

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 35

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ALAN L. EPSTEIN
and CLIVE R. TAYLOR

Appeal No. 96-2137
Application 07/668,920¹

HEARD: November 10, 1997

Before WILLIAM F. SMITH, ELLIS, and WEIMAR, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

¹ Application for patent filed March 13, 1991. According to appellants, the application is a division of 07/314,437, filed February 23, 1989, now Patent No. 5,019,368; which is a division of Application 06/938,425, filed December 5, 1986, now Patent No. 4,861,581.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 18, 19, 21 through 38, and 40 through 42. Subsequently, claims 29 through 38, 40, and 42 were canceled, leaving claims 18, 19, 21 through 28, and 41 for our consideration. Claims 18 and 41 are illustrative of the subject matter on appeal and read as follows:

18. A method for measuring neoplastic tissue in a mammal, comprising the steps of:
obtaining an antibody that binds to insoluble intracellular antigens of necrotic neoplastic tissue but does not substantially bind to living neoplastic tissue, said antibody being labeled;
contacting said labeled antibody in vivo with necrotic neoplastic tissue of said mammal, thereby permitting said antibody to bind preferentially to said necrotic neoplastic tissue; and
measuring the binding of said labeled antibody to said necrotic neoplastic tissue, wherein the amount of binding of said antibody is indicative of the presence of neoplastic tissue.

41. The method of Claim 18, wherein said neoplastic tissue comprises a particular neoplastic cell type, and wherein said antibody exhibits at least twice the level of binding to a preparation of cell ghosts of said neoplastic cell type than to a preparation of living cells of said neoplastic cell type in an in vitro assay for determining the level of antibody binding.

The references relied upon by the examiner are:

Laster et al. (Laster), "Tumor Necrosis Factor can Induce Both Apoptotic and Necrotic Forms of Cell Lysis," Journal of Immunology, vol. 141, no. 8, pp. 2629-34 (1988)

Curnow et al. (Curnow), "The Role of Apoptosis in Antibody-Dependent Cellular Cytotoxicity," Cancer Immunology Immunotherapy, vol. 36, no. 3, pp. 149-55 (1993)

Appeal No. 96-2137
Application 07/668,920

Carbonari et al. (Carbonari), "Detection and Characterization of Apoptotic Peripheral Blood Lymphocytes in Human Immunodeficiency Virus Infection and Cancer Chemotherapy by a Novel Flow Immunocytometric Method," Blood, vol. 83, no. 5, pp. 1268-77 (1994)

The reference relied upon by appellants is:

Epstein et al. (Epstein), "Radioimmunodetection of Necrotic Lesions in Human Tumors Using I-131 Labeled TNT-1 F(ab')s Monoclonal Antibody," Antibody, Immunoconjugates, and Radiopharmaceuticals, vol. 4, no. 2, pp. 151-62 (1991)

Claims 18, 19, 21 through 28, and 41 stand rejected under 35 U.S.C. § 112, first paragraph, as being nonenabled. We vacate and enter a new ground of rejection under 37 CFR § 1.196(b).

BACKGROUND

Appellants describe their invention at page 4, lines 19-27 of the specification as follows:

The present invention exploits the observation that antibodies to insoluble intracellular components of cells can be administered in such a way as to show preferential localization to neoplastic cells in vivo, in spite of the known fact that the relevant antigens also are present in known fact that the relevant antigens also are present in normal cells. Such localization is based upon the demonstrated abnormal permeability of a proportion of cancer cells, as well as the specificity and character of the antibody.

The antibodies of the present invention are also described at page 6, lines 15-21,

of the specification as follows:

[T]he antibody has been selected by screening a library of antibodies that have been generated to insoluble intracellular antigen and selecting those antibodies that are specific to insoluble intracellular antigen present in both neoplastic and normal cells, but not to antigen released into the general circulation upon cell death or to antigen on the exterior of living cells.

