

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 52

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte LAURA K. SHAWVER,
JOHN W. BRANDIS,
ELAINA MANN,
MIRIAM E.C. HANCOCK,
RONALD P. MISCHAK, and
JOHN J. MONAHAN

Appeal No. 2004-0005
Application No. 07/644,361

HEARD: March 4, 2004

Before WINTERS, WILLIAM F. SMITH, and GREEN, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 through 10 and 13 through 24, all the claims pending in the application. Claims 1 and 9 are representative of the subject matter on appeal and read as follows:

1. A drug combination cytotoxic to tumor cells expressing c-erbB-2 protein comprising (a) an anti-neoplastic agent and (b) a molecule, not conjugated to the anti-neoplastic agent, that binds said c-erbB-2 protein on the tumor cells and induces an increase in the phosphorylation of c-erbB-2 protein when placed in contact with the tumor cells.

9. The drug combination of claim 1 wherein the molecule is T Ab 250 or fragments thereof.

The references relied upon by the examiner are:

Drebin et al. (Drebin I), "Monoclonal Antibodies Reactive With Distinct Domains of the neu Oncogen-Encoded p185 Molecule Exert Synergistic Anti-Tumor Effect In Vivo," Oncogen, Vol. 2, pp. 273-277 (1988)

Drebin et al. (Drebin II), "Monoclonal Antibodies Specific for the neu Oncogen Product Directly Mediate Anti-Tumor Effects In Vivo," Oncogen, Vol. 2, pp. 387-394 (1988)

Aboud-Pirak et al. (Aboud-Pirak), Efficacy of Antibodies to Epidermal Growth Factor Receptor Against KB Carcinoma In Vitro and in Nude Mice," J. Nat'l Cancer Institute, Vol. 80, pp. 1605-1611 (1988)

Read, "Hormonal Modulation on HER-2/neu Protooncogene Messenger Ribonucleic Acid and p185 Protein Expression in Human Breast Cancer Cell Lines," Cancer Research, Vol. 50, pp. 3947-3953 (1990)

Documents relied upon by appellants are:

Hudziak et al. (Hudziak '692)
(PCT Application)

WO 89/06692

July 27, 1989

Alberts et al. (Alberts)(Exhibit B), "Many Catalytic Receptors Are Single-Pass Transmembrane Glycoproteins with Tyrosine-specific Protein Kinase Activity," Molecular Biology, 2d ed. pp. 706-707, 726(1989)

Documents discussed by this merits panel are:

Erickson et al. (Erickson)
Shawver et al. (Shawver)
Lippman et al. (Lippman)

6,632,979
6,123,939
5,578,482

Oct. 14, 2003
Sep. 26, 2000
Nov. 26, 1996

Claim 9 stands rejected under 35 U.S.C. § 112, first paragraph (enablement).

Claims 1 through 8, 10 and 13 through 24 stand rejected under 35 U.S.C. § 103(a) with the examiner relying upon Drebin I, Drebin II, Aboud-Pirak, and Read as evidence of obviousness. We reverse the enablement rejection and affirm the obviousness rejection.

Background

c-erbB-2 is a cell-surface oncogene, the amplification of which indicates a very poor clinical prognosis, especially in breast and ovarian cancer. Specification, page 2, lines 11-27. The present invention is directed toward a drug combination which comprises an anti-neoplastic agent and a molecule that binds c-erbB-2 protein on tumor cells. The molecule that binds c-erbB-2 protein must not be conjugated to the anti-neoplastic agent and must induce an increase in the phosphorylation of c-erbB-2 protein when placed in contact with the tumor cells. Claim 1.

The molecule required by claim 1 on appeal is defined in the specification as follows:

A molecule that binds tumor cells for the purposes of the inventions herein is one that is reactive with the c-erbB-2 protein. By 'reactive' it is meant that the molecule binds the c-erbB-2 protein as measured or determined by standard ligand-receptor binding assays, for example, competitive binding assays or saturation assays or standard immunoassays such as ELISA or RIA.

Specification, page 14, 2nd paragraph. Preferred molecules are stated to be monoclonal antibodies that bind to the c-erbB-2 protein. Id., page 16, lines 25-28. A preferred monoclonal antibody is denominated TAb 250. See, e.g., id., page 16, line 25 - page 17, line 2 and claim 9.

