

The opinion in support of the decision being entered today was not written for publication in a law journal and is not binding precedent of the Board.

Paper No. 60

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte HUGO KATUS, ANNELIESE BORGYA,  
KLAUS HALLERMAYER, and SIEGRIED LOOSER

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Appeal No. 1999-1368  
Application 08/487,540

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HEARD: July 24, 2001

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Before WILLIAM F. SMITH, MILLS and GRIMES Administrative Patent Judges.

WILLIAM F. SMITH, 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 8, 10, 11, 13 through 15, 20 through 22 and 24 through 31. Subsequently, appellants canceled claim 25 and added claim 32. The examiner indicated at page 1 of the Examiner's Answer that claims 13-15 were allowed.<sup>1</sup> This leaves claims 1 through 8, 10, 11, 20 through 22, 24, and 26 through 32 for our review.

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<sup>1</sup> Appellants filed an amendment on October 23, 2000 canceling claims 13-15. Upon return of the application, the examiner should review the amendment and take appropriate action. We also note that Application No. 09/505,854 has been filed which is stated to be a division of this application. The examiner should review the new application and determine whether double patenting issues exist.

Claims 22, 29, and 32 are representative of the subject matter on appeal and read as follows:

22. A kit for immunoassay determination of myocardial necroses in a patient, said kit comprising an antibody to human cardiac muscle troponin T, having a cross reactivity to troponin I and other myofibrillar proteins of less than 2% as determined by ELISA and cross reactivity to human skeletal muscle troponin T of less than 5% as determined by ELISA, and, in a separate container, a binding partner B for either human cardiac muscle troponin T or for said antibody, with one of said antibody and said binding partner being labeled with a determinable group.

29. A method for the immunoassay determination of myocardial necroses in a patient, wherein detecting cardiac muscle injury can be accomplished for at least 150 hours after occurrence of an infarction, said method comprising:

- a) incubating a body fluid sample of the patient with
  - i) at least one antibody to human cardiac muscle troponin T, and
  - ii) a binding partner B for either human cardiac muscle troponin T or the antibody, wherein either the antibody or the binding partner B is labeled with a determinable group, to form an immunological complex containing a determinable group; and
- b) determining the determinable group as an indicator of the human cardiac muscle troponin T in the sample to thereby determine the occurrence of injury to a cardiac muscle, wherein the at least one antibody to human cardiac muscle troponin T has a cross-reactivity to human skeletal muscle troponin T which is less than 5% as determined by ELISA and cross-reactivity to troponin I and other myofibrillar proteins of less than 2% as determined by ELISA.

32. A conjugate of an antibody to human cardiac muscle troponin T having a cross-reactivity to human skeletal muscle troponin T which is less than 5% as determined by ELISA and cross-reactivity to troponin I and other myofibrillar proteins of less than 2% as determined by ELISA, and a determinable group.

The references relied upon by the examiner are:

Cummins et al. (Cummins) "Cardiac-specific troponin-I radioimmunoassay in the diagnosis of acute myocardial infarction." American Heart Journal, Vol. 113, No. 6, pp. 1333-1344, June 1987

Gahlmann et al. (Gahlmann) "Differential Expression of Slow and Fast Skeletal Muscle Troponin C." Journal of Molecular Biology, Vol. 201, pp. 379-391, (1988)

Lim<sup>2</sup> et al. (Lim) "Anti-troponin-T monoclonal antibody crossreacts with all muscle types." Chemical Abstracts, Vol. 102, No. 7, p. 452, abstract 102:60465q, Feb. 18, 1985

Sevier et al. (Sevier) "Monoclonal Antibodies in Clinical Immunology." Clinical Chemistry, Vol. 27, No. 11, pp. 1797-1806, (1981)

Leszyk et al. (Leszyk) "Bovine Cardiac Troponin T: Amino Acid Sequences of the Two Isoforms." Biochemistry, Vol 26, pp. 7035-7042 (1987)

Elvin A. Kabat (Kabat) "Basic Principles of Antigen-Antibody Reactions." Methods in Enzymology, Vol.70, pp.3 and 31-35, (1980).

