

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

Paper No. 45

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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

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Ex parte MARCUS A. HORWITZ

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Appeal No. 2002-1740  
Application 08/447,398

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ON BRIEF

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Before William F. Smith, 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 47-67 and 70, which are all of the claims pending in this application.

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Claim 47 is illustrative of the claims on appeal and reads as follows:

47. A vaccinating agent for use in immunizing a mammalian host susceptible to disease caused by a pathogen from the genus *Mycobacterium*, comprising a recombinant purified *Mycobacterium* 32 kD extracellular protein, and an adjuvant, with the proviso that said vaccinating agent does not contain an immunologically protective amount of unpurified *Mycobacterium* extracellular protein.

The prior art references relied upon by the examiner are:

Borremans, M., et al., "Cloning, Sequence Determination, and Expression of a 32 - Kilodalton-Protein Gene of *Mycobacterium tuberculosis*," Infection and Immunity, Vol. 57, No. 10, pp. 3123-3130 (1989)

Pal, P.G., et al., "Immunization with Extracellular Proteins of *Mycobacterium tuberculosis* Induces Cell-Mediated Immune Responses and Substantial Protective Immunity in a Guinea Pig Model of Pulmonary Tuberculosis," Infection and Immunity, Vol. 60, No. 11, pp 4781-4792 (1992)

Salata, R.A., et al., "Purification and Characterization of the 30,000 dalton Native Antigen of *Mycobacterium tuberculosis* and Characterization of Six Monoclonal Antibodies Reactive with a Major Epitope of This Antigen," Journal of Laboratory and Clinical Medicine, Vol. 118, pp. 589-598 (1991)

Wallis, R.S., et al., "Identification by Two-Dimensional Gel Electrophoresis of a 58 Kilodalton Tumor Necrosis Factor-Inducing Protein of *Mycobacterium tuberculosis*," Infection and Immunity, Vol. 61, No. 2, pp. 627-632 (1993)

Zhang, Y., et al., "Genetic Analysis of Superoxide Dismutase, the 23 Kilodalton Antigen of *Mycobacterium tuberculosis*," Molecular Microbiology, Vol. 5, No. 2, pp. 381-391 (1991)

Munk, M.E., et al., "T Cell Responses of Normal Individuals Towards Recombinant Protein Antigens of *Mycobacterium tuberculosis*," European Journal of Immunology, Vol. 18, pp. 1835-1838 (1988)

Verbon, A., et al., "Ontwikkeling van een seriolgische test voor tuberculose," Nederlands Tidschrift voor Geneeskunde, Vol. 135, No. 4, pp. 134-138 (1991)

Wiegshauss, E., et al., "Evaluation of Protective Potency of New Tuberculosis Vaccines," Reviews of Infectious Diseases, Vol. 11, Suppl. 2, pp. S484-S490 (1989)

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Reference cited by Appellant:

Kubica, George, ed., The Mycobacteria: A Sourcebook, Marcel Dekker, Inc., New York, pp. 929-930, (1984)

### Grounds of Rejection

Claims 47-67 and 70 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement as to how to make and use the invention within the scope of the claims.

Claims 47-49, 52, 53, 55, 57, 59, 60, 62 and 63 stand rejected under 35 U.S.C. § 103(a) as unpatentable in view of Pal in light of Borremans, Salata, Wallis, Zhang, Munk and Verbon.

We reverse the rejection for lack of enablement and affirm the rejection of the claims for obviousness.

### DISCUSSION

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

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellant regarding the noted rejection, we make reference to the examiner's Answer for the examiner's reasoning in support of the rejection, and to the appellant's

Brief and Reply Brief for the appellant's arguments thereagainst. As a consequence of our review, we make the determinations which follow.

### Background

According to the specification, the invention relates to immunotherapeutic agents and vaccines against pathogenic organisms such as bacteria, protozoa, viruses and fungus. Specification, page 1. The specification, page 2, states that "*M. tuberculosis* is particularly well suited for demonstrating the principles and advantages of the present invention."