Example 8D of the present specification sets forth work stated to establish that TAb 250 induces an increase in the phosphorylation of c-erbB-2 protein when placed in contact with tumor cells expressing c-erbB-2. Specifically, SKBR3 cells were labeled with ³²p-orthophosphate and then incubated with TAb 250. Lysates were centrifuged and immunoprecipitations carried out using a polyclonal anti-peptide directed against the

C-terminus of the c-erbB2 protein. Specification, page 41, lines 25-34. Samples were analyzed by SDS-PAGE and autoradiography. Id., page 41, lines 35-38. Appellants state that “[t]reatment of SKBR3 with TAb 250 resulted in ~5-fold increase in the phosphorylation of c-erbB-2. ³²P-labeled c-erbB-2 from cells treated with TAb 250 was stable to base hydrolysis suggesting that phosphorylation was on tyrosine residues.” Id., page 42, lines 22-26 (emphasis added).

Discussion

1. Enablement Rejection of Claim 9.

As explained on pages 4-6 of the Examiner’s Answer, the enablement rejection is premised upon the examiner’s concern that hybridoma cell line HB 10646 has not been deposited under the conditions set forth in 37 CFR §§ 1.801-1.809. Appellants did not address this rejection in the Appeal Brief under the apparent assumption the rejection would no longer be maintained by the examiner. This assumption was apparently mistaken since the rejection appears in the Examiner’s Answer. In reviewing the matter, it appears that this rejection has been overtaken by events outside of this appeal proceeding. We refer to Shawver, which issued from an application stated to be a continuation of this application, claims 2, 11, 20, and 26 of which specifically require the use of TAb 250 (ATCC No. HB 10646).

Since appellants have gained allowance of claims similar to claim 9 in this appeal in Shawver, it appears they have complied with the formal and legal requirements of depositing HB 10646. Absent further explanation from the examiner as to which deposit

requirements have not been met, we will reverse the rejection of claim 9 under 35 U.S.C. § 112, first paragraph (enablement).¹

2. Obviousness.

Appellants state that the claims stand or fall together. Appeal Brief, page 2. Accordingly, we shall decide the issues raised under 35 U.S.C. § 103(a) in the examiner's rejection as they pertain to claim 1 on appeal. 37 CFR § 1.192(c)(7).

The examiner has determined that the Drebin references "show that mab 7.16.4 recognizes [c-erbB-2], [c-erbB-2] is found on breast cancer cells, and the mechanism of tumor inhibition is through rapid internalization and down-modulation." Examiner's Answer, page 6. The examiner relies upon Aboud-Pirak for its disclosure that antibodies to epidermal growth factor receptor in combination with the anti-neoplastic agent cisplatin result in a more effective antitumor composition. The examiner makes reference to Figure 6 of Aboud-Pirak in support of this finding. Id., page 7. The examiner concludes that it would have been obvious to one of ordinary skill in the art to combine the monoclonal antibody 7.16.4 described in the Drebin references with cisplatin for the expected benefit of creating an anti-tumor composition using higher anti-tumor effect. Id.

In regard to the claim requirement that the molecule that binds c-erbB-2 protein induce an increase in phosphorylation of c-erbB-2 protein the examiner states "while the

¹ By this action, claim 9 is free of rejection. If appellants intend to permit claim 9 to issue, they and the examiner should ensure that all formal requirements in regard to deposit of the hybridoma have been met in this application. See 37 CFR §§ 1.801-1.809.

references are silent as to the increase phosphorylation of the c-erbB-2, this property is an expected property that follows in ligand-receptor internalization/down modulation systems.”

Appellants do not argue that the examiner’s references fail to suggest a drug combination that comprises an anti-neoplastic agent and a molecule that binds to c-erbB-2 cell protein on tumor cells. Rather, appellants “argue the single point of whether it would have been expected that such c-erbB-2 antibodies, in the context of the claimed invention, would induce an increase in c-erbB-2 phosphorylation.” Appeal Brief, page 4.

