

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte MICHAEL G. ROSENBLUM and CLYDE W. WELLEN

Appeal No. 2001-2347
Application No. 08/251,574

ON BRIEF

Before WINTERS, MILLS and GRIMES, 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 claims 1, 3-4 and 11, which are all of the claims pending in this application.

Appeal No. 2001-2347
Application No. 08/251,574

Claim 1 is representative of the claims on appeal and reads as follows:

1. A conjugate, comprising an antibody directed toward a cell surface associated antigen, wherein said antigen is selected from the group consisting of 15A8 antigen and ZME-018 antigen; and a biological response modifier moiety, wherein said moiety is selected from the group consisting of TNF-alpha, TNF-beta and Interleukin-1.

The references relied upon by the examiner are:

Rodwell et al. (Rodwell)	4,671,958	June 9, 1987
Huston et al (Huston) PCT Publication	WO 88/09344	Dec. 1, 1988
Hudziak et al. (Hudziak) PCT Publication	WO 89/06692	July 27, 1989
Zimmerman (Zimmerman) European Patent	EP 281070	Sept. 7, 1988
Houston et al. (Houston) European Patent	EP 256714	Feb. 24, 1988

White et al. (White), "Two Monoclonal Antibodies Selective for Human Mammary Carcinoma," Cancer Research, Vol 45, pp. 1337-1343 (1985)

Shultz et al. (Shultz), "Monoclonal Antibody-Directed Effector Cells Selectively Lyse Human Melanoma Cells *In Vitro* and *In Vivo*," Proc. Natl. Acad. Sci., Vol 80, pp. 5407-5411 (1983)

Claim Grouping

According to appellants, the claims stand or fall together. Brief, page 6. We decide this appeal on the basis of claim 1, as representative of the claims before us.

In Young, 927 F.2d 588, 590, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991).

Grounds of Rejection

Appeal No. 2001-2347
Application No. 08/251,574

Claims 1, 3-4 and 11 stand rejected under 35 U.S.C. § 103(a) as obvious over Huston or Rodwell in view of White or Shultz and in further view of Zimmerman, Houston or Hudziak.

We affirm.

DISCUSSION

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 for the examiner's complete reasoning in support of the rejection, and to the appellants' Brief for the appellants' arguments thereagainst. As a consequence of our review, we make the determinations which follow.

35 U.S.C. § 103

Claims 1, 3-4 and 11 stand rejected under 35 U.S.C. § 103(a) as obvious over Huston or Rodwell in view of White or Shultz and in further view of Zimmerman, Houston or Hudziak.

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,

Appeal No. 2001-2347
Application No. 08/251,574

1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). With this as background, we analyze the prior art applied by the examiner in the rejection of the claims on appeal.

According to the examiner, “[b]oth Huston and Rodwell teach that immunoconjugates ... of antibody and biological response modifiers were known at the time of the invention. Huston et al teach that [sic] a single chain multifunctional biosynthetic protein, which comprises a biosynthetic antibody binding site molecules [sic] BABS and a protein which is an effector protein having a biological activity to effect a biological function.... Huston teach the BABS to be antibodies or antigen binding fragments.” Answer, page 4.

Rodwell et al teach antibody conjugates whereby bioactive and cytotoxic agents are targeted to tumour sites, and that these were desirable for targeting biological agents to specific sites. Rodwell et al also teach working protocols for making these conjugates. While the above two references essentially teach the making and use of antibody-conjugates of virtually any specificity, i.e. a tumour, and that these were known and routine in the prior art, they do not specify the antibodies were directed to the 15A8 or ZME-018 antigens.

Id.

In addition, the examiner argues (Answer, page 4):

Appeal No. 2001-2347
Application No. 08/251,574

White and Schultz teach that antibodies binding to the two claimed antigens were known or obvious at the time of the claimed invention. White et al taught the 15A8 antigen and Schultz et al taught a melanoma specific antigen that appears to be an obvious variant of ZME-018 antigen directed against melanomas (the ZME-018 antigen does not appear to have any functional difference from the melanoma antigen of Schultz et al and therefore the antibodies against this antigen would have been obvious variants of those against other melanoma antigens).

The examiner summarizes (Answer, page 5):

[o]ne of ordinary skill in the art would have found it prima facie obvious to substitute the specificity of the antibodies in the immunoconjugates taught by Huston et al or Rodwell et al with the antibody specificities of White et al or Schultz et al because, since the art indicated that antibody/biological response modifiers were known and available in the prior art, then antibodies of any specificity would have been obvious substitutions for those of Huston or Rodwell. ...

It is well accepted in the art that biological response modifiers which include TNFs and IL-1 can exert a toxic effect on a variety of cancers as taught by Zimmerman, or Houston et al or Hudziak, who also teach that biological response modifiers were able to be effectively used to treat cancer cells when given with or without tumour specific antibodies. Therefore, one of ordinary skill in the art would have found it prima facie obvious at the time of the claimed invention to produce the immunoconjugates as taught by Huston et al and Rodwell et al, wherein the specificities and the nature of the biological response modifiers have been substituted with those taught by White et al or Schultz et al and Houston, or Zimmerman or Hudziak.

