

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 26

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte FRANK M. LA DUCA

Appeal No. 1996-1811
Application No. 08/169,968¹

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and SPIEGEL, Administrative Patent Judges.
SPIEGEL, 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 through 24, which are all of the claims pending in this application.

Claims 1, 14 and 20 are illustrative and are attached as an appendix to this decision.

¹ Application for patent filed December 17, 1993. According to appellant, this application is a continuation of Application 07/978,190 filed November 18, 1992, now abandoned, which is a continuation of Application 07/758,741 filed September 12, 1991, now abandoned, which is a divisional of Application 07/583,164 filed September 17, 1990, now U.S. Patent 5,089,415, issued February 18, 1992.

Appeal No. 1996-1811
Application No. 08/169,968

The references relied on by the examiner are:

Naoi (JP 58-1460) ² (Japanese Kokai)	58-1460	Jan. 06, 1983
Sawai et al. (JP 61-53567) ³ (Japanese Kokai)	61-53567	Mar. 17, 1986

Lewis et al. (Lewis), "Antithrombin Pittsburgh: An α_1 -Antitrypsin Variant Causing Hemorrhagic Disease," 51 Blood 1, 129-137 (January 1978).

Claims 1-24 stand rejected under 35 U.S.C. § 103 as being unpatentable over JP 58-1460 in combination with Lewis and JP 61-53567. We REVERSE.

In reaching our decision in this appeal we have given careful consideration to the appellant's specification and claims and to the respective positions articulated by the appellant and the examiner. We make reference to the examiner's answer (Paper No. 22, mailed June 6, 1995) for the examiner's reasoning in support of the rejection and to the appellant's brief (Paper No. 21, filed March 27, 1995) and to appellant's reply brief (Paper No. 23, filed June 26, 1995) for the appellant's arguments thereagainst.

The claimed invention is directed to a reagent for rapidly clotting blood to produce a serum wherein the reagent does not alter the blood chemistry values in the resultant serum. The reagent comprises three compounds, i.e., thrombin, snake venom and a heparin

² We refer in our opinion to the translation of JP 58-1460 prepared for the PTO by The Ralph McElroy Translation Company in July 1993, a copy of which is attached to this decision.

³ We refer in our opinion to the translation of JP 61-53567 prepared for the PTO by FLS, Inc. In April 1996, a copy of which is attached to this decision.

neutralizing substance. Claim 1 specifies the concentration of these compounds as they would be present when mixed with a given volume of blood, i.e., about 0.2-3.0 U thrombin/ml blood mixture, about 0.005-0.2 mg snake venom/ml blood mixture and about 0.02-0.8 mg protamine sulfate (i.e., a heparin neutralizing substance)/ml blood mixture. Claim 14 recites functional amounts of these three compounds, i.e., thrombin, a generic heparin neutralizing substance and snake venom capable of converting fibrinogen to fibrin in "sufficient amounts to rapidly clot ... [a] highly heparinized blood sample." According to the specification,

[b]y applying this reagent combination in very low concentration it is possible to clot non anticoagulated blood from normal individuals within two minutes and blood from patients receiving heparin therapy within five minutes. Prior to the development of this clot promoting preparation, non anticoagulated blood required three to five times as long to clot (i.e., 6-10 minutes) and heparinized blood would not clot for several hours. [Page 6, lines 6-14.]

According to the specification, "[t]ypically highly heparinized blood is between 2-5 units per milliliter and possibly higher" (page 3, lines 8-9). Claim 20 recites preparation of a clotting reagent containing 0.5 U thrombin, 0.01 mg snake venom and 0.05 mg protamine sulfate per ml of reagent.

JP 58-1460 discloses blood collecting tubes containing, as a blood coagulation (i.e., clot) accelerating agent, either 10-200 µg (i.e., 0.01-0.20 mg) protamine sulfate or 10 µg or more (i.e., 0.01 mg or more) of thrombin-like enzyme contained in snake venom per ml of added heparinized blood sample (page 4, lines 11-24). "[T]he serum sample could

be rapidly obtained from the blood sample added with heparin without affecting the results of blood biochemistry tests” (page 4, lines 7-9). The blood sample clotted within 30 minutes (page 7, line 10).

Table 4 (page 132) in Lewis compares the effect of various clotting reagents on citrated normal and citrated heparinized plasma. The clotting reagents are (1) bovine thrombin, (2) human thrombin, (3) *Crotalus h. horridus* snake venom, (4) Arvin (*Ancestrodon rhodostoma*) snake venom, (5) bovine thrombin combined with BaCl₂ and (6) bovine thrombin combined with protamine. According to Lewis,

Heparin inhibits the thrombin clotting of fibrinogen but not the clotting caused by some snake venoms. Heparin is adsorbed from citrated plasma onto insoluble barium citrate, which is formed when barium chloride is added to citrated plasma. Heparin is neutralized by protamine sulfate. [Page 132, second full paragraph.]

JP 61-53567 describes preparing a thrombin-like enzyme from *Trimeresurus okinavensis* snake venom for use as a blood coagulation enhancing agent (page 4). Approximately 1.5 µg thrombin-like enzyme (i.e., 50 µg/ml x 0.30 µl used) can coagulate 5 ml of normal human blood or heparinized blood within 20 to 25 minutes (page 6).