The specification also describes the antigens to which the present antibodies bind at page 7, lines 2-13, as follows:

Upon cell death and lysis in an animal, soluble components of the cell, primarily from the cytoplasm, are released. The remainder of the necrotic cell comprises a "cell ghost" made up of various generally insoluble materials that remain "fixed" in situ in the tissue. The insoluble cell ghost is gradually destroyed by phagocytosis and enzymatic degradation. At least a portion of the cell ghost remains intact for as long as several weeks. It has been discovered that certain intracellular cell ghost constituents are antigenic. These antigens include nuclear antigens, structural elements, and organelles.

The initial screening procedure used in the present invention in order to make a first determination of antibodies which would be candidates for use in the present invention is described at page 8, lines 15-32, of the specification as follows:

In order to screen for monoclonal antibodies that bind specifically to cell ghosts with little or no binding to live cells, equal aliquots of normal and neoplastic live cells are prepared. To obtain cell ghosts, one aliquot each of neoplastic and normal cells is subjected to several rapid freeze-thaw cycles, and is then washed with buffer to remove soluble components. The ability of monoclonal antibody from each tested culture to bind, respectively, the cell ghosts and the intact cells is then quantitatively measured. One appropriate measurement technique is a radioimmunoassay. Thus, when using murine monoclonal antibody,

radiolabeled anti-mouse IgG may be used to quantitate the amount of bound mouse antibody. Direct or indirect immunofluorescence screening techniques may also be used. Specificity for insoluble intracellular antigens may be determined by comparing the amount of antibody bound to cell ghosts with that bound to intact cells.

The specification also describes the manner in which hybridomas which produce monoclonal antibodies to nuclear antigens were prepared. As set forth in Example 1 (the paragraph bridging pages 16-17 of the specification):

In order to generate hybridomas producing monoclonal antibody to nuclear antigens, eight human malignant lymphoma and leukemia cell lines were used as a source of antigens. These include the EBV-positive nonproducer Raji and producer AG876 African Burkitt's lymphoma cell lines; the T-cell acute lymphoblastic leukemia CEM cell line; the IgE secreting multiple myeloma U-266 cell line; the erythroleukemia K562 cell line; and the histiocytic type SU-DHL-1 and U-937 and B-cell type SU-DHL-4 diffuse histiocytic lymphoma cell lines. In addition to these cultures, normal peripheral blood lymphocytes pooled from several individuals and separated by the ficoll-hypaque technique were used alone and after four days of stimulation with 5ug/ml of Pokeweed mitogen.

Example 2 of the specification discusses the results obtained when certain monoclonal antibodies were screened. As set forth at page 20 of the specification, the monoclonal antibodies screened in this example were selected "from a library of monoclonal antibodies to intracellular antigens that includes the antibodies produced by the hybridomas of Example 1." The selected antibodies were screened using large cell lymphoma cells (SU-DHL-2) and adenocarcinoma lung cancer cells (A549). The results of the screening are set forth at Table 1 of the specification as follows:

TABLE 1.

Data are expressed as counts per minute (CPM) High counts denote antibody binding				
Monoclonal Antibody	SU-DHL-2		A549	
	Live Cells	Dead Cells	Live Cells	Dead Cells
244-7	5,934	6,772	3,426	5,509
364-5	769	622	656	1,036
372-2	1,592	437	2,024	1,896
443-4	1,211	919	560	1,337
652-2	6,019	1,355	11,697	9,176
780-3	557	1,063	3,163	1,205
785-5	746	648	1,211	2,197
841-19	1,645	1,851	3,478	2,517
859-4	327	1,504	1,974	3,604
* 877-8	1,481	1,833	1,641	4,680
891-5	1,247	2,834	2,856	5,973
* 898-9	3,442	2,726	2,317	13,942
* 899-4	1,980	8,193	2,232	3,534
1415-1	5,550	6,158	3,821	6,363
1702-5	4,711	1,786	4,696	2,666
NS-1 (neg. control)	552	507	346	738

The three monoclonal antibodies identified by an asterisk in Table 1 are stated at page 21 of the specification to be “[t]hree candidate antibodies.” Furthermore, the specification puts the data reported in Table 1 in perspective in the paragraph bridging pages 22-23 of the specification as follows:

In order to understand the significance of the data in Table 1, it is important to realize that even a “live” *in vitro* culture will contain a relatively large proportion of necrotic cells, as opposed to a population of similar cells *in vivo*. Thus, some binding to the “live” cell culture can be expected, even with an antibody that is specific to only insoluble intracellular antigen. It should also be recognized that even though the

antibody may not be specific to any surface protein or antigen of the cell line employed in the screening process, certain tumor cell lines (such as histiocytic cell lines) have surface components that exhibit generalized binding of immunoglobulins.

