

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 17

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte YAN-PING YANG, ALI KANDIL, LUCY GISONNI,
RAAFAT E.F. FAHIM, and MICHEL H. KLEIN

Appeal No. 1999-1271
Application No. 08/467,883

ON BRIEF

Before ROBINSON, SCHEINER, and GRIMES, Administrative Patent Judges.

GRIMES, 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 29-46, all of the claims remaining in the application.

Claim 29 is representative and reads as follows:

29. A process for individually isolating P1, P2 and P6 outer membrane protein from a Haemophilus strain, comprising the steps of:

- (a) providing a cell paste of the Haemophilus strain;

- (b) selectively extracting P2 protein from the cell paste to produce a first supernatant containing said P2 protein substantially free from P1 and P6 protein and a residual precipitate containing P1 and P6 protein;
- (c) separating the first supernatant from said residual precipitate;
- (d) concentrating the P2 protein in said first supernatant to produce a second supernatant;
- (e) purifying P2 protein in said second supernatant substantially free from pyrogens, lipopolysaccharides and other impurities solubilized from said paste by said selective extraction step;
- (f) selectively extracting P1 protein from the residual precipitate from step (b) to produce a third supernatant containing P1 protein and a P6-containing precipitate;
- (g) separating said third supernatant from said P6-containing precipitate;
- (h) concentrating the P1 protein in said third supernatant to produce a fourth supernatant;
- (i) purifying P1 protein in said fourth supernatant substantially free from pyrogens, lipopolysaccharides, P2 protein and other impurities solubilized in step (f);
- (j) selectively extracting the P6-containing precipitate to produce a P6-containing supernatant and a first extracted precipitate;
- (k) separating said P6-containing supernatant from said first extracted precipitate;
- (l) concentrating the P6 protein in said P6-containing supernatant to produce a fifth supernatant; and
- (m) purifying P6 protein in said fifth supernatant substantially free from pyrogens, lipopolysaccharides, P1 protein and other impurities solubilized in step (j).

The examiner relies on the following references:

Kuo et al. (Kuo) 5,192,540 Mar. 9, 1993

Munson et al. (Munson), "Purification and Partial Characterization of Outer Membrane Proteins P5 and P6 from Haemophilus influenzae Type b," Infection and Immunity, Vol. 49, No. 3, pp. 544-549 (1985)

Loeb, "Protection of Infant Rats from Haemophilus influenzae Type b Infection by Antiserum to Purified Outer Membrane Protein a," Infection and Immunity, Vol. 55, No. 11, pp. 2612-2618 (1987)

Claims 29-46 stand rejected under 35 U.S.C. § 103 as obvious over the combined disclosures of Kuo, Loeb, and Munson.

We reverse.

Discussion

Appellants' specification discloses a method of isolating three outer membrane proteins, known as P1, P2, and P6, from a single preparation of Haemophilus influenzae cells. See pages 13-17. The claims on appeal are directed to this method.

The examiner rejected the claims as obvious over Kuo, Loeb, and Munson. Kuo discloses a method of isolating H. influenzae outer membrane protein P2. See column 2, lines 32-35. In Kuo's method, H. influenzae cells were lysed and mixed with 2% hexadecyltrimethylammonium bromide; the soluble components were then removed and the P2-containing precipitate was resuspended in CaCl₂ solution. Col. 4, lines 12-22. Ethanol (20%) was then added to selectively precipitate some components, leaving P2 in solution (col. 4,

lines 22-28), then 80% ethanol was added to precipitate “major outer membrane protein-containing material.” Col. 4, lines 27-32. P2 was then further purified.

Loeb discloses a method of isolating H. influenzae outer membrane protein P1.¹ See pages 2612-2613. In Loeb’s method, H. influenzae cells are treated to produce a preparation rich in outer membranes, then that preparation is treated with NaCl and a nonionic detergent to extract the P1 from the membranes. Page 2613, left-hand column. The extract was then subjected to further purification. See id.

Munson discloses a method of isolating H. influenzae outer membrane protein P6. See pages 544-545. Munson discloses that “P6 was the only Hib [H. influenzae type b] protein insoluble in 1% SDS-0.1 M Tris-0.5 M NaCl-0.1% β -mercaptoethanol (β ME) (pH 8.0) at 37°C (buffer B).” Page 544. Munson discloses purification of P6 by precipitation in buffer B. See id.

Thus, each of Kuo, Loeb, and Munson teaches a method for purifying one of the H. influenzae outer membrane proteins P1, P2, and P6. The examiner concluded that “it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the purification processes of Kuo et al., Loeb et al. [sic], and Munson et al. into a single isolation scheme.” Examiner’s Answer, page 5.

