

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

Paper No. 22

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BINIE V. LIPPS

Appeal No. 1999-2141
Application No. 08/657,164

ON BRIEF

Before WILLIAM F. SMITH, ADAMS, and MILLS, 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 8-11, which are all of the claims pending in this application.

We reverse.

Claims 8 and 11 are illustrative of the claims on appeal and read as follow:

8. A method for preparing beta taipoxin from taipan snake venom in a single pass through a high pressure liquid chromatograph, said method comprising:

diluting the taipan snake venom with phosphate buffer saline,

separating a supernatant liquid from the diluted venom, and

fractionating the supernatant liquid on a high pressure liquid chromatograph, using an ion exchange column and a gradient buffer consisting essentially of (2-amino-2(hydroxymethyl)propane-1,3-diol)-HCl and water and having a pH in the range of 6.0 - 8.0 to elute a venom fraction consisting essentially of beta taipoxin.

11. A method for separating beta taipoxin from a snake venom fraction which comprises beta taipoxin together with alpha taipoxin and gamma taipoxin, said method comprising

fractionating the snake venom fraction on a high pressure liquid chromatograph, using an ion exchange column and a gradient buffer consisting essentially of (2-amino-2(hydroxymethyl)propane-1,3-diol)-HCl and water and having a pH in the range of 6.0 - 8.0 to elute the beta taipoxin separately from the alpha taipoxin and the gamma taipoxin.

The prior art references relied upon by the examiner are:

Haast (Haast '762)	4,341,762	Jul. 27, 1982
Haast (Haast '902)	4,741,902	May 3, 1988

Fohlman et al. (Fohlman), "Taipoxin, an Extremely Potent Presynaptic Neurotoxin from the Venom of the Australian Snake Taipan (Oxyuranus s. scutellatus)," Eur. J. Biochem., Vol. 68, pp. 457-469 (1976)

Lind, "Amino-Acid Sequence of the β 1 Isosubunit of Taipoxin, and Extremely Potent Presynaptic Neurotoxin from the Australian Snake Taipan (Oxyuranus s. scutellatus)," Eur. J. Biochem., Vol. 128, pp. 71-75 (1982)

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Bougis et al. (Bougis), "Characterization of Elapidae Snake Venom Components Using Optimized Reverse-Phase High-Performance Liquid Chromatographic Conditions and Screening Assays for " -Neurotoxin and Phospholipase A₂ Activities," Biochem., Vol. 25, pp. 7235-7243 (1986)

Tyler et al. (Tyler), "Studies on the subunit structure of textilotoxin, a potent neurotoxin from the venom of the Australian common brown snake (Pseudonaja textilis)," Biochim. Et Biophys. Acta, Vol. 915, pp. 210-216 (1987)

Hearn, "General strategies in the separation of proteins by high-performance liquid chromatographic methods," Journal of Chromatography, Vol. 418, pp. 3-26 (1987)

Robert K. Scopes (Scopes), Protein Purification Principles and Practice 3rd Ed., 154-158 (Charles Cantor, ed., Springer-Verlag) (1993)

Grounds of Rejection

1. Claims 8-11 stand rejected under 35 U.S.C. § 103 as unpatentable as obvious over Lind and Fohlman taken with Scopes, Tyler and Bougis.
2. Claims 8-11 stand rejected under 35 U.S.C. § 103 as unpatentable as obvious over Haast '762 and '902 in view of Tyler and Bougis.
3. Claims 8-10 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as now claimed.

DECISION

In reaching our decision in this appeal, we have given careful 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.

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Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellant regarding the above-noted rejections, we make reference to the examiner's Answer (Paper No. 21, January 27, 1999) for the examiner's complete reasoning in support of the rejection, and to the appellant's Brief (Paper No. 20, December 21, 1998) for the appellant's arguments thereagainst. As a consequence of our review, we make the determinations which follow.

DECISION ON APPEAL

35 U.S.C. § 103

Claims 8-11 stand rejected under 35 U.S.C. § 103 as unpatentable for obviousness over Lind and Fohlman taken with Scopes, Tyler and Bougis.

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). It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629, (Fed. Cir. 1996). Furthermore, the conclusion that the claimed subject matter is prima facie obvious must be supported by evidence, as shown by some objective teaching

in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to combine the relevant teachings of the references to arrive at the claimed invention. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). With this as background, we analyze the prior art applied by the examiner in the rejection of the claims on appeal.

The examiner finds that Lind establishes the amino acid sequence of the \$1 isosubunit of taipoxin from the Australian taipan snake. Lind describes the preparation and isolation of \$-taipoxin according to the method of Fohlman. Fohlman states that the " and \$ subunits of taipoxin "are the same size and cannot be separated from each other by molecular sieve chromatography" ... and "the only method found so far for the separation of " and \$ is electrophoresis at pH 1.9". Fohlman, page 465, column 2; page 467, column 1. Fohlman teaches the isoelectric point for the \$1 and \$2 isosubunits of taipoxin to be about pH 7. Fohlman, page 465.