No further information is given as to how the live cell data are to be interpreted to take into account that the reported values represent counts of binding to both live and dead cells.

Upon filing of this application on March 13, 1991, claim 18 was presented, which was and is the only independent claim pending in the application. Claim 18 as originally presented read as follows:

18. A method for measuring necrotic tissue in a mammal, comprising the steps of:

obtaining monoclonal antibody that is specific to necrotic tissue of substantially all tissues of said mammal but not to living tissue, said monoclonal antibody being labeled;

contacting said labeled antibody in vivo with tissue of said mammal, which tissue includes necrotic tissue, thereby permitting said antibody to bind preferentially to said necrotic tissue; and

measuring the binding of said labeled antibody to said necrotic tissue.

As can be seen, claim 18 was directed to a method for measuring necrotic tissue in a mammal. Claim 18 was amended in Paper No. 19, inter alia, to recite "a method for measuring necrotic neoplastic tissue in a mammal" In response to a new ground of rejection in the Examiner's Answer, appellants amended claim 18 in Paper No. 28 to

delete the word “necrotic” from the preamble. Thus claim 18 as presented in this appeal is directed to “a method for measuring neoplastic tissue in a mammal . . .”

DISCUSSION

Having reviewed the record, it is our view that the metes and bounds of the claims on appeal cannot be readily discerned, i.e., the claims are indefinite under 35 U.S.C. § 112, second paragraph. As indicated in In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971), one is not in a position to determine whether a claim is enabled under the first paragraph of 35 U.S.C. § 112 until the metes and bounds of the claim are determined under the second paragraph of this section of the statute. Accordingly, we vacate the rejection under 35 U.S.C. § 112, first paragraph, as being nonenabled and make the following new ground of rejection.

NEW GROUND OF REJECTION UNDER 37 CFR § 1.196(b)

Under the provisions of 37 CFR § 1.196(b), we make the following new ground of rejection.

Claims 18, 19, 21 through 28, and 41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

1. Neoplastic tissue.

As presently drafted, claim 18 makes reference to neoplastic tissue at least three times. First, the preamble of claim 18 indicates that neoplastic tissue in a mammal is being measured. Second, the antibody used in the claimed method must bind to insoluble intracellular antigens of necrotic neoplastic tissue. Third, that antibody does not substantially bind to living neoplastic tissue.

It appears from the disclosure of this application that the neoplastic tissue to be measured can differ, e.g., tumor type or source, from the necrotic neoplastic tissue and living neoplastic tissue used to define the differential binding ability of the claimed antibody. What is not clear is whether the necrotic neoplastic tissue and the living neoplastic tissue used to define the differential binding ability of the claimed antibody must be from the same tissue source or tumor or whether these materials can be from different tissue sources or tumors. This is an open question since the wording of the first clause of claim 18, in defining the differential binding ability of the antibody, does not require that the necrotic neoplastic tissue originate from the living neoplastic tissue. Clarification of this ambiguity is required.

2. Binding of the antibody.

As set forth above, the first clause of claim 18 requires the use of an antibody that exhibits a differential binding ability in that the antibody must bind to insoluble

intracellular antigens of unspecified necrotic neoplastic tissue but not substantially bind to unspecified living neoplastic tissue. Reviewing this portion of claim 18 in light of the specification, it is not clear what is meant by the phrase the antibody “does not substantially bind to living neoplastic tissue.”

