

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 14

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte TZE-CHEIN WUN

Appeal No. 1998-0350
Application 08/453,937

ON BRIEF

Before WINTERS, 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 1-6, all of the claims remaining in the application.

Claims 1, 3, and 4 are representative and read as follows:

1. A composition essentially free from antithrombin and consisting essentially of LACI and an anticoagulant sulfated polysaccharide in proportions that provide a synergistic anticoagulation effect upon administration to a warm-blooded mammal.

3. A composition according to Claim 1 in which heparin and LACI are in proportions of from about 0.1 to about 4 units of said heparin and from about 0.1 to about 5 µg of LACI.

4. A method of inhibiting blood coagulation in whole blood plasma of a warm blooded mammal comprising exogenously administering to said mammal an effective synergistic anticoagulant amount of an anticoagulant sulfated polysaccharide and LACI essentially free from antithrombin.

The examiner relies on the following references:

Broze, Jr. et al. (Broze), "The Lipoprotein-Associated Coagulation Inhibitor That Inhibits the Factor VII-Tissue Factor Complex Also Inhibits Factor Xa: Insight Into Its Possible Mechanism of Action," Blood, Vol. 71, No. 2, pages 335-343 (1988).

Sandset et al. (Sandset),"Heparin Induces Release of Extrinsic Coagulation Pathway Inhibitor (EPI)," Thrombosis Research, Vol. 50, No. 6, pages 803-813 (1988).

Rapaport, "Inhibition of Factor VIIa/Tissue Factor-Induced Blood Coagulation: With Particular Emphasis Upon a Factor Xa-Dependent Inhibitory Mechanism," Blood, Vol. 73, No. 2, pages 359-365 (1989).

Girard et al. (Girard), "Inhibition of Factor VIIa-Tissue Factor Coagulation Activity by a Hybrid Protein," Science, Vol. 248, pages 1421-1424 (1990).

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as anticipated by Broze.

Claims 4 and 5 stand rejected under 35 U.S.C. § 103 as obvious over Broze and Sandset.

Claims 3 and 6 stand rejected under 35 U.S.C. § 103 as obvious over Broze, Sandset, Rapaport, and Girard.

We reverse.

Background

Blood clotting can be activated via the intrinsic or the extrinsic coagulation pathway. Specification, page 1. Lipoprotein-associated coagulation inhibitor

(LACI)¹ was known to interfere with the extrinsic blood coagulation pathway. Id., page 2. Heparin was also known in the prior art to be an anticoagulant. Id., page 1. Anticoagulants are used in treating thrombotic diseases such as disseminated intravascular coagulation. Id., page 3. The specification discloses pharmaceutical compositions comprising heparin or another sulfated polysaccharide and LACI.

The specification states that the combination of LACI and a sulfated polysaccharide such as heparin produces a synergistic anticoagulant effect in whole blood plasma. Page 3. The specification presents several working examples showing the effects of heparin and LACI on extrinsic pathway coagulation, both alone and in combination. See pages 16-19 and Figure 4. The evidence of record also includes two declarations under 37 CFR § 1.132 by Appellant Tze-Chein Wun and one declaration under 37 CFR § 1.132 by George J. Broze, Jr. See Paper Nos. 9 and 13 in parent application 08/166,186, and Paper No. 5 in the instant application, respectively.

Discussion

1. Procedural History

According to Appellant, the instant application is a continuation-in-part of application 08/166,186, which is a continuation of application 07/573,083. The '083 grandparent application was the subject of a previous appeal to this Board. The claims in the '083 grandparent application were rejected as anticipated or

¹ LACI is also known in the art as tissue factor inhibitor (TFI) and extrinsic pathway inhibitor (EPI). Specification, page 2.

obvious over the same Broze reference cited by the examiner in this case, either alone or in combination with other prior art. The panel in that appeal affirmed the rejections.

We note that the record in this appeal differs substantially from that of the '083 grandparent application. During the prosecution of the instant application and the intervening parent application, the claims were amended and the record was supplemented with additional arguments and evidence, including the three declarations referred to above. The changed record requires us to consider the merits of this case anew, uninfluenced by the decision that was reached in the previous case. See In re Hedges, 783 F.2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986) (“[I]f the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed.”). See also In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976) (“When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over. . . . [A] final finding of obviousness may of course be reached, but such finding will rest upon evaluation of all facts in evidence, uninfluenced by any earlier conclusion reached . . . upon a different record.”).

2. The rejection under 35 U.S.C. § 102(b)

The examiner rejected claims 1 and 2 as anticipated by Broze. Claim 1 is directed to a composition “essentially free from antithrombin and consisting essentially of LACI and an anticoagulant sulfated polysaccharide,” such as heparin. Broze discloses a composition containing LACI, activated factor VII

("VIIa"), activated factor X ("Xa"), Ca²⁺, and tissue factor ("TF"), together with either or both of antithrombin IIIa and heparin. See the legend to Figure 3. The composition containing heparin but not antithrombin therefore is "essentially free" of antithrombin, as required by the claim; the question is whether the disclosed composition "consists essentially of" LACI and heparin.

"By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." PPG Indus. Inc. v. Guardian Indus. Corp., 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998).

Thus, the composition of claim 1 is open to the inclusion of other ingredients that do not "materially affect the basic and novel properties" of the composition. One of the "basic and novel properties" of the claimed composition is recited in the claim itself: "provid[ing] a synergistic anticoagulation effect upon administration to a warm-blooded mammal."

The composition disclosed by Broze contains the clotting factors VIIa, Xa, and tissue factor, which carry out enzymatic reactions that cause blood to coagulate. See the specification, page 1:

[T]he extrinsic pathway is initiated when plasma factor VII/VII_a binds to tissue factor (TF; thromboplastin) to form a complex which proteolytically activates factors IX and X. Once factor X_a is formed, . . . it can . . . form the prothrombinase complex which converts prothrombin to thrombin. Ultimately, thrombin causes the fibrin clot to form.

Therefore, the clotting factors VIIa, Xa, and tissue factor would tend to negate the anticoagulant effect of LACI and heparin, if the disclosed composition itself were administered to a mammal. Therefore, factor VIIa, factor Xa, and tissue factor affect the “basic and novel properties” of the composition, and their inclusion in the composition of claim 1 is excluded by the “consisting essentially of” language of the claim.

Claim 1 does not read on the composition disclosed by Broze. The rejection under 35 U.S.C. § 102(b) is reversed.

3. The rejections under 35 U.S.C. § 103

The examiner rejected claims 4 and 5 as obvious over Broze and Sandset, and rejected claims 3 and 6 as obvious over Broze, Sandset, Rapaport, and Girard. The examiner argues that “Broze et al. teach the in vitro use of the LACI/heparin composition as an anticoagulant,” and Sandset teaches that administration of heparin causes a several-fold increase in plasma LACI activity. Examiner’s Answer, pages 4-5.²

Appellant argues the references do not support a prima facie case of obviousness because Broze’s data show that, in the presence of antithrombin, the combination of LACI and heparin actually has lower anticoagulant activity than LACI alone. Appellant argues that this teaching would not have led the skilled artisan to combine LACI and heparin as an anticoagulant in whole blood,

² The examiner relies on Rapaport and Girard for teaching the specific dosages recited in claims 3 and 6. Examiner’s Answer, page 6. Because we conclude that Broze and Sandset would not have led those skilled in the art to combine LACI and heparin at all, we will not further discuss the teachings of Rapaport and Girard.

because whole blood plasma contains antithrombin. Brief, page 7. Appellant has submitted a declaration by George J. Broze, Jr., one of the authors of the Broze reference, which supports Appellant's position on how the Broze reference would have been viewed by those skilled in the art.

The examiner addresses this argument as follows:

In spite of the well-known fact that normal plasma or whole blood by definition would contain a high concentration of antithrombin III (AT III) and in spite of the fact that Broze teaches that AT III with heparin abrogated the TF [tissue factor] inhibition by LACI or in other words, abrogated the anticoagulant effects of LACI, . . . th[e] reference by Sandset et al. taken together with Broze et al. establishes that one of ordinary skill in the art would have recognized that in vitro results of the anticoagulant activity of compositions are generally predictive of in vivo efficacy and therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made, that administering LACI **and** heparin to animals in vivo, . . . would result in an effective synergistic form of anticoagulant therapy.

Examiner's Answer, pages 5-6.

We find that the weight of the evidence in the record supports Appellant's reading of the prior art. Broze discloses that, in vitro, the presence of antithrombin III interferes with the anticoagulant activity of LACI and heparin, so that in the presence of antithrombin III, LACI and heparin together have lower anticoagulant activity than LACI alone. See Figure 3 of Broze and the Broze declaration, page 3, second paragraph ("LACI-mediated inhibition of factor VIIa/tissue factor was reduced by heparin when antithrombin III, a normal plasma component, was present.").

The examiner has conceded that "normal plasma or whole blood by definition would contain a high concentration of antithrombin III." Nevertheless,

the examiner argues that Sandset would have led those skilled in the art to expect LACI and heparin to act synergistically in vivo, because Sandset teaches that administration of heparin, alone, resulted in a several-fold increase in LACI³ activity in patients. Id.