Claims 1 through 3, 5, 7, 8, 10, 20 through 22, 24, and 26 through 32 stand rejected under 35 U.S.C. § 103(a). As evidence of obviousness the examiner relies upon Cummins, Gahlmann, Lim, Sevier, and Leszyk. Claims 4, 6, and 11 stand rejected under this section of the statute on the basis of the same evidence and Kabat. We reverse.

### BACKGROUND

Troponin is a regulatory structural protein found in muscle tissue. Specification, page 1. Troponin consists of three different proteins, troponin C, troponin I, and troponin T. Id. Appellants explain in the paragraph bridging pages 2-3 of the specification that troponin I is found in blood plasma after severe ischaemia or muscle cell necrosis and thus is a parameter for diagnosing and monitoring those events. However, a disadvantage of using troponin I for this purpose is that normal serum contains a concentration of the protein. In addition the increase in troponin I reaches its "absolute diagnostic sensitivity" during the 10<sup>th</sup> to 50<sup>th</sup> hour after the occurrence of an

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<sup>2</sup> This reference is an abstract of an article authored by Lim et al. (Lim). Appellants attached a full text copy of the Lim article to the Appeal Brief. Our consideration of the issues in this appeal has been based upon the full text article.

infarction. Specification, page 3. Thus, use of troponin I as a marker for the occurrence of an infarct is problematic.

As explained at page 4 line 21- page 5 line 7 of the specification:

Surprisingly, it turned out that a significantly higher sensitivity can be obtained by a troponin T immunoassay in the determination of myocardial necroses (such as e.g. by cardiac infarction, ischaemia or angina pectoris) than by the determination of other parameters such as CK, CK-MB, GOT, LDH or troponin I. As established by the inventors the reason for this is that in contrast to other proteins of the contractile apparatus no serum concentration can be measured for troponin T up to the detection limit of the test (0.25 ng/ml) in normal patients (who have not suffered myocardial necroses).

This is particularly surprising since, because of the functional relationship between the troponins, a similar serum concentration to that for troponin I would be expected for troponin T. Furthermore, the serum concentration curve of troponin T differs significantly, for example in a transmural infarction, from the curve for troponin I. In contrast to troponin I the curve of the time course is in three phases instead of two phases and troponin T is found to be increased on average for up to 300 hours after the onset of pain. The time interval for absolute diagnostic sensitivity lasts from the 6<sup>th</sup> to the 195<sup>th</sup> hour. The time interval for the absolute diagnostic sensitivity is thus nearly four times as long as that known for troponin I.

Appellants' invention involves the use of an antibody to troponin T as a means to diagnose and monitor myocardial necroses in a patient. Troponin exists in human skeletal muscle as well as human cardiac muscle. Thus, in order to monitor myocardial necroses it is important that an antibody be able to differentiate between the two proteins. As the claims now read, all claims require the use of at least one antibody to human cardiac muscle troponin T having cross-reactivity to human skeletal muscle troponin T which is less than 5% as determined by ELISA and cross-reactivity to troponin I and other myofibrillar proteins of less than 2% as determined by ELISA.

## DISCUSSION

We agree with appellants that the evidence relied upon by the examiner does not establish a prima facie case of obviousness against the claimed subject matter. The examiner now agrees that the first reference relied upon, Cummins, does not directly suggest the use of troponin T as a means for diagnosing and/or monitoring myocardial necroses. Rather, as clarified at page 10 of the Examiner's Answer, the rejection is based upon the purported obviousness of one of ordinary skill in the art to select one of the troponins as a marker for diagnosis of myocardial infarction. From the examiner's perspective once one selects troponin T as the marker, it would have required routine skill to develop an appropriate antibody to implement this use. In this regard, the examiner relies upon Lim for its teaching of a monoclonal antibody to troponin T, albeit one that does not distinguish between cardiac muscle troponin T and human skeletal muscle troponin T as required by the claims on appeal.