"[In] an exemplary embodiment of the present invention, the target pathogen is *M. tuberculosis* and the majorly abundant products released extracellularly by *M. tuberculosis* into broth culture are separated from other bacterial components and used to elicit an immune response in mammalian hosts. Individual proteins or groups of proteins are then utilized in animal based challenge experiments to identify those which induce protective immunity making them suitable for use as vaccines." Specification, page 18.

"More specifically, following the growth and harvesting of the bacteria, by virtue of their physical abundance the principal extracellular products are separated from intrabacterial and other components through centrifugation and filtration. If desired, the resultant bulk filtrate is then subjected to fractionation using ammonium sulfate precipitation with subsequent dialysis to give a mixture of extracellular products,

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commonly termed EP.” Specification, pages 18-19. “Solubilized extracellular products in the dialyzed fractions are then purified to substantial homogeneity using suitable chromatographic techniques as known in the art.” *Id.* Such procedure results in fourteen individual proteinaceous major extracellular proteins ranging from 110 kD to 12 kD. Specification, page 19.

The immunoprotective products may be chemically synthesized using known techniques or directly expressed in host cells. “Whatever production source is employed, the immunogenic components may be separated and subsequently formulated into deliverable vaccines using common biochemical procedures such as fractionation, chromatography or other purification methodology and conventional formulation techniques or directly expressed in host cells containing directly introduced genetic constructs encoding therefor.” Specification, page 18.

#### Claim Interpretation

Our appellate reviewing court stated in Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567-1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), cert denied, 481 U.S. 1052 (1987):

Analysis begins with a key legal question -- what is the invention claimed? Courts are required to view the claimed invention as a whole. 35 U.S.C. 103. Claim interpretation, in light of the specification, claim language, other claims and prosecution history, is a matter of law and will normally control the remainder of the decisional process. [Footnote omitted.]

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To that end, we also note that during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Claim 47 is directed to a vaccinating agent for use in immunizing a mammalian host susceptible to disease caused by a pathogen from the genus *Mycobacterium*, comprising a recombinant purified *Mycobacterium* 32 kD extracellular protein, and an adjuvant, with the proviso that said vaccinating agent does not contain an immunologically protective amount of unpurified *Mycobacterium* extracellular protein.

The preamble of the claim uses the language “comprising” and thus the claim does not exclude the inclusion of other components in the vaccine. Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)[The term “comprising” is inclusive and does not exclude additional, unrecited elements or method steps.]. This is also consistent with the specification, page 17, which states that it is “anticipated that the present invention will consist of at least one, two or, possibly even several well defined immunogenic determinants.”

The term “purified” has not been defined in the specification. We interpret the term “purified” broadly to encompass any separation or isolation technique, as the term in its broadest sense means to “rid of unwanted elements”. Websters II New Riverside Dictionary, The Riverside Publishing Co., p. 956, 1994. Such a broad reading of the claims is consistent with the specification, page 18, indicating vaccine components may be obtained by fractionation, chromatography or other purification methodology,

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suggesting that fractionation is a form of purification methodology. The specification also suggests that immunogenic components of a vaccine may be directly expressed in host cells containing directly introduced genetic constructs encoding therefor.

Specification, page 18.

35 U.S.C. § 112, first paragraph

Claims 47-67 and 70 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement as to how to make and use the invention within the scope of the claims. The examiner relies on *Wiegshauss* as evidence of lack of enablement.

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 Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988). 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).

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

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why the scope of protection provided by a claim is not adequately enabled by the disclosure). See also In re Morehouse, 545 F2d 162, 192 USPQ 29 (CCPA 1976).

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. (footnote omitted). In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988). 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.

The examiner finds the claimed invention is “enabling for immunizing a guinea pig host susceptible to disease caused by *Mycobacterium tuberculosis* comprising purified extracellular proteins from *Mycobacterium tuberculosis*”, but “does not reasonably provide enablement for immunizing all other mammalian hosts susceptible to disease caused by any pathogen from the genus *Mycobacterium* using purified extracellular proteins from any other species of *Mycobacterium*.” Answer, page 4.