According to the examiner, “[t]he references disclose only the use of venom alone or protamine alone or thrombin in combination with protamine to clot heparinized blood or plasma” (answer, page 4, last sentence). Thus,

... it is prima facie obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a

third composition which is useful for the purpose. [Answer, page 5, lines 11-14.]

The examiner further concludes that variations in the concentrations of the ingredients claimed from the concentrations disclosed in the prior art are matters of experimental design and optimization (answer, page 5, lines 6-9) and that dissolving three known components in a well known buffer is an obvious method of making an obvious solution (answer, sentence bridging pages 5-6).

When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. In In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987), the Federal Circuit held that although the prior art disclosed the separate components of the claimed new compositions for the same general use of treating cooling water systems, a prima facie case of obviousness was not established “absent some teaching, suggestion, or incentive supporting the combination.” Here, there is nothing in the prior art to lead a person of ordinary skill in the art to the claimed combination of clot enhancing agents. On the contrary, the prior art suggests using these agents in the alternative.

Lewis discloses using snake venom as an alternative clotting reagent to a combination of thrombin and a heparin neutralizing substance (i.e., protamine sulfate or barium chloride). JP 58-1460 discloses using snake venom or protamine sulfate as alternative clotting reagents. JP 61-53567 discloses an alternative snake venom

Appeal No. 1996-1811
Application No. 08/169,968

preparation. The only place we find the suggested combination of all three compounds into a single clot accelerant reagent is in appellant's specification. Therefore, we find that the examiner has relied on impermissible hindsight in making her determination of obviousness. In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps"). Accordingly, the rejection of claims 1-24 under 35 U.S.C.

§ 103 is reversed. Having concluded that the examiner has not established a *prima facie* case of obviousness, we need not consider the appellant's rebuttal evidence (see brief, pages 2, 4 and 6, referring to "the test results submitted by the applicant in Paper No. 16.")⁴ In re Fine, 837 F.2d 1071, 1076, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

CONCLUSION

To summarize, the decision of the examiner to reject claims 1-24 under 35 U.S.C. § 103 as being unpatentable over JP 58-1460 in combination with Lewis and JP 61-53567 is reversed.

⁴ Appellant's reference to Paper No. 16 is apparently an inadvertent typographical error. Paper No. 16 (filed December 1, 1994) is an extension of time request. The amendment concurrently filed on December 1, 1994 (Paper No. 17) with the extension of time request is evidently intended.

Appeal No. 1996-1811
Application No. 08/169,968

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

REVERSED

SHERMAN D. WINTERS)	
Administrative Patent Judge)	
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)	BOARD OF PATENT
WILLIAM F. SMITH)	APPEALS
Administrative Patent Judge)	AND
)	INTERFERENCES
)	
)	
)	
CAROL A. SPIEGEL)	
Administrative Patent Judge)	

APPENDIX

1. A reagent preparation for the rapid production of serum when said preparation is mixed with a given volume of blood, wherein said mixture includes thrombin in a concentration range of about 0.2-3.0 units per ml, snake venom having a concentration in the range of about 0.005-0.2 mg per ml, and a heparin neutralizing substance including a protamine salt having a concentration in the range of about 0.02-0.08 mg per ml, said preparation causing said blood to rapidly clot to enable one to obtain a serum providing clinically accurate blood chemistry analysis.

14. A cocktail preparation to enable relatively rapid clotting of highly heparinized blood when said cocktail is mixed with a given volume of blood, comprising thrombin, a heparin neutralizing substance, and a snake venom which snake venom is capable of converting fibrinogen to fibrin and is unaffected by the presence of heparin, said thrombin, heparin neutralizing substance, and snake venom present in sufficient amounts to rapidly clot said highly heparinized blood sample and to enable the serum to be separated from said clotted matter, said serum to be chemically tested to provide clinically accurate blood chemistry results.

20. A method of preparing a cocktail reagent for rapidly producing serum from blood, comprising:
preparing a first solution by dissolving bovine thrombin in barbital buffered saline to a concentration of 100 units per ml;
preparing a second solution by dissolving a snake venom in barbital buffered saline to a concentration of 1 mg per ml;
preparing a third solution by dissolving protamine sulfate in a sodium chloride solution to a concentration of 10 mg per ml; and
combining a predetermined amount of said first, said second and said third solutions to form a mixture such that the final concentration of said mixture contains 0.5 units thrombin per ml, 0.01 mg snake venom per ml, and 0.05 mg protamine sulfate per ml.

Appeal No. 1996-1811
Application No. 08/169,968

ARTHUR L. PLEVY
PLEVY & ASSOCIATES
146 ROUTE 1 NORTH
P.O. BOX 1366
EDISON, NEW JERSEY 08818-1366

APPEAL NO. 1996-1811 - JUDGE SPIEGEL
APPLICATION NO. 08/169,968

APJ SPIEGEL

APJ WINTERS

APJ ELLIS

DECISION: **REVERSED**

Prepared By:

DRAFT TYPED: 13 Jul 01

FINAL TYPED: