

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte YASUSHI SHIRAHASE, KENJI ISSHIKI and
YOSHIFUMI WATAZU

Appeal No. 1997-0838
Application 08/235,238¹

HEARD: September 14, 2000

Before WILLIAM F. SMITH, SCHEINER and ADAMS, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 4 through 6, 10, 11, 13, 15 and 16, all the claims remaining in the application.

¹Application for patent filed May 2, 1994. According to appellants, this application is a continuation of Application Serial No. 07/646,999, filed January 29, 1991, now abandoned, which is a continuation-in-part of Application Serial No. 07/375,951, filed July 6, 1989, now abandoned.

Appeal No. 1997-0838
Application 08/235,238

Humans produce five lactate dehydrogenase (LDH) isozymes, LDH₁, LDH₂, LDH₃, LDH₄, and LDH₅, which catalyze the same reaction, but differ in certain of their physical and/or chemical properties. Each isozyme is composed of four subunits which may be heart muscle type (H), or skeletal muscle type (M), or both. For example, LDH₁ is composed of four H subunits, LDH₂, LDH₃ and LDH₄ are composed of various combinations of the H and M subunits, while LDH₅ is composed of four M subunits.

According to appellant,

Each of organs has its own composition of the isozymes. For example, LDH₁ is present in a myocardium in the largest amount. Since LDH₁ escapes from the myocardium into blood under a condition of a myocardial infarction, a rise in serum LDH₁ level can be diagnostic for such a disease. (Specification, page 1).

In its broadest aspect, the invention is directed to selective determination of LDH₁ in human serum or plasma (using an assay for total LDH activity), wherein LDH₂, LDH₃, LDH₄ and LDH₅, also present in the samples, are inhibited with a combination of " -chymotrypsin and a protein denaturing agent.

Obviousness

Claims 1, 4 through 6, 10, 11, 13, 15 and 16 stand rejected as unpatentable over latron, Selmecci and Sanford.

latron selectively measures residual LDH₁ activity in human serum using a protein denaturing agent (urea, thiourea, guanidine, etc.) in an alkaline buffer (pH 10-11) to inactivate LDH₂, LDH₃, LDH₄, and LDH₅.

Selmeci teaches that “susceptibility of LDH isozymes to proteolysis varies,” and mentions subtilisin as an example of a peptidase that digests LDH₅, but leaves LDH₁ unaltered. Because conformational changes induced by coenzymes and substrates also affect susceptibility of isozymes to proteolysis, Selmeci investigates the effect of NAD⁺ and NADH on the proteolysis of LDH₁ and LDH₅ by trypsin. Trypsin alone rapidly denatures LDH₁, and to a lesser extent, LDH₅; NADH has virtually no effect on proteolysis by trypsin, but NAD⁺ has an initial protective effect on LDH₁.

Sanford briefly discusses several methods of selectively inhibiting LDH isozymes, among them, denaturation with urea or oxalate, and concludes that “[t]he physical-chemical procedures suffer from lack of sufficient specificity.”

The examiner believes that:

It would have been obvious to one of ordinary skill in the art at the time the invention was made to selectively determine LDH₁ isoenzyme activity by combining the differential inhibitors of IATRON/SANFORD (protein denaturing agents) and SELMECI (protease) because their expected combined effect would be to more effectively eliminating [sic] the enzymatic activity of LDH₂-LDH₅ isoenzymes. Such a combination of inhibitors would have been further motivated by SANFORD’S disclosure that agents such as urea alone suffer from lack of sufficient specificity - - i.e. they do not adequately distinguish between heart isoenzymes, LDH₁ and LDH₂ - - and SELMECI’S disclosure that LDH₂-LDH₅ show a variable susceptibility to protease inhibition, while LDH₁ activity is unaffected.
(Examiner’s Answer, pages 7 and 8)

Appellants argue that the combined references not only fail to suggest the general concept of combining a protease with a denaturing agent to inhibit LDH₂, LDH₃, LDH₄, and LDH₅ (for a number of reasons set forth on pages 10 through 16 of the Brief), but most

Appeal No. 1997-0838
Application 08/235,238

importantly, “-chymotrypsin which is required by the claims, is not mentioned at all.” Brief, page 15.

The examiner addresses this last issue in the statement of the rejection only to the extent that he concludes that “it would have been obvious to use any known and conventional protein denaturing agent or proteolytic enzyme (protease) for their known and expected results.” Examiner’s Answer, page 8.