The examiner provides evidence (Wiesgeshaus), which according to the examiner, indicates that at “the time of filing of the instant specification, there remained a lack of correlation of success in animal models with successful vaccination of humans against mycobacterial disease....” Answer, page 5. The examiner further argues that “there would not be a reasonable expectation of success that the guinea pig model for vaccination would correlate to success in humans, and there would not be an expectation of success using an extracellular 32 KD protein from one species, e.g. *M. xenopi*, to vaccinate successfully against disease caused by *M. leprae* or *M. tuberculosis*.” Id.

We disagree with the examiner, and find that the evidence of record supports the position that the guinea pig model, while agreeably may not be an exact model of human *Mycobacterium tuberculosis*, is well accepted and recognized in the art as an animal model of *Mycobacterium tuberculosis* which can be reasonably correlated to the disease in humans. The specification page 6, suggests that the guinea pig model of *Mycobacterium tuberculosis* closely resembles the human pathology of the disease. In addition, several of the cited references, including Pal, Salata and Wiegshaus also recognize the guinea pig model. Appellant, similarly proffers Kubica to establish that the guinea pig model is a recognized model for *Mycobacterium tuberculosis*. Brief, pages 10-11.

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Thus, we do not find the examiner has met his burden and established a reasonable basis to question the enablement provided for the claimed invention. Nor has the examiner provided any evidence to support the position that the specification does not reasonably provide enablement for immunizing all other mammalian hosts susceptible to disease caused by any pathogen from the genus *Mycobacterium* using purified extracellular proteins from any other species of *Mycobacterium*.

The rejection of claims 47-67 and 70 for lack of enablement is reversed.

35 U.S.C. § 103(a)

Claims 47-49, 52, 53, 55, 57, 59, 60, 62 and 63 stand rejected under 35 U.S.C. § 103(a) as unpatentable in view of Pal in light of Borremans, Salata, Wallis, Zhang, Munk and Verbon.

According to appellant, the claims stand or fall together with respect to each rejection. Brief, page 4. Since the individual claims are not argued, we decide this appeal with respect to the prior art rejection on the basis of claim 47, as representative of claims 47-49, 52, 53, 55, 57, 59, 60, 62 and 63. 37 CFR §1.192(c)(7) (2000).

It is the examiner's position that Pal teach a vaccinating agent for use in promoting an effective immune response in a mammalian host against an infectious pathogen from the genus *Mycobacterium* (*M. tuberculosis*) comprising at least one majorly abundant extracellular product of *M. tuberculosis*. Answer, page 7. According to the examiner Pal teach the "presence of the extracellular products of  $\geq 30,000$

daltons in the vaccinating agent by using a Millipore filter with a molecular weight cutoff of 30,000 to concentrate the extracellular products (page 4782, column 2, line 43, and Figure 2).” Id. The examiner finds, however, that Pal uses isolated but not purified components. Id.

The examiner indicates Pal establishes that “a subunit vaccine against tuberculosis is feasible, and that extracellular molecules of *M. tuberculosis* are potential candidates for a subunit vaccine.” Answer, page 6. According to Pal, “a subunit vaccine may induce a higher level of immune protection than whole mycobacterial vaccine. Second, if a subunit vaccine excludes the structural surface proteins of the bacterium, the subunit vaccine theoretically should not induce opsonizing antibody, which may enhance infection by promoting uptake of *M. tuberculosis* into host cells in which the bacteria multiply. Third, because it need contain only one or a few molecules or submolecular fragments, a subunit vaccine is likely to be less toxic than a whole bacterial vaccine that contains thousands of different molecular species. Finally, in contrast to a live vaccine, a subunit vaccine would not cause disseminated disease in immunocompromised persons.” Pal, page 4791, column 1.

As indicated in our claim interpretation set forth above, we do not fully agree with the examiner’s characterization that Pal uses isolated but not purified components. We find that isolation or fractionation is a form of purification encompassed by the pending claims.

Borremans is relied on for the disclosure of the gene and protein sequence of a 32kD antigen from *Mycobacterium tuberculosis*. Borremans found the 32 kD extracellular protein to be a major stimulant of cellular and humoral immunity against mycobacterium (abstract). Answer, page 7.

