClercq et al. (DeClercq), "Generation of Rat - Rat Hybridomas with the Use of the LOU IR983F Nonsecreting Fusion Cell Line," Methods in Enzymology, Vol. 121, pp. 234-238 (1986).

Brady et al. (Brady), "Therapeutic and Diagnostic Uses of Modified Monoclonal Antibodies," L.J. Radiation Oncology Biology Physics, Vol. 13, No. 10, pp.1535-1544 (1986).

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Reference relied on by appellant:

Ritz et al. (Ritz), "Expression of Common Acute Lymphoblastic Leukemia Antigen (CALLA) by Lymphomas of B-Cell and T-Cell Lineage," Blood, Vol. 58, No. 3, pp. 648-662 (1981).

### OPINION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, to the applied prior art references, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellants regarding the above-noted rejection, we make reference to the examiner's answer (Paper No. 12, mailed February 12, 1997) for the examiner's complete reasoning in support of the rejection, and to the appellants' brief (Paper No. 9, filed May 23, 1996) for the appellants' arguments thereagainst. As a consequence of our review, we make the determinations which follow.

#### Issues

1. The specification is objected to and claims 3 and 14 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.
2. Claim 14 stands rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which appellants regard as the invention.

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3. Claims 1, 2, 6, 7, 11, 12, 16 and 17 stand rejected under 35 U.S.C. § 103 over Julius and Kung, taken with Lambert and Taylor.

4. Claims 3, 4, 14 and 15 stand rejected under 35 U.S.C. § 103 over Julius and Kung, taken with Lambert and Taylor and further in view of De Clercq.

5. Claims 5 and 13 stand rejected under 35 U.S.C. § 103 over Julius and Kung, taken with Lambert and Taylor, as applied to claims 1, 2, 5-7, 11-13, 16 and 17, and further in view of Brady.

#### DECISION ON APPEAL

##### 35 U.S.C. § 112, first paragraph

The specification is objected to and claims 3 and 14 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.<sup>1, 2</sup>

In the present case, the rejected claims are directed to an anti-IgM antibody conjugate wherein the antibody portion of the conjugate is produced from specific hybridoma, i.e., 2G10 (claim 3) and 1C2 (claim 14). It is the examiner's position that the methods set forth in the specification will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. Furthermore,

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<sup>1</sup> The Answer has withdrawn a rejection of claims 5, 7, 13 and 17 under 35 U.S.C. § 112, first paragraph for lack of enablement. Answer, page 3.

<sup>2</sup> The Answer, page 8 contains a typographical error, and inaccurately indicates claims 3 and 4 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement instead of claims 3 and 14, as set forth in the final rejection, Paper No. 5, page 2.

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the examiner states that the specification fails to provide an adequate written description of the invention and fails to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials. Paper No. 5, page 2. The examiner acknowledges that appellants have made reference to a deposit of 2G10 hybridoma ATCC HB10436 on page 19 of the specification, but indicates that appellants have failed to provide sufficient assurances that the required deposit has been made and that all the conditions of 37 CFR § 1.801-1.809 have been met. In addition, the examiner indicates that appellants have failed to address the requirement for deposit of 1C2 hybridoma reference in claim 14.

In order to sustain a rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. See In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In the present case, we believe that the examiner has met this burden.

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Thus, the burden shifts to the appellants to rebut the prima facie case of lack of enablement established by the examiner. Appellants respond to this rejection by indicating that the 2G10 cell line was deposited with the ATCC on April 23, 1990 and was given Deposit Accession No. ATCC HB 10436. Appellants do not provide arguments or evidence as to why a deposit of 2G10 and IC2 are not required.

As acknowledged by the examiner, the appellants have failed to provide sufficient assurances that the required deposit has been made and all the conditions of 37 CFR § 1.801-1.809 have been met. In addition, appellants have failed to address the requirement for deposit of 1C2 hybridoma reference in claim 14.