For the reasons indicated herein, we find the examiner has provided sufficient evidence to establish a prima facie case of obviousness. In particular, Huston provides those of ordinary skill in the art with detailed disclosure as to how to prepare and preserve functionality of protein conjugates. Huston teaches specific conjugates including an antibody coupled with tumor necrosis factor or interleukin-2. Huston, page

14. It would reasonably appear that White provides a sufficient motivation or reason for one of ordinary skill in the art to substitute the 15A8 as the antibody in the antibody conjugate of Huston through its disclosure of the selectivity of the 15A8 antibody and its use as a diagnostic for breast cancer. White, page 1339, column 2. Where the prior art, as here, gives reason or motivation to make the claimed invention, the burden then falls on an appellant to rebut that prima facie case. Such rebuttal or argument can consist of any other argument or presentation of evidence that is pertinent. In re Dillon, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991).

In response, appellants “contend[s] that Huston et al do not disclose or suggest ‘a conjugate’” ... Brief, page 7. According to appellants, Rodwell et al. teach different functional linkers than those used in appellants' conjugates, when producing conjugates between an antibody recognition domain and a covalently attached compound. Id. Appellants further argue that Rodwell does not provide a suggestion or motivation to produce the particular conjugate claimed. Brief, page 7.

The examiner responds to the argument of appellants finding that, contrary to appellants' assertion, Huston does teach conjugates (two polypeptide domains connected by a polypeptide linker) at page 5, pages 14-15, pages 67-68 and in claim 22. The examiner finds that Rodwell also suggests that non-cleavable linkers can also be used as linkers in their antibody conjugates. Answer, page 6. We also note that the pending claims do not specify a specific linker for the claimed conjugate, and therefore,

appellants' argument comparing the linker of the claimed conjugate to that of Rodwell is not relevant to the claims before us.

We agree with the examiner's characterization of Huston's disclosure of protein conjugates. Huston indicates at page 20, that in their conjugates "an essentially limitless combination of binding sites and bioactive proteins is possible, each of which can be refined as disclosed herein to optimize independent activity at each region of the synthetic protein." Huston, pages 26-28, provides a detailed discussion to one of ordinary skill in the art as to how various linkers can be selected to preserve the functionality of the neighboring structure (antibody). Huston indicates, "[t]he primary function of the spacer is to separate the active protein regions to promote their independent bioactivity and permit each region to assume its bioactive conformation independent of interference from its neighboring structure." Huston, page 28. Huston, page 25, particularly indicates linker sequences which should be avoided in preparing protein conjugates. Therefore, Huston describes how to prepare and link functional proteins to prepare protein conjugates.

Appellants argue that White teaches away from the present invention because the 15A8 antibody cross-reacts with numerous tissues other than human breast cancer cells toward which the 15A8 antibody is directed. Brief, pages 7-8. In response, the examiner finds that the White "claims recite antibodies targeted to cell surface receptor and the 15A8 antibody." Answer, page 7. White also discloses the selectivity of the 15A8 antibody and its use as a diagnostic for breast cancer. White, page 1339, column

2. Therefore, it would reasonably appear that those of ordinary skill in the art reviewing White would have recognized the disclosed use of the 15A8 antibody as a diagnostic.

Appellants additionally submit that, at the time of the present invention, it was unclear if either or both targeted antibodies would be functional subsequent to conjugation and that “obvious to try” is not the legal standard for obviousness. Brief, page 11.

Appellants, in essence, argue that the examiner has not shown a reasonable expectation of success of achieving functional conjugates having the claimed specificities, and that the examiner’s evidence would merely support that it would have been “obvious-to-try” preparation of the claimed conjugates in view of the prior art.

We disagree. In our view, Huston provides those of ordinary skill in the art with detailed disclosure as to how to preserve functionality of the conjugate components. Huston teaches specific conjugates including an antibody coupled with tumor necrosis factor or interleukin-2. Huston, page 14. It would reasonably appear that White provides a sufficient motivation or reason for one of ordinary skill in the art to substitute the 15A8 as the antibody in the antibody conjugate of Huston through its disclosure of the selectivity of the 15A8 antibody and its use as a diagnostic for breast cancer. White, page 1339, column 2. Since we find the combination of Huston with White to be sufficient to support a prima facie case of obviousness to defeat claim 1, we do not reach the rejection in view of Schultz. We also find Houston, Zimmerman and Hudziak further support the Huston disclosure that biological response modifiers were known at

Appeal No. 2001-2347
Application No. 08/251,574

the time of the invention to be effectively used to treat cancer cells when given with or without tumour specific antibodies.

Appellants have not come forth with evidence to support his position that those of ordinary skill in the art would still find uncertainty and unpredictability in choosing an appropriate linker sequence which would not interfere with the functionality of the conjugate, in view of the detailed disclosure in Huston as to how to select a linker so as not to affect the function of the components of the conjugate and how to avoid inoperable embodiments. Such arguments of counsel cannot take the place of evidence. In re DeBlauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984), In re Payne, 606 F.2d 303, 315, 203 USPQ 245, 256 (CCPA 1979).

Thus, we find that the examiner's evidence supports a prima facie case of obviousness, which has not been sufficiently rebutted by appellants with appropriate evidence.

Appeal No. 2001-2347
Application No. 08/251,574

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

AFFIRMED

SHERMAN D. WINTERS)	
Administrative Patent Judge)	
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)	BOARD OF PATENT
DEMETRA J. MILLS)	
Administrative Patent Judge)	APPEALS AND
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)	INTERFERENCES
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Appeal No. 2001-2347
Application No. 08/251,574

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