To make up for this shortcoming, the examiner relies upon Sevier, a review article concerning monoclonal antibody technology. Specifically, Sevier discusses the possibility of eliminating unwanted cross-reactivity in monoclonal antibodies through appropriate screening. The examiner does not allege that Sevier provides any evidence which is directly related to raising antibodies which distinguish between human cardiac muscle troponin T and human skeletal muscle troponin T in the manner required by the claims on appeal. Gahlmann and Leszyk are relied upon for their discussion that cardiac muscle troponin T and human skeletal muscle troponin T are two different proteins having differing amino acid sequences.

The examiner's position is summarized in the paragraph bridging pages 4-5 of the Examiner's Answer as follows:

It would have been obvious for one of ordinary skill in the art to select one of the troponins as a marker for diagnosis of myocardial infarction, since Cummins et al. specifically teach that any of the contractile proteins of the myofibril could meet the requirements for a suitable cardiagnostic marker, and that the troponin complex proteins in particular would be desirable since they are single polypeptides and display a relatively simple tissue isotype distribution when compared to either myosin or tropomyosin isotypes. One of ordinary skill in the art would not have utilized troponin-C, since Gahlmann et al. specifically teaches that the cardiac form of troponin-C is also expressed in skeletal muscle and in certain fibroblasts. One of ordinary skill in the art would have expected success in raising antibodies to troponin-T, since Lim et al. were successful in raising a monoclonal antibody which was specific for troponin-T. Although the antibody of Lim et al. did crossreact with both the skeletal and cardiac forms, one of ordinary skill in the art would have expected success in producing a cardiac specific antibody, since Sevier et al. specifically teaches that "unwanted" reactivity may be eliminated from consideration in the production of monoclonal antibodies by merely selecting against antibodies responsible for such cross reactivity during the screening phase and Leszyk et al. specifically teach that cardiac troponin-T has an extended amino terminus that is rich in glutamic acid, so that cardiac troponin-Ts are acidic, while skeletal TnTs are basic.

Viewing the references relied upon by the examiner apart from appellants' disclosure of the present invention, as we must, we do not find that the references would have reasonably suggested the claimed subject matter. For example, no reference directly suggests the use of troponin T as a marker for myocardial necroses. Even if one of ordinary skill in the art would have found it obvious to use troponin T as a marker for myocardial necroses, the references at best suggest that antibodies might be developed which could distinguish between cardiac muscle troponin T and human skeletal muscle troponin T. The fact that the two proteins have different amino acid sequences only creates the possibility that antibodies could be formed which would

recognize one protein but not the other to some degree. The examiner has not relied upon any evidence which establishes that one of ordinary skill in the art would be able to obtain an antibody having the properties required by the claims on appeal with a reasonable expectation of success.

In any event, notably missing from the examiner's statement of the rejection on pages 3-4 of the Examiner's Answer is any acknowledgement and discussion of the specific cross-reactivity requirements of the claims on appeal. Obviousness must be based upon the claimed subject matter as a whole. 35 U.S.C. § 103(a). This has not occurred here.

Our review of the record leads us to conclude that the examiner's combination of the references is based upon an impermissible consideration of appellants' invention and not upon the teachings of the references themselves. We do not find any guidance in the references to use troponin T as a marker in the manner required by the claimed invention. Nor do we find guidance in the references to develop an antibody as required by the claims on appeal. The Kabat reference relied upon by the examiner in rejecting claims 4, 6, and 11 does not rectify the deficiencies we have found in the other references.

Having determined that the references relied upon by the examiner do not establish a prima facie case of obviousness, we need not review appellants' evidence of non-obviousness.

The decision of the examiner is reversed.

REVERSED

William F. Smith  
Administrative Patent Judge

Demetra J. Mills  
Administrative Patent Judge

Eric Grimes  
Administrative Patent Judge

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Appeal No. 1997-0798  
Application 08/128,020

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