It would appear that the appellants have failed to meet their burden in rebutting the examiner's prima facie case of lack of enablement and, therefore, the rejection under 35 U.S.C. § 112, first paragraph for lack of enablement is sustained.

35 U.S.C. § 112, second paragraph

Claim 14 stands rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which appellants regard as the invention. The examiner states that claim 14 is indefinite due to the recitation of "either" in the claim, which renders the claim confusing.

The appellants acquiesce to this rejection. Brief, page 5.

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In view of the above, the rejection of claim 14 under 35 U.S.C. § 112, second paragraph is sustained.

35 U.S.C. § 103

Claims 1, 2, 6, 7, 11, 12, 16 and 17 stand rejected under 35 U.S.C. § 103 over Julius and Kung, taken with Lambert and Taylor.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is established by presenting evidence that the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the proposed combination or other modification. See In re Lintner, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Furthermore, the conclusion that the claimed subject matter is prima facie obvious must be supported by evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to combine the relevant teachings of the references to arrive at the claimed invention. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Rejections based on § 103 must rest on a factual basis with these facts being interpreted without hindsight reconstruction of the invention from the prior art. The

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examiner may not resort to speculation, unfounded assumption or hindsight reconstruction to supply deficiencies in the factual basis for the rejection. See In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968). With this as background, we analyze the prior art applied by the examiner in the rejection of the claims on appeal.

As background, the anti-IgM antibody conjugate, as claimed, may be used, for example, for in vivo suppression of IgM producing cells (specification page 11), as cytotoxic radiopharmaceuticals for eliminating IgM producing hybridoma cells (specification, page 12), and in cell sorting procedures to separate IgM producing hybridoma cells from IgG producing hybridoma cells (specification page 12).

Julius discloses the production and isolation of hybridomas which secrete IgG monoclonal antibodies which are specific for mouse IgM, do not bind to IgG isotypes, and which bind to surface IgM on B cells. Julius, page 764, column 1 and page 756, column 2. Julius assesses the effects of antibodies specific for surface immunoglobulins on B cell growth and differentiation. The antimouse IgM antibodies of Julius are used to stimulate splenic B cells and induce DNA synthesis in the B cells. Julius, abstract and page 754, column 2.

Kung indicates that IgG1 monoclonal rat anti-mouse IgM antibodies Bet 1 and Bet 2 bind to surface IgM on B lymphocytes but do not bind to IgG isotypes. Kung also

discloses the antibodies may be fluorescein-labeled. Kung, abstract and page 874, column 1. Kung provides rat anti-mouse IgM antibodies bind to an allotypic determinant of mouse IgM. The examiner acknowledges that neither Julius nor Kung teach the referenced monoclonal antibodies linked to a cytotoxic moiety. Answer, page 10.

The examiner relies on Lambert for the production of several different immunotoxins specific for surface markers on B cells and other lymphoid cells. The immunotoxins are prepared by conjugating monoclonal antibodies to cytotoxic moieties, including the ribosome inactivating protein, gelonin, and pokeweed anti-viral protein. Lambert, page 12035. Lambert describes seven different monoclonal antibodies of the IgG class which bind to four different antigens on human B cells and other lymphoid cells which may be used to prepare the immunotoxins. Lambert suggests that receptor-mediated endocytosis of an antigen/immunotoxin complex may be essential for cytotoxicity and provides evidence that CALLA and Ia antigens are internalized by B cells and that the B1 antigen shows no tendency of being internalized. Lambert, page 12036. The lack of cytotoxicity of the anti-B1 immunotoxins is attributed to the fact that anti-B1 immunotoxins are not internalized and are not transported into the cell. Lambert does not specifically suggest that the antibody linked to the immunotoxin be specific for IgM antigen on B cells. The disclosure of Taylor is cumulative in some respects to that of Lambert,

indicating that antibodies against surface immunoglobulins, such as IgM, cause antibody bound surface IgG molecules to cap and then be internalized.