The examiner finds that both Lind and Fohlman teach ion exchange and gel filtration methods for the purification of taipoxin, but admits that these publications do not teach the use of high performance liquid chromatography (HPLC) and choosing a gradient buffer comprising the Tris-HCL buffer. Answer, page 4.

To cure the deficiencies of Lind and Fohlman the examiner relies on Scopes for establishing the selection of elution buffers for ion exchange chromatography. Scopes

describes that in the pH range of 6-8, suitable buffers for ion exchange chromatography may be selected from four possible buffers, including Tris [tris(hydroxymethyl) amino methane]. The examiner indicates that given the isoelectric information for β -taipoxin described in Fohlman, it would have been obvious to one of ordinary skill in the art to employ the common Tris buffer at a pH range of around 7 to elute β -taipoxin purified fraction. Answer, page 5.

The examiner relies on Tyler and Bougis for establishing that “HPLC affords a convenient, high resolution method of separation by means of a single step.” Answer, page 6. Bougis suggests that the isolation of toxins from venom is “consistently a thorny problem in biochemistry”, and deals only with isolation of toxins from Elapidae snake venoms of the genus Naja using reverse phase HPLC. See Bougis page 7235, column 1, and 7236, column 2. Similarly, Tyler uses reverse phase HPLC to isolate textilotoxin from Australian brown snake, consisting of five non-covalently linked subunits. Tyler suggests that while textilotoxin shows some similarity with taipoxin, the toxins are “definitely not identical”. Tyler, page 215.

The examiner concludes that it would have also been obvious that in following these teachings, the subject matter as a whole would have been obvious, i.e., the separation of beta taipoxin subunits and the separation of non-toxic and toxic parts, would have been achieved by following HPLC techniques. The examiner further finds the “steps of adding a

saline buffer to the venom before centrifuging to obtain a supernatant to apply to HPLC column and fractionating by choosing a buffer within the pH of 7, to be within the skill of the art". Answer, page 5. The examiner suggests that at the time of the invention it was well known that HPLC affords a convenient, high resolution method of separation by means of a single step.

We do not find the examiner has established a prima facie case of obviousness on the evidence of record. The examiner fails to provide evidence of record describing a step of "diluting the taipan snake venom with phosphate buffer saline", as claimed. The examiner merely concludes the step of adding a saline buffer to the venom before centrifuging to obtain a supernatant to apply to HPLC column and fractionating by choosing a buffer within the pH of 7, to be within the skill of the art. Answer, page 5.

What is further missing from the examiner's analysis is why one of ordinary skill in the art would have been motivated to combine or substitute a single pass reverse phase HPLC method as described by Tyler and Bougis (a method based on a hydrophobic separation parameter), with or in place of an ion exchange HPLC method as described by Lind and Fohlman (a method based on a net molecular charge separation parameter) to arrive at the method of preparing α -taipoxin, as claimed. See, for example Hearn, Table 3. Other than the ability of reverse phase HPLC to isolate specific venom components in a single pass, Tyler and Bougis have little indicated relevance to the isolation of α -taipoxin

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from taipan snake venom and fail to cure the deficiencies of Lind taken with Fohlman and Scopes. Interestingly, neither Tyler nor Bougis use the claimed 2-amino-2-(hydroxymethyl)propane-1,3-diol-HCl buffer in their reverse phase HPLC single pass method.

Moreover, Appellant argues 1) the disclosed \$ taipoxin isolation techniques of Fohlman involve at least 4 steps, at least 3 of which are fractionation steps, whereas the method of the invention includes a single fractionation step (Brief, page 6), 2) the use of reverse phase chromatography (based on hydrophobic separation) in Tyler and Bougis teaches away from the ion exchange column HPLC method of the claimed invention (Brief, page 8), 3) the claimed method does not employ a pH gradient as in Scopes, and Scopes teaches the use of potassium or sodium chloride as an ionic strength gradient to elute proteins and does not suggest the use of Tris-HCl and water buffer (Brief, pages 7-8). These arguments of appellant remain unrefuted by the examiner.

Rejections based on § 103 must rest on a factual basis with these facts being interpreted without hindsight reconstruction of the invention from the prior art. The examiner may not resort to speculation, unfounded assumption or hindsight reconstruction to supply deficiencies in the factual basis for the rejection. See In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968). Our reviewing court has repeatedly cautioned against employing hindsight by using the

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appellant's disclosure as a blueprint to reconstruct the claimed invention from the isolated teachings of the prior art. See, e.g., Grain Processing Corp. v. American Maize-Products Co., 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988). The Federal Circuit states that "[the] mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." In re Fritch, 972 F.2d 1260, 1266 n.14, 23 USPQ2d 1780, 1783-84 n.14 (Fed. Cir. 1992), citing In re Gordon, 773 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

In the present case the examiner has failed to provide a fact based explanation premised on the correct legal standard. It appears that the primary reason, suggestion or motivation for combining the cited references as suggested by the examiner appears to come from appellant's disclosure. The examiner points to no scientific or technical reasoning within the references themselves which would suggest modification of the method of Fohlman to obtain the appellant's claimed method.