¹ Loeb refers to P1 as “protein a.” See page 2612, left-hand column (“protein a is equivalent to P1.”).

“In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art.” In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992). Prima facie obviousness cannot be shown unless the prior art provides “a reason, suggestion, or motivation to lead an inventor to combine [the] references.” Pro-Mold and Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

The prima facie case must take into account all of the limitations recited in the claim. See In re Angstadt, 537 F.2d 498, 501, 190 USPQ 214, 217 (CCPA 1976) (“[W]e must give effect to all claim limitations.” (emphasis in original)). Therefore, where the claims require that certain steps be performed in a certain order, the prior art must suggest the recited steps in the recited order.

In this case, the examiner has not met her burden of showing that the cited references would have suggested the claimed process to those skilled in the art. We can agree, at least for argument’s sake, that those skilled in the art would have been motivated to purify multiple Haemophilus membrane proteins from a single cell preparation, because doing so would reduce the amount of starting material required. We can also agree that purified P1, P2, and P6 membrane proteins would have been recognized as desirable, since the prior art teaches that these proteins each raise protective antibodies (see Kuo, col. 2, lines 57-64; Loeb, abstract; Munson, abstract).

However, the process that the examiner alleges to be made obvious by the prior art is different from the instantly claimed process. The examiner argues that it would have been obvious

to combine the purification processes of Kuo et al., Loeb et al. [sic], and Munson et al. into a single isolation scheme. . . . [I]t would have been obvious to one of ordinary skill in the art to take the proteins from the same type of sample because one of ordinary skill in the art would know that once P1 were extracted from the paste, P2 and P6 would remain in the paste so that one could go back to the original sample to extract the others.

Examiner's Answer, page 5. Thus, the examiner argues that the prior art would have made it obvious to extract P1 from Haemophilus cell paste, then separate the P2 and P6 remaining in the paste. In the claimed process, however, P2 is isolated first, leaving P1 and P6 in the cell paste. Thus, the process that is alleged to be obvious is different from the claimed process.

Even assuming that the examiner intended to say that it would have been obvious to extract P2 first, as required by the claims, we do not agree that the cited references render the claimed process prima facie obvious. In the claimed process, P2 is selectively extracted from Haemophilus cell paste to produce a supernatant containing P2 and a precipitate containing P1 and P6. The cited references suggest that each of P1, P2, and P6 can be isolated from Haemophilus cells. However, the examiner has pointed to nothing in the references that would have motivated a skilled artisan to first carry out the P2 isolation disclosed by Kuo, then apply the P1 isolation process disclosed by Loeb.

As discussed above, Kuo's method involves lysing H. influenzae cells and mixing the cell lysate with 2% hexadecyltrimethylammonium bromide. The soluble cell components were then discarded and the P2-containing precipitate was resuspended in CaCl₂ solution. Ethanol (20%) was added, and the precipitated cellular components were discarded. The soluble P2 was then precipitated with 80% ethanol and further purified. See column 12-45.

Presumably, under the examiner's rationale, the skilled artisan would have found it obvious to take the precipitate from Kuo's 20% ethanol precipitation and recover P1 protein from that, using the procedure disclosed by Loeb. We do not find any suggestion to do so in the cited references. Loeb's P1 purification protocol begins with H. influenzae cells, then separates the outer membranes from the cells by treatment with Tris. The isolated membranes are then treated with 0.25 M NaCl and a nonionic detergent to solubilize P1 protein from the membranes, and the P1 protein is further purified. Nowhere does Loeb suggest that his procedure would benefit from, or even be compatible with, the initial steps in Kuo's P2 purification (specifically, cell lysis, addition of hexadecyltrimethylammonium bromide, precipitation, resuspension in CaCl₂, and 20% ethanol precipitation).

In short, the only suggestion we find in the record to carry out the steps of the claimed process, in the order recited, comes from Appellants' specification. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing

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together the prior art to defeat patentability—the essence of hindsight.” In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

Summary

The cited references do not provide adequate motivation to combine the cited references. We therefore reverse the rejection under 35 U.S.C. § 103.

REVERSED

DOUGLAS W. ROBINSON)	
Administrative Patent Judge)	
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)	BOARD OF PATENT
TONI R. SCHEINER)	
Administrative Patent Judge)	APPEALS AND
)	
)	INTERFERENCES
)	
ERIC GRIMES)	
Administrative Patent Judge)	

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SIM & McBURNEY
SUITE 701
330 UNIVERSITY AVENUE
TORONTO ON M5G 1R7
CANADA

EG/jlb