The most relevant portion of the disclosure of this application which aids in interpreting this aspect of the claimed invention is Table 1. However, it is not clear how the data presented in this table are to be interpreted nor how the binding requirements of claim 18 are to be interpreted in light of these data. As seen from the heading of the table, high counts denote antibody binding. Appellants do not explain what is meant by high counts. The table contains negative control values but the specification does not explain how these negative controls were obtained or how they are to be used in interpreting the count values resulting from the assays using live cells of SU-DHL-2 and A549. For example, if the negative control value of 552 set forth for the live cells of SU-DHL-2 is to be interpreted as a background control value, all of the monoclonal antibodies with the exception of 859-4 and 780-3, appear to “substantially bind” rather than “not substantially bind” living neoplastic tissue, i.e., living SU-DHL-2 cells. The same observation is seen from viewing the data presented for the A549 live cells. There, all of the monoclonal antibodies appear to “substantially bind” rather than “not substantially bind” living neoplastic tissue, i.e., live A549 cells.

It may be that appellants intend the differential binding function of the claimed antibody to be determined in a relative manner on the basis of the ratio of dead cell count:live cell count with the higher ratio denoting an antibody which would be within the scope of claim 18. See, e.g., page 8, lines 29-32, of the specification (“Specificity for insoluble intracellular antigens may be determined by comparing the amount of antibody bound to ghost cells with that bound to intact cells.”). However, it is not clear whether appellants intend the claims to be so limited. If appellants intend the differential binding required by claim 18 to be determined on the basis of such a relative ratio measured on the basis of the dead cells and live cells originating from the same source/tumor, it becomes more important that the claim specify that the necrotic neoplastic tissue and the living neoplastic tissue used to determine the differential binding ability be from the same source.

In any event, in analyzing the data of Table 1, it must be kept in mind that appellants state at page 22 of the specification that the “live cells” used in the assay will “contain a relatively large proportion of necrotic cells.” Appellants do not explain how the live cell data is to be analyzed in order to take into account the fact that dead cells are included in the reported count values as well as live cells. Thus, it is unclear as to what the count values set forth for “live cells” actually represent.

We also note that appellants state at page 21 of the specification that three so-called candidate antibodies 877-8, 898-9, 899-4 were identified through this limited screening. However, appellants have not explained on what basis these three antibodies were picked as candidates as opposed to the other monoclonal antibodies listed in Table 1. Were these three antibodies picked because of the values found on an absolute basis over the negative control values or were they picked on the basis of a higher ratio of count values of dead cells:live cells?

If the differential binding of the antibody of claim 18 is to be determined on the basis of the ratio of values obtained for binding to dead cells:live cells for a given cell line, it is not clear then how to analyze the values given in Table 1 for monoclonal antibodies such as 898-9. That monoclonal antibody bound strongly to dead cells of A549 compared with its binding to live cells of A549. However, that antibody bound more strongly to live cells of SU-DHL-2 than to dead cells of SU-DHL-2. It is not clear then whether 898-9 would meet the differential binding requirements of claim 18. It would appear that if the differential binding is measured on the basis of the values reported for A549 cells, 898-9 meets the requirements of claim 18. However, if the differential binding is measured on the basis of the values reported for SU-DHL-2, it is not clear that 898-9 meets the requirements of claim 18. Clarification of this ambiguity is required.

3. Claim 19.

Claim 19 appears to be redundant to claim 18 in that claim 18 already requires that the contacting step be performed in vivo. Clarification is needed.

4. Claim 21.

It is not clear what appellants mean by the requirement of claim 21 that the necrotic tissue is surrounded by living tissue. Which necrotic tissue of claim 18 is intended to be modified? Presumably this claim is directed to that aspect of claim 18 wherein the labeled antibody is contacted in vivo with necrotic neoplastic tissue of the mammal. If so, it would appear, by definition, the contacting step of claim 18 already requires that the necrotic tissue is “surrounded by living tissue.” In other words, is it possible for necrotic neoplastic tissue not to be “surrounded” by living tissue regardless of its neoplastic state? Clarification is needed.

5. Claim 41.

Claim 41 is not clear as to antecedent support for the phrase “said neoplastic tissue comprises a particular neoplastic cell type.” Of the various “neoplastic tissues” set forth in claim 18, which one is modified by claim 41?