Appellants explain:

To support this position, [Hudziak ‘692] was cited. This application disclosed a method for treating a tumor with antibodies to the HER2 receptor (also known as c-erb-B2 or p185) and a therapeutically effective amount of a ‘cytotoxic factor.’ See, e.g., [Hudziak] ‘692 application, Page 6, lines 24-27 and Page 7, lines 9-14. The cytotoxic factor described in the ‘692 application included anti-neoplastic agents, such as those disclosed for the present application. Compare, e.g., [Hudziak] ‘692 application, Page 12, lines 1-10. Like the drug combination claimed by Applicant, the combination of Genentech’s antibody and cytotoxic factor was cytotoxic to breast tumor cells. See, e.g., [Hudziak] ‘692 application, Page 34, lines 15-35; Figs. 5 and 6; Page 8, lines 5-10. Significantly, the Genentech antibody inhibited the tyrosine kinase activity of the receptor. See, e.g., [Hudziak] ‘692 application, Page 9, lines 28-29. Since tyrosine kinase activity is responsible for receptor phosphorylation, inhibiting it would also inhibit the appearance of any phosphorylation.

Appeal Brief, page 4. Alberts is relied upon by appellants for the proposition that “phosphorylation as described in [Hudziak] ‘692 application referred to the receptor protein itself.” Id., page 5.

We have carefully considered appellants' arguments, Alberts and Hudziak '692 but do not find that they constitute a sufficient rebuttal of the examiner's prima facie case of obviousness.

We first note that appellants have overstated the disclosure of Hudziak '692. To put the statement in Hudziak '692 appellants rely upon in proper context, we reproduce that portion of the reference that contains the statement:

While not wishing to be constrained to any particular theory of operation of the invention, it is believed that the antibodies inhibit growth factor receptor biological function in one or more of the following ways:

- (a) The antibodies bind to the extracellular domain of the receptor and inhibit the ligand from binding the receptor;
- (b) The antibodies bind the ligand (the growth factor) itself and inhibit the ligand from binding the receptor;
- (c) The antibodies down regulate the growth factor receptor;
- (d) The antibodies sensitize tumor cells to the cytotoxic effects of a cytotoxic factor such as TNF- α ;
- (e) The antibodies inhibit the tyrosine kinase activity of the receptor.

Hudziak '692, page 9, lines 17-29.

As seen, Hudziak '692 states as only one of five possible theories of operation that the antibodies inhibit the tyrosine kinase activity of the receptor of that invention. Appellants have not established that any of the specific antibodies described in the reference do in fact inhibit the tyrosine kinase activity of the receptor.

Appellants' reliance upon Hudziak '692 can also be seen as a red herring since the examiner relies upon the antibodies described in the Drebin references in support of the prima facie case of obviousness, not those described in Hudziak '692. As appellants and the examiner appreciate, the Drebin references do not address whether any of the antibodies described therein do or do not inhibit the tyrosine kinase activity of

the receptor, i.e., induce or not induce an increase in the phosphorylation of c-erbB-2 protein. Under these circumstances, it has been held that it is reasonable to shift the burden to appellants to establish by way of objective evidence whether the antibodies described in the Drebin references do or do not induce an increase in the phosphorylation of c-erbB-2 protein. As stated in In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977)(footnote omitted):

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on `inherency' under 35 U.S.C. § 102, on `prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

Viewed in light of this legal standard, appellants' reliance upon Hudziak '692 is best viewed as indirect evidence that the antibodies described in the Drebin references may not possess the claimed activity. However, the relevance of Hudziak '692 in considering whether the antibodies of the Drebin references do or do not possess the claimed property is not seen. On this record, it is appropriate to shift the burden to appellants to provide direct objective evidence in support of their assertion regarding the properties possessed by the Drebin antibodies. For these reasons, the examiner's rejection is affirmed.

Other Issues

As discussed above, the central issue in this appeal is whether the antibodies described in the Drebin references induce phosphorylation of the c-erbB-2 protein. We

have uncovered additional information that appellants and the examiner should take into account if prosecution is resumed on this subject matter.

