

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 35

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte YUPIN CHAROENVIT, STEPHEN L. HOFFMAN,
RICHARD L. BEAUDOIN, DECEASED, BY BARBARA A. BEAUDOIN

Appeal No. 1999-1413
Application No. 08/176,024

ON BRIEF

Before SCHEINER, 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 final rejection of claims 1 through 7, 11, and 12, which are all of the claims pending in the application.

Claims 1, 4, and 11 are representative and read as follows:

1. A formulation protective against Plasmodium vivax for a time commensurate with the time monoclonal antibody Navy Vivax Sporozoite 3 (HB10615) remains at pharmacologically active levels in a subject's blood stream, comprising a pharmaceutical amount sufficient to provide passive immunization of Navy Vivax Sporozoite 3 (HB10615) in a pharmaceutically suitable injectable solution.

4. A method of providing protection from Plasmodium vivax induced malaria for subjects experiencing exposure to infected mosquitoes, for a time commensurate with the time monoclonal antibody Navy Vivax Sporozoite 3 (HB 10615) remains at pharmacologically active levels in a subject's blood stream, that comprises introducing and circulating the antibody Navy Vivax Sporozoite 3 (HB 10615) in the subject's blood stream.

11. A humanized antibody capable of providing passive protection against Plasmodium vivax wherein said antibody has a variable region comprising the hyper variable regions of the heavy and light chains of monoclonal antibody Navy Sporozoite 3 (HB10615) and human antibody framework regions.

The examiner relies on the following references:

McCutchan et al (McCutchan 1) 4,694,944 Sept. 15, 1987

McCutchan, T.F. et al (McCutchan 2). "Sequence of the Immunodominant Epitope for the Surface Protein Sporozoites of Plasmodium vivax," Science, Vol. 23, pp. 1381-1383 (1985)

Harlow et al. (Harlow), Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory pp. 287 (1988)

Charoenvit, Y. et al. (Charoenvit), "Inability of Malaria Vaccine to Induce Antibodies to a Protective Epitope Within its Sequence," Science, Vol. 251, pp. 668-671 (1991)

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Harris et al. (Harris), "Therapeutic Antibodies - The Coming of Age," Tibtech, Vol. 11, pp. 42-44 (1993)

Mitchell, G. H., (Mitchell), "An Update on Candidate Malaria Vaccines," Parasitology, Vol. 98, New York, pp. S29-S46 (1989)

Grounds of Rejection

1. Claims 1-3 stand rejected under 35 U.S.C. §103. As evidence of obviousness, the examiner cites McCutchan (1 and 2) and Harlow.

2. Claims 1-7, 11 and 12 stand rejected under 35 U.S.C. §112, first paragraph. As evidence of nonenablement, the examiner cites Charoenvit, Harris, and Mitchell.

We reverse both rejections.

DISCUSSION

Procedural Matters

In this case, an Appeal Brief with four attached 1.132 declarations was filed concurrent with a proposed amendment, on March 1, 1996. After several interviews and written communications, amended claims were entered by the Examiner, the effect of amendment entry on the rejections of record was communicated to the appellant on August 21, 1996, and a Substitute Brief was filed September 20, 1996, containing arguments directed to the amended claims. The Substitute Brief also refers to the

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declarations by Drs. Steven L. Hoffman (1st and 2nd declarations), Yupin Charoenvit, and Thomas F. McCutchan, which were attached to the original Brief.

In the Examiner's Answer, four rejections under 35 U.S.C. § 103 were withdrawn. No new grounds of rejection were made, and no Reply Brief was filed.

Background

Plasmodium vivax is one of the four species of parasite causing malaria in humans (specification, page 1). Despite major efforts over at least 20 years, a commercially viable malaria vaccine has not been achieved (page 2 of the December 28, 1993 amendment to the specification). The present invention involves a monoclonal antibody, here designated NVS3. The monoclonal antibody has been described in the prior art (specification, page 2). This antibody binds to an epitope within a repeated nine amino acid sequence of the circumsporozoite protein of P. vivax (specification, page 8). Prior to the invention, recombinant proteins comprising the P. vivax repeated amino acid sequence failed to induce a significant protective effect in Saimiri monkeys in active immunization experiments (specification, pages 3-4). An object of this invention is to provide passive protection against P. vivax by administering the antibody to a subject, where the antibodies

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bind to P. vivax sporozoites in the circulation of the host and render the sporozoites noninfectious thereby preventing malarial disease (specification, pages 4 and 7-8).