Salata teaches a purified Mycobacterium 30kD extracellular protein. From guinea pig skin testing Salata concluded that the “30,000 dalton antigen of *M. tuberculosis* may possess greater tuberculin sensitivity than PPD-S [tuberculin-purified protein derivative].” Salata, page 594, column 2. Wallis teaches a purified *Mycobacterium* 58kD extracellular protein, Verbon teaches purified *Mycobacterium* 24, 16 and 12kD extracellular proteins, Zhang teaches a purified *Mycobacterium* 23kD extracellular protein, and Munk teaches purified *Mycobacterium* 71 and 12 kD extracellular proteins. Answer, pages 7-8.

The examiner summarizes (Answer, page 8):

It would have been obvious at the time the invention was made to a person having ordinary skill in the art to follow the teachings and suggestions of Pal et al concerning subunit vaccines by using individual, purified extracellular proteins of the other cited references in order to reduce any unwanted side effects caused by inclusion of components which may result in unwanted and/or unnecessary immune responses while providing an agent for vaccination.

Upon review of the evidence of record, we agree that the examiner has provided sufficient evidence to support a prima facie case of obviousness. In particular, Pal discloses a “purified”, e.g., isolated EP extracellular protein fraction from *Mycobacterium tuberculosis*. The EP extracellular protein fraction was filtered,

fractionated and dialysed from other cellular components. Pal, page 4782, column 2. The EP fraction was found to induce protective immunity. See, Abstract. Thus, Pal suggests the use of purified subunit vaccines from extracellular proteins of *Mycobacterium tuberculosis*. Borremans further purified and characterized a 32 kD extracellular protein from *M. tuberculosis*, and found the 32 kD extracellular protein to be a major stimulant of cellular and humoral immunity against *mycobacterium*. We find, the cited references, in combination would have reasonably suggested the claimed vaccinating agent, and provided a reasonable expectation of success to one of ordinary skill in the art of obtaining protective immunity from a 32 kD extracellular protein as described by Borremans, in purified form, as suggested by Pal.

In response, appellant summarily argues that the examiner has not set forth a prima facie case of obviousness, as the cited references, alone or in combination, “fail to teach or describe that the 32 kD protein could be utilized as a vaccinating agent, or to provide a reasonable expectation of success to one of ordinary skill in the art that such an agent could be made and utilized to provide a protective immune response.” Brief, page 17.

However, where the prior art gives reason or motivation to make the invention of representative claim 47, 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).

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Appellant has come forth with no evidence to support his position that there would not have been a reasonable expectation of success on the part of one of ordinary skill in the art of obtaining a vaccine providing a protective immune response. Nor has appellant put forth any other argument or reasoning which would suggest that the examiner has not properly established a prima facie case of obviousness. To this end we note 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).

We do not further address the disclosures of Salata, Wallis, Zhang, Munk and Verbon, as we find the combination of Pal and Borremans renders the invention of claim 47 obvious. Additional claims stand or fall with claim 47. The other references relied upon by the examiner address limitations in the dependent claims which have not been separately argued by appellant. We do not comment further upon these references as they are not necessary to support rejection of claim 47.

We find the examiner has established a prima facie case of obviousness which has not been rebutted by appellant with appropriate argument or evidence. The rejection of the claims for obviousness is affirmed.

CONCLUSION

The rejection of claims 47-67 and 70 under 35 U.S.C. § 112, first paragraph for lack of enablement to make and use the invention within the scope of the claims is reversed. The rejection of claims 47-49, 52, 53, 55, 57, 59, 60, 62 and 63 under 35 U.S.C. § 103(a) as unpatentable in view of Pal in light of Borremans, Salata, Wallis, Zhang, Munk and Verbon is affirmed. It would appear that, in view of the disposition in this appeal, claims 50-51, 54, 56, 58, 61, 64-67 and 70 are free of rejection.

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

William F. Smith	)	
Administrative Patent Judge	)	
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	)	BOARD OF PATENT
Demetra J. Mills	)	
Administrative Patent Judge	)	APPEALS AND
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