Where, as here, the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In view of the above, the rejection of claims 8-11 is reversed.

35 U.S.C. § 103

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Claims 8-11 stand rejected under 35 U.S.C. § 103 as unpatentable for obviousness over Haast '762 and '902 in view of Tyler and Bougis.

The examiner finds that Haast '762 and '902 evidence the preparation of presynaptic neurotoxin from viperid snake venom and its use for the treatment of neurological disorders. Haast '762 suggests that presynaptic neurotoxins from taipoxin may also be used for the treatment of neurological disorders. The Haast patents generally describe the centrifugation and separation of a supernatant from elapid or viperid snake venoms, and loading of supernatant onto an ion exchange column to fractionate the supernatant in the presence of sodium acetate, sodium chloride and Thimerosal. Haast '762, column 9, lines 28-67. The Haast patents are indicated by the examiner to lack a disclosure of a particular buffer and pH for such fractionation of viperid venom. Answer, page 5. Tyler and Bougis, are described above.

The examiner concludes that "it would have also been obvious that in following these teachings, the subject matter as a whole would have been obvious and the separation of non-toxic and toxic parts would have also been achieved by following HPLC techniques." Answer, page 6. The examiner finds the steps of adding a saline buffer to the venom before centrifuging to obtain a supernatant to apply to HPLC column and

fractionating by choosing a buffer within the pH of 7 to be within the skill of the art. Answer, page 6.

In addition to failing to provide evidence of record describing a step of “diluting the taipan snake venom with phosphate buffer saline”, the examiner fails to provide evidence of the use of 2-amino-2-(hydroxymethyl)propane-1,3-diol)-HCl in ion exchange chromatography to prepare β -taipoxin, as claimed.¹

In addition to the cited references, the examiner appears to rely on a review article by Hearn as representative of the state of the art regarding HPLC and reverse phase HPLC, suggesting that choosing a buffer or gradient for HPLC cannot be said to be a basis for patentability. Answer pages 7-8. In so much as Hearn is not relied on as a basis for the present rejection, it cannot and does not cure the deficiencies of the cited references.

It appears that the primary reason, suggestion or motivation for combining the cited references as suggested by the examiner comes from appellant’s disclosure. The examiner points to no scientific or technical reasoning within the references themselves which would suggest modification of the venom purification method of Haast to obtain the appellant’s specific claimed method of preparation of beta taipoxin.

¹ Note the failure to cite Scopes in the statement of rejection.

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The examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In view of the above, the rejection of claims 8-11 is reversed.

35 U.S.C. § 112, first paragraph

Claims 8-10 stand rejected under 35 U.S.C. § 112 first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The examiner finds that the claim term “in a single pass” in claim 8 is not supported by the original disclosure.

The purpose of the written description requirement under 35 U.S.C. § 112, first paragraph is to convey with reasonable clarity to those skill in the art, that, as of the filing date sought, appellants were in possession of the invention now claimed. Vas-Cath Inc. v. Makurar, 935 F.2d 1555, 1564, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The description of the invention is provided using descriptive means such as words, structures, figures, diagrams, formulas, etc. The exact terms need not be used in haec verba. Lockwood v. American Airlines, Inc., 107 F.2d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); citing: Eiselstein v. Frank, 52 F.3d 1035, 1038, 34 USPQ2d 1467, 1470 (Fed.

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Cir. 1995). Thus, as stated above, all that is necessary to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, is to convey to those skilled in the art, that, as of the filing date the applicant's were in possession of the invention. Vas-Cath Inc. v. Makurar, supra.

Appellant argues that the invention as now claimed is supported by the specification at pages 4-5. The specification page 5, line 5 appears to indicate that the fraction 6 obtained by HPLC can be used in the form obtained directly as a cell growth promoter or subjected to further purification. Thus, the specification would appear to support purification of the protein in a single HPLC pass. The specification would reasonably appear to convey to those skilled in the art, that, as of the filing date, the applicant's were in possession of the invention. The rejection of claims 8-10 under 35 U.S.C. § 112 first paragraph is reversed.

CONCLUSION

The rejections of claims 8-11 under 35 U.S.C. § 103 are reversed. The rejection of claims 8-10 under 35 U.S.C. § 112, first paragraph is reversed.

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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WILLIAM F. SMITH
Administrative Patent Judge

DONALD E. ADAMS
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

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