Enablement

Claims 1-7, 11 and 12 stand rejected under 35 U.S.C. §112, first paragraph. As evidence of nonenablement, the examiner cites Charoenvit, Harris, and Mitchell.

Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." In re Wands, 858 F.2d 73, 736-37, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

An analysis of whether the claims under appeal are supported by an enabling disclosure requires a determination of whether that disclosure contained sufficient information regarding the subject matter of the appealed claims as to enable one skilled in the pertinent art to make and use the claimed invention. In order to establish a prima facie

case of 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) (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 also In re Morehouse, 545 F2d 162, 165, 192 USPQ 29, 32 (CCPA 1976). The threshold step in resolving this issue is to determine whether the examiner has met his burden of proof by advancing acceptable reasoning inconsistent with enablement.

Factors to be considered by the examiner in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman, [230 USPQ 546, 547 (Bd Pat App Int 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. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the present case, the examiner cites the state of the art and the lack of working examples involving humans as the factors leading to a conclusion of non-enablement. Specifically, the examiner argues (Answer, page 6):

The state of the art to which the invention pertains is such that as of this date passive immunization has not been used to prevent malaria in humans and that there are no vaccines for active or passive immunization that are accepted as being effective for prevention of P. vivax malaria. Charoenvit et al. (Science 251) states that it has never been definitively established in humans that circulating antibodies to the sporozoite of Plasmodium can prevent infection. Furthermore, Harris et al. establishes the use of monoclonal antibodies for in vivo human therapy is art-recognized to be highly experimental and unpredictable to those of skill in the art. The record contains no working examples relating to the use of the NVS3 antibody for treatment of P. vivax malaria in humans....

The invention has been exemplified using the monkey model. However, the evidence obtained using the monkey model is not sufficient to allow one of ordinary skill in the art to predict the ability to practice the claimed invention for treatment of humans given that the monkey model used to exemplify the claimed invention is not an art-accepted model which is recognized as having a clear correlation with human efficacy for the evaluation of agents for passive immunotherapy of malaria.

On the other hand, the appellants argue that proof of efficacy in humans is not required, and that the monkey animal model tests disclosed in the specification are accepted by experts in the field. Substitute Brief, pages 13-15.

The specification provides a working example demonstrating efficacy of the claimed formulation in a nonhuman primate, the Saimiri monkey. Example 3, pages 13-15. In addition, the Hoffman Declaration of record provides an expert opinion that "most experts in the field consider this monkey model to be the most reliable system for predicting what will occur in humans." Hoffman Declaration, page 6. The Hoffman Declaration also cites long-held knowledge in the art of passive immunotherapy for acute malaria in human children. Hoffman Declaration, pages 4-5.

Although the examiner considered several scientifically conservative statements regarding the acceptability of the animal model of record, such as, “this monkey model system has not been validated” (Hoffman declaration, page 6), and “[w]ith the exception of the work carried out in man, the validity of all the experimental systems is open to challenge” (Mitchell, page 2), we do not find that the examiner has reviewed the evidence of enablement provided by appellants as a whole.

The cases of In re Fouche, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971) and In re Brana, 51 F.3d 1560, 1563, 34 USPQ2d 1436, 1439 (Fed. Cir. 1995), recognize that 35 U.S.C. §101 rejections for utility present similar issues as 35 U.S.C. §112 rejections for nonenablement. Thus, it is appropriate to consider relevant utility case law to the present enablement issue.

In Brana, the Federal Circuit stated, “Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility.” In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995); In re Krimmel, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961). In addition, “...pharmacological testing of animals is a screening procedure for testing new drugs for practical utility.” Cross v. Iizuka, 753 F.2d 1040, 1051, 224 USPQ 739, 747 (Fed. Cir. 1985); In re Jolles, 628 F.2d 1324, 1327, 206 USPQ 885, 890 (CCPA 1980).

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It is appellants' position that successful in vivo testing for a particular pharmacological activity in an art accepted model (monkeys) establishes a significant probability that in vivo testing for this particular pharmacological activity will be successful in humans. On the facts before us, we agree.

Appellants submit that they have provided evidence of efficacy of the claimed formulation protective against Plasmodium vivax in the most reliable and standard animal model accepted by experts in the field for predicting the likelihood of success of the claimed invention in humans. Substitute Brief, page 13.