The examiner's argument is not persuasive. It is true that Sandset teaches that "[a]fter intravenous injection [of heparin], EPI activity increased dose-dependently." See the abstract. Sandset's data, however, led him to "conclude that EPI probably is produced in endothelial cells and may be released by heparin." Id. Sandset therefore would have led those skilled in the art to expect that administration of heparin would lead to an increase in plasma LACI activity as a result of releasing endogenous LACI into the blood. However, Sandset does not suggest that heparin increases the activity of LACI already in circulation. That is, Sandset suggests that heparin increases the level, and therefore the activity, of LACI in plasma by releasing stored LACI from endothelial cells, but Sandset does not suggest that heparin affects the activity of LACI after the LACI is present in the plasma. Thus, while Sandset would have led those skilled in the art to expect administration of heparin alone to cause an increase in plasma LACI levels, Sandset would not have motivated those skilled in the art to combine LACI and heparin and administer them together as an anticoagulant composition.

In addition, even if the prior art supported a prima facie case of obviousness, Appellant's specification presents evidence that the claimed

³ Sandset refers to LACI by its alternative name of extrinsic pathway inhibitor, or EPI.

composition and method are unexpectedly superior to what would have been expected based on the prior art. Broze shows that when LACI and heparin are combined in the presence of 65 µg/ml of antithrombin III (AT III), they have a combined anticoagulant activity that is lower than the anticoagulant activity of LACI alone in the presence of AT III. See Figure 3 of Broze (compare results shown as filled squares (LACI + AT III) with those shown as filled upright triangles (LACI + heparin + AT III)).

Normal plasma contains about 290 µg/ml of AT III. See the Wun declaration filed June 17, 1994, page 3. Given this level of endogenous AT III and the teaching of Broze, those skilled in the art would have expected the combination of LACI and heparin to have a lower anticoagulant activity in whole plasma than LACI alone.

Contrary to this expected result, however, Appellant's data show that the combination of LACI and heparin has a higher anticoagulant activity in whole plasma than LACI alone. See Figure 4 in the specification. Figure 4 shows that, in whole plasma,⁴ LACI alone and heparin alone have roughly equivalent anticoagulant activities. For example, when LACI was added to plasma at 2.5 µg/ml, coagulation required about 100 seconds, about the same anticoagulant effect as that caused by heparin at 0.5 U/ml of plasma. However, when both LACI (at 2.5 µg/ml) and heparin (at 0.5 U/ml) were added, coagulation

⁴ The plasma was depleted of endogenous LACI. See the specification at page 6. Normal plasma, however, contains only 0.1 µg/ml of LACI. See the Wun declaration filed December 15, 1994. The plasma used in Figure 4 was supplemented with exogenous LACI at well over 0.1 µg/ml and therefore the experimental results cannot be attributed to removal of the endogenous LACI.

required about 1000 seconds. Thus, Appellant's data show that, even in the presence of antithrombin III, LACI and heparin together have much greater anticoagulant activity than LACI alone.

Thus, even if the cited references supported a prima facie case of obviousness, Appellant's data show results that are unexpectedly superior to what would have been expected based on the prior art. The evidence of unexpected results provides a second basis for reversing the § 103 rejections. "If rebuttal evidence of adequate weight is produced, the holding of prima facie obviousness, being but a legal inference from previously uncontradicted evidence, is dissipated." In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984). "There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious." In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Other Issues

Claims 3 and 6 recite a composition "in which heparin and LACI are in proportions of from about 0.1 to about 4 units of said heparin and from about 0.1 to about 5 µg of LACI." The specification states that "[u]se of from about 0.1 to about 4 units of said heparin per ml of plasma in combination with from about 0.1 µg to about 5 µg of LACI per ml of plasma is preferred." Page 4, lines 2-6 (emphasis added). Appellant may wish to consider whether the present wording of claims 3 and 6 accurately reflects the intended scope of the claims.

Summary

We reverse the rejection for anticipation because Broze does not disclose a composition “consisting essentially of” LACI and heparin. We reverse the rejections for obviousness because the prior art would not have led a person of ordinary skill in the art to make a composition consisting essentially of LACI and heparin or to expect the results disclosed in Appellant’s specification.

REVERSED

SHERMAN D. WINTERS)	
Administrative Patent Judge)	
)	
)	
)	BOARD OF PATENT
TONI R. SCHEINER)	
Administrative Patent Judge)	APPEALS AND
)	
)	INTERFERENCES
)	
ERIC GRIMES)	
Administrative Patent Judge)	

EG:psb

Appeal No. 1998-0350
Application No. 08/453,937

Roger A. Williams
G D Searle & Co.
Corporate Patent Law Dept.
P.O. Box 5110
Chicago, IL 60680-5110