This application was filed on January 18, 1991 and is stated to be a continuation-in-part of an application filed on February 1, 1990, which in turn is stated to be a continuation-in-part of an application filed on August 4, 1989. It does not appear that the examiner has determined whether the claims on appeal are entitled to the benefit of the earlier filing date of either parent application. This is important because the information which will be discussed may or may not be prior art to the claims on appeal depending upon the exact filing date to which the claims are entitled. In any event, the information may be relevant in determining the patentability of the claims on appeal since it has been held that non-prior art publications may be relied upon to establish characteristics of the prior art products. In re Wilson, 311 F.2d 266, 268-69, 135 USPQ 442, 444 (CCPA 1962).

We direct attention to Lippman and its disclosure of ligands to c-erbB-2 protein. Specifically, Lippman states:

In accordance with the present invention, it has been surprisingly discovered that a number of structurally distinct polypeptides function as ligands for p185^{erbB-2}. These ligands include polypeptides of about 20-26kDa (which are glycosylated to form ligands of 30-45kDa apparent molecular weight) and also include polypeptides of about 75 kDa which are not glycosylated. These ligands share the properties of specifically binding to p185^{erbB-2} and inducing autophosphorylation thereof. The ligands differ in structure and some other biological activities. All of the polypeptides which specifically induce autophosphorylation of p185^{erbB-2} are termed "erbB-1 ligands" herein. The low molecular weight glycosylated species of erbB-2 ligands are variously described herein by the terms "heregulin", "gp30", "30 KDa growth factor", "30 kDa ligand", or "TGF α -like polypeptide". the higher molecular weight species is additionally identified as "p75".

Lippman, col. 9, lines 11-27. Lippman summarizes their work as follows:

In brief, we have identified a novel polypeptide of 75 kDa that binds to the p185^{erbB-2} receptor. The effects of p75 on cells with very high levels of erbB-2 were similar to the reported effects of the other ligand, gp30. In contrast to gp30, p75 appears to be specific for p185^{erbB-2} receptor. Furthermore, we have provided evidence that cells that overexpress the erbB-2 receptor may also secrete one of its ligands, which is required for their proliferation, therefore implying an autocrine loop. We believe that manipulation of this and other erbB-2 ligands may turn out to have an important biological effect on growth of human neoplasia.

Id., col. 56, lines 26-36.

Apart from whether the disclosure of Lippman is prior art to the claims on appeal, this disclosure should be taken into account in the event of further prosecution of this subject matter since it raises questions as to the results reported in appellants' Example 8D relied upon in support of their assertion that TAb 250 induces phosphorylation of c-erbB-2 protein. If the autocrine loop described by Lippman exists in the cells used in appellants' Example 8D, it does not appear that one can reasonably ascribe the induction of phosphorylation to TAb 250 as opposed to the ligands described in Lippman.

Another document that appellants and the examiner should consider in the event of further prosecution is Erickson. Erickson states that ErbB2, ErbB3 and ErbB4 have nearly identical molecular sizes and it is not possible to discern which protein is becoming tyrosine phosphorylated when whole-cell lysates are evaluated by Western blot analysis. Id., col. 28, lines 55-64. It appears that appellants' Example 8D used whole-cell lysates. Thus, if the cells used in Example 8D also express ErbB3 and ErbB4, it may not be reasonable for appellants to conclude that the work described in

Example 8D establishes that c-erbB-2 was phosphorylated as opposed to other cell surface receptors such as ErbB3 and/or ErbB4.

Finally, another issue which appellants and the examiner need to consider if prosecution is resumed on this subject matter is the issuance of Shawver, claims 25 and 27 of which read as follows:

25. A drug combination cytotoxic to tumor cells which express c-erbB-2 protein, comprising synergistically effective amounts of (a) an antiestrogen and (b) an antibody, or divalent fragments thereof, that binds specifically to said c-erbB-2 protein on said tumor cells, wherein said antibody, or divalent fragments thereof, causes internalization of said c-erbB-2 protein.

27. A drug combination of claim 25, wherein said antibody induces an increase in phosphorylation of said c-erbB-2 protein.

Since the antiestrogen required by claims 25 and 27 of Shawver is an anti-neoplastic agent as required by claim 1 on appeal, it appears that the claims in this application, including claim 9, should be rejected on the judicially created obviousness-type double patenting grounds. In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998).

The examiner's decision is affirmed-in-part.

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

AFFIRMED-IN-PART

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Sherman D. Winters)	
Administrative Patent Judge)	
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Administrative Patent Judge)	APPEALS AND
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