Based upon the relevant evidence as a whole, we find there to be a reasonable correlation between the disclosed in vivo utility and an in vivo activity in humans, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. Compare Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980). Therefore, we will not sustain the rejection of the claims for lack of enablement.

Obviousness

Claims 1-3 stand rejected under 35 U.S.C. §103. As evidence of obviousness, the examiner cites McCutchan (1 and 2) and Harlow.

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 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). A reference is considered in its entirety for what it fairly suggests to one skilled in the art. In re Wesslau, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965). 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, McCutchan 1 and 2 describe monoclonal antibodies which are specific for epitopes of a peptide which corresponds to a region of the P. Vivax CS (circumsporozite) protein. The specification, page 2, states that the monoclonal antibody disclosed by McCutchan et al (Science 230) and McCutchan et al (U.S. Patent No. 4,693,994) is the monoclonal antibody of the instant invention which is designated NVS3. Answer, page 5. The examiner acknowledges that the McCutchan references do not teach a composition comprising a pharmaceutical amount of a monoclonal antibody NVS3 in a pharmaceutically acceptable carrier. Id.

Harlow is cited by the examiner as establishing that it was well known in the art at the time of the invention to produce solutions of monoclonal antibodies in phosphate

buffered saline (PBS) which is considered to be a pharmaceutically acceptable diluent for storage of antibodies.

The examiner summarizes (Answer, pages 5-6),

It would have been obvious for one of ordinary skill in the art to produce solutions consisting of NVS3 monoclonal antibody as taught by McCutchan et al references. One of ordinary skill in the art would have been motivated to produce such compositions in order to form stable storage compositions, or working solutions for use in assays, etc. The antibody concentrations in such compositions would have been those which would be considered to be pharmaceutical amounts, and solutions comprising the NVS3 antibody PBS would be considered to be pharmaceutically injectable solutions given that the buffer PBS is a pharmaceutically acceptable diluent. Even though the appellants characterize the claimed formulations as being for use in passive protection against *P. vivax*, the claims read on the ingredients *per se*, which in the case of the instant claims are NVS3 antibody in a pharmaceutically acceptable carrier.

Appellants argue in response to this rejection that, at best the examiner has argued that it would be obvious to try using the NVS3 monoclonal antibody for passive immunization and that it would have some protective activity. Substitute Brief, page 24. Appellants argue the examiner has failed to provide evidence to support a reasonable expectation of the success of passive immunization using the monoclonal antibody, as claimed. *Id.* Furthermore, appellants argue that Harlow teaches away from the invention by recommending addition of sodium azide, a poison, as a preservative in monoclonal antibody solutions. Substitute Brief, page 32.

We agree with appellants that the examiner has failed to establish a prima facie case of obviousness on the record before us. McCutchan teaches the claimed monoclonal

antibody in the context of an analytical tool. Harlow, the secondary reference, states that when preparing a PBS solution of monoclonal antibodies in the laboratory, “[i]f there is no reason to avoid the use of sodium azide, add to 0.02%”. Harlow, page 287. In our view, neither reference, however, provides any reason for one of ordinary skill in the art to avoid the use of sodium azide in preparing a monoclonal antibody solution, such as for preparing a composition for use in vivo.

The diagnostic use of a monoclonal antibody as described by McCutchan 1 and 2, in view of Harlow, would reasonably appear to have suggested that sodium azide be used in preparing such monoclonal antibody solutions. Therefore, taking the teachings of the references in their entirety, the references as a whole would have suggested to one of ordinary skill in the art a composition comprising a monoclonal antibody, PBS and sodium azide in an antibody solution, leading to a solution which is not a pharmaceutically acceptable formulation, as claimed. Moreover, we find no evidence of record suggesting the use of, or supporting a reasonable expectation of success for the use of the monoclonal antibody for preparation of a pharmaceutical formulation for passive immunization against P. vivax. Therefore, we will not sustain the rejection of the claims for obviousness.

CONCLUSION

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The rejection of claims 1-3 under 35 U.S.C. §103 in view of McCutchan (1 and 2) and Harlow is reversed.

The rejection of claims 1-7, 11 and 12 under 35 U.S.C. §112, first paragraph is reversed.

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

REVERSED

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Toni R. Scheiner)	
Administrative Patent Judge)	
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)	BOARD OF PATENT
Demetra J. Mills)	
Administrative Patent Judge)	APPEALS AND
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Eric Grimes)	
Administrative Patent Judge)	