In our judgment, the combined disclosures of the cited references are insufficient to support a conclusion of obviousness for claims requiring “-chymotrypsin (especially as Selmececi shows that two other proteases, trypsin and subtilisin, affect the LDH₁ isozyme differently). 35 U.S.C. § 103 requires that obviousness be determined based on the claimed subject matter as a whole. Where, as here, the determination of obviousness is based on less than the entire claimed subject matter, the examiner’s conclusion is legally unsound and cannot be sustained. On this record, we reverse Rejection I under 35 U.S.C. § 103.³

Enablement

Claims 10 and 11 stand rejected under 35 U.S.C. § 112, first paragraph, as based on a non-enabling disclosure. These claims require “preserving more than 50% of LDH₁ activity” during the process of the invention. According to the examiner:

³ Having determined that a prima facie case of obviousness has not been established, we find it unnecessary to comment on appellants’ arguments regarding unexpected results attributable to the present invention.

Appeal No. 1997-0838
Application 08/235,238

Examples 1-4 in the specification show the claimed process where it is implied the LDH1 activity is preserved, however, it is not clearly shown what the activity was before and after the inhibiting step. Such a claimed limitation must be specifically recited in the specification. (Examiner's Answer, page 5).

This conclusory statement does not satisfy the examiner's initial burden of establishing unpatentability. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). The specification need only teach how to make and use the claimed invention. The examiner has not done the factual analysis necessary to establish that appellants' specification does not meet this standard, especially in light of Examples 1, 2 and 4, wherein LDH₁ retains 69% or more of its initial activity (i.e., wherein LDH₁ has a "residual activity" of 69% or more) in the presence of a protein denaturing reagent and " - chymotrypsin.

Accordingly, Rejection II of claims 10 and 11 as lacking enablement under 35 U.S.C. § 112, first paragraph, is reversed.

Written Descriptive Support

An issue arising under the written description requirement of 35 U.S.C. § 112, first paragraph, is a question of fact. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). "[T]he 'written description' requirement most often comes into play where claims not presented in the application when filed are presented thereafter . . . The question raised by these situations is most often phrased as whether the

Appeal No. 1997-0838
Application 08/235,238

application provides 'adequate support' for the claim(s) at issue." *Id.*, 935 F.2d at 1560, 1111 USPQ at 1114.

As the result of amendment, claims 10 and 11 require "preserving more than 50% of LDH₁ activity" during the process of the invention. Appellants argue that this limitation is adequately supported inasmuch as the invention "provid[es] an LDH₁ assay which is useful for clinical examinations," while prior art methods are described in the specification as "unsatisfactory for clinical examinations because more than 50 percent LDH₁ may be inactivated during the inhibition of the other enzymes." Brief, page 24.

In context, and under the heading "Description of the Related Art," the portion of the specification cited by appellants reads as follows:

In a most common LDH isozyme assay, LDH₁, LDH₂, LDH₃, LDH₄ and then LDH₅ are fractionated in the order of electrophoretic mobility. An immunological LDH assay is also known. In other LDH assay . . . a coenzyme derivative . . . is used. In addition, LDH assays wherein a sample is treated under an alkaline condition are described . . .

The above-mentioned electrophoretic or immunological assay is unsuitable for clinical autoanalysis because of complicated process and long operation time. In addition, the LDH isozymes may be insufficiently fractionated by the electrophoretic method.

[I]t is impossible to assay the LDH isozyme fractions by the method wherein the coenzyme derivative is used . . .

In the method comprising the alkaline treatment of the sample, more than 50 % of LDH₁ may be inactivated during the inhibition of the other isozymes. In addition, the process is complicated and takes a long time.

Thus, the above-mentioned conventional LDH assays are unsatisfactory for a clinical examination. (pages 1 and 2, emphasis added).

Appeal No. 1997-0838
Application 08/235,238

We agree with the examiner that, based on the specification, “there could be many other issues that render the prior art unsatisfactory.” Examiner’s Answer, page 9. In our view, appellants’ original disclosure would not convey to persons skilled in the art that “more than 50% LDH₁ activity” represents a limit on the range of LDH₁ activity for a clinically useful assay. Accordingly, we find no error in the examiner’s determination that the limitation “preserving more than 50% of LDH₁ activity” is not supported by the specification as originally filed.

Rejection III of claims 10 and 11 under § 112, first paragraph, is affirmed.

CONCLUSION

We have affirmed Rejection III of claims 10 and 11 under 35 U.S.C. § 112, first paragraph, and reversed Rejection I of claims 1, 4 through 6, 10, 11, 13, 15 and 16 under 35 U.S.C. § 103, as well as Rejection II of claims 10 and 11 under 35 U.S.C. § 112, first paragraph. Thus, by our action today, claims 1, 4 through 6, 13, 15 and 16 are free of rejection.

Appeal No. 1997-0838
Application 08/235,238

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
Toni R. Scheiner)	
Administrative Patent Judge)	APPEALS AND
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)	INTERFERENCES
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Appeal No. 1997-0838
Application 08/235,238

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