It would appear from Lambert that certain antibody-toxin conjugates to human lymphoid cell surface antigens are known in the prior art. It would appear from Julius and Kung that anti-IgM antibodies having the claimed properties are also known in the prior art. The question then becomes whether the examiner has established a factual basis providing a reason, suggestion or motivation for using the known antibodies to form the claimed antibody-toxin conjugates, and whether one of ordinary skill in the art would have had an expectation of success that the antibody-toxin conjugates would function as claimed.

It is the examiner's position that [Answer, page 11]:

[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the cited prior art and to conjugate the anti-IgM monoclonal antibodies taught by Kung et al. and Julius et al. according to the methods of Lambert et al. One of ordinary skill in the art would have been motivated to do so in view of the teaching of Lambert et al., that immunotoxins comprising monoclonal antibodies specific for surface markers on lymphoid cells conjugated to cytotoxic moieties such as gelonin and PAP were considered to be useful for in vitro assays in order to examining [sic, examine] the effect of various parameters on cytotoxicity of immunotoxins in order to determine how to improve the efficacy of immunotoxins.

One of ordinary skill in the art would have expected that anti-IgM immunotoxins would be internalized after binding IgM molecules on the surface of a B cell and once internalized, to exhibit toxicity as did the immunotoxins made by Lambert, et al.

Thus, the examiner urges that Lambert provides a reason, suggestion or motivation for using anti-IgM antibodies in in vitro assays and an expectation of success that such antibodies, when in the form of conjugates, would be cytotoxic. Answer, page 12.

What appears to be missing from the examiner's analysis is why one of ordinary skill in the art would have been motivated to link the antibodies of Julius or Kung to a cytotoxic moiety to form an immunotoxin to destroy B-cells. The antimouse IgM antibodies of Julius were used to stimulate and induce DNA synthesis in B cells, not to destroy the B cells. Julius, abstract and page 754, column 2. In view of this, the examiner has not indicated why one of ordinary skill in the art would use the antimouse IgM antibodies of Julius for the purpose of destroying B cells. If taken to its logical conclusion, the combination of Lambert with Julius would render Julius inoperable for its intended purpose, which is to stimulate DNA synthesis in B cells, not destroy B cells. In re Gordon, 733 F. 2d 900, 221 USPQ 1125 (Fed. Cir. 1984); In re Schulpen, 390 F.2d 1009, 1013, 157 USPQ 52, 55 (CCPA 1968). Nor do we find the proper motivation to be supplied by Kung.

Additionally, an artisan is not compelled to blindly follow the teaching of one prior art reference over the other without the exercise of independent judgment. See Lear Siegler, Inc. v. Aeroquip Corp., 733 F.2d 881, 889, 221 USPQ 1025, 1032 (Fed. Cir.

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1984). Our reviewing court in In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1331 (Fed. Cir. 1994) stated:

A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.

In the present case, Julius would appear to teach one of ordinary skill in the art away from using the anti-mouse IgM monoclonal antibodies of Julius to destroy B cells as Julius suggests that such antibodies be used to induce DNA synthesis in B-cells.

Appellants submit that Lambert does not teach or suggest that one could target B-cells for destruction using IgM as the target cell surface antigen. Brief, page 10.

Appellants also argue “that there is no teaching, suggestion or incentive in the cited references which would motivate one with ordinary skill in the art to use an immunotoxin to kill IgM bearing normal B-cells” and that the examiner has not indicated such motivation. Brief, page 11. We agree.

Furthermore, it is well settled that in making obvious determinations, one must look to the problem solved by the inventors in relation to those solved by the prior art. When comparing the differences between the structure and properties taught in the prior art and those of the applicants' invention, there is a need to include consideration of the problems solved by the inventor. See In re Wright, 848 F.2d 1216, 6 USPQ2d 1959 (Fed. Cir. 1988).