OTHER ISSUES

1. Enablement.

We emphasize that in vacating the examiner's rejection under 35 U.S.C. § 112, first paragraph, lack of enablement, we take no position on the merits of the matter. Rather, consideration of the issue is premature until the scope of the claims on appeal can be readily ascertained. However, we make the following comments in an effort to provide some guidance on the issue in the event prosecution is continued in front of the examiner.

Assuming the claims are presented which are definite under 35 U.S.C. § 112, second paragraph, the examiner and appellants should take the issue of enablement under consideration in light of the relevant legal standings. To be enabling, a disclosure must teach persons skilled in the art to make and use the claimed invention without undue experimentation. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). As set forth in In re Wands, 858 F.2d 731, 736, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)(footnote omitted):

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized . . . in Ex parte Forman, [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

If the examiner determines that any claim presented in response to the new ground of rejection is not enabled by the original disclosure of this application, we urge the examiner to consider the issue of enablement in light of the factors enumerated above and structure any further rejection so that specific findings are made as to the factors which are relevant under the facts of this case.

As we understand appellants' position regarding the current claims on appeal, appellants believe these claims are enabled when one considers the screening method set forth in Example 2 of the specification including the data set forth in Table 1, prophetic Example 3 and the disclosure of the Epstein reference. Apart from the problems outlined above regarding how the data set forth in Table 1 should be interpreted, we note that the specification does not describe with any specificity how each of the monoclonal antibodies listed in Table 1 were made. Significantly missing from the disclosure of this application is any mention or disclosure of the antigen used as the immunogen in the preparation of the hybridomas which produce those monoclonal antibodies. Furthermore, appellants have not described in the specification how the negative control values in Table 1 were obtained nor explained their significance in interpreting the data in Table 1.

As to appellants reliance upon Epstein to establish that the claimed invention is enabled, we point out that Epstein was published after the effective filing date of the

claims on appeal. As set forth in In re Glass, 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974)(footnote omitted):

It is an applicant's obligation to supply enabling disclosure without reliance on what others may publish after he has filed an application on what is supposed to be a completed invention. If he cannot supply enabling information, he is not yet in a position to file.

Appellants rely upon Epstein for its later published results obtained from a labeled monoclonal antibody denominated TNT-1. As in the case of the monoclonal antibodies set forth in Table 1 of the specification, appellants have not described with sufficient specificity the starting antigen used in the preparation of the hybridoma. None of the hybridomas which produce the monoclonal antibodies described in Table 1 or the hybridoma which produces TNT-1 appear to have been deposited under appropriate conditions so that they would be available to the public if this application matured into a patent. It is not apparent on this record how one skilled in the art would go about re-creating any one of these monoclonal antibodies or make a monoclonal antibody having the differential binding ability required by the present invention. Furthermore, in reviewing the disclosure of Epstein, it does not appear that TNT-1 was obtained from using the screening method set forth in Example 2 of the present application. In other words, there does not appear to be a nexus linking the screening method set forth in Example 2 of the present specification and the results obtained in Epstein. Thus, it

Appeal No. 96-2137
Application 07/668,920

does not appear that the results reported in Epstein are necessarily based upon information in the specification of this application.

TIME PERIODS FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 CFR § 1.196(b)(amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53,131, 53,197 (Oct. 10, 1997), 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)). 37 CFR § 1.196(b) provides that, "A new ground of rejection shall not be considered final for purposes of judicial review."

37 CFR § 1.196(b) also provides that appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

- (1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .
- (2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record. . . .

Appeal No. 96-2137
Application 07/668,920

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

REVERSED - 37 CFR § 1.196(b)

William F. Smith)	
Administrative Patent Judge)	
)	
)	
)	BOARD OF PATENT
Joan Ellis)	APPEALS AND
Administrative Patent Judge)	INTERFERENCES
)	
)	
Elizabeth C. Weimar)	
Administrative Patent Judge)	

Appeal No. 96-2137
Application 07/668,920

Knobbe, Martens, Olson & Bear
620 Newport Center Drive, Sixteenth Floor
Newport Beach, CA 92660