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In the present case, appellants provide for a method of killing IgM producing hybridoma or B cells by contacting the cells with a cytocidally effective amount of the immunotoxins. Specification pages 4, 11 and 12. The appellants recognize a problem in the hybridoma art, wherein, in mixed cultures of IgM and IgG secreting hybridoma cells, IgM secreting cells often over grow the IgG secreting cells. This problem calls for the elimination of IgM producing hybridoma cells after cell fusion. Specification, page 2. Appellants' anti-IgM antibody-cytotoxin conjugate and method provide a solution to this problem. The examiner has provided no evidence as to why one of ordinary skill in the art would link the antibodies of Julius or Kung to a cytotoxic moiety as disclosed by Lambert, to destroy B-cells. None of the cited references recognize or provide a solution to the problem addressed by appellants' conjugate.

After evidence or arguments are submitted by the appellants in response to rejection based on obviousness, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of the argument. We have carefully studied the arguments and evidence of record. On balance, we believe that the totality of the evidence presented by the examiner and appellants weighs in favor of finding the claimed invention nonobvious in view of the cited references. The rejection of claims 1, 2, 6, 7, 11, 12, 16 and 17 under 35 U.S.C. § 103 for obviousness is reversed.

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35 U.S.C. § 103

Claims 3, 4, 14 and 15 stand rejected under 35 U.S.C. § 103 over Julius and Kung, taken with Lambert and Taylor and further in view of De Clercq.

The examiner relies on De Clercq for the disclosure of methods for generating rat-rat hybridomas and argues that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use either mouse or rat myeloma as an immortalizing fusion partner for making rat or mouse myeloma and represents an experimental design choice between two equally appropriate alternatives. The examiner argues that there is no evidence of record to establish that the claimed immunotoxins made with a rat monoclonal antibody are unobviously or unexpectedly different from immunotoxins made with a mouse monoclonal antibody.

The examiner argues that claims to specific monoclonal antibodies are obvious because they appear to be functionally the same as those taught in the prior art and that the record contains no evidence to establish that the 1C2 and 2G10 monoclonal antibodies or conjugates comprising those antibodies differ in any unexpected or unobvious manner from those that one of ordinary skill in the art would have expected to obtain in view of the teachings of the cited prior art.

Appellants argue the primary combination of references is without proper motivation. As indicated above, we agree. Furthermore, DeClercq does not cure the

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deficiencies of the primary references. In view of the above, the rejection of claims 3, 4, 14 and 15 under 35 U.S.C. § 103 is reversed.

#### 35 U.S.C. § 103

Claims 5 and 13 stand rejected under 35 U.S.C. § 103 over Julius and Kung, taken with Lambert and Taylor, as applied to claims 1, 2, 5-7, 11-13, 16 and 17, and further in view of Brady.

The examiner relies on Brady for the teaching of the production of radionucleotides for use in diagnostic imaging. The examiner argues that it would have been obvious to one of ordinary skill in the art at the time of the present invention to produce immunotoxins containing radiolabelled <sup>131</sup>I as the cytotoxic agent moiety in view of the demonstrated use of <sup>131</sup>I for this purpose.

Having found the primary combination of references to be without proper motivation and that Brady does not cure the deficiencies of the primary references, the rejection of claims 5 and 13 under 35 U.S.C. § 103 is reversed.

#### Other Issue

We also note that the oath or declaration filed in the application remains defective, as set forth in Paper No. 2, page 3. Should prosecution of the subject

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matter of the present application continue, submission of an appropriate oath or declaration in compliance with 37 CFR §§ 1.63(5)(e) and 1.67 is required.

CONCLUSION

To summarize, the decision of the examiner to reject claims 3 and 14 under 35 U.S.C. § 112, first paragraph is affirmed, to reject claim 14 under 35 U.S.C. § 112, second paragraph is affirmed and to reject claims 1-7 and 11-17 under 35 U.S.C. § 103 is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRM-IN-PART

WILLIAM F. SMITH	)
Administrative Patent Judge	)
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	)
	) BOARD OF PATENT
CAROL A. SPIEGEL	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
	)
DEMETRA J. MILLS	)
Administrative Patent Judge	)

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BENJAMIN ADLER  
GILBRETH & ADLER  
8011 CANDLE LANE  
HOUSTON, TX 77071

DJM/jlb