

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte ROBERT M. SENIOR

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Appeal No. 1997-2140  
Application 08/357,820<sup>1</sup>

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ON BRIEF

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Before WILLIAM F. SMITH, SPIEGEL and SCHEINER, 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 3 and 4, the only claims remaining in the application. The claims are reproduced below:

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<sup>1</sup> Application for patent filed December 16, 1994.

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3. The cDNA sequence which encodes the truncated mutant, SEQ ID NO:1, of the 92 kDa gelatinase having an amino acid sequence as shown in FIG. 2 consisting of residues 106-216 fused to residues 391-443 of the parent molecule.

4. The cDNA which encodes the truncated mutant of the 92 kDa gelatinase of claim 3 containing an additional Met-Gly residue at the N-terminus.

The references relied on by the examiner are:

Goldberg et al. (Goldberg)                      4,992,537                      Feb. 12, 1991

Liotta et al. (Liotta)                              5,270,447                      Dec. 14, 1993

Hirel et al. (Hirel), "Extent of N-terminal methionine excision from Escherichia coli proteins is governed by the side-chain length of the penultimate amino acid," Proc. Natl. Acad. Sci. USA, Vol. 86, pp. 8247-8251 (November 1989).

Thomas et al. (Thomas), "Expression in Escherichia coli and characterization of the heat-stable inhibitor of the cAMP-dependent protein kinase," Journal of Biological Chemistry, Vol. 266, No. 17, pp. 10906-10911 (June 15, 1991).

Murphy et al. (Murphy), "Assessment of the role of the fibronectin-like domain of gelatinase A by analysis of a deletion mutant," Journal of Biological Chemistry, Vol. 269, No. 9, pp. 6632-6636 (March 4, 1994).

O'Connell et al. (O'Connell), "Analysis of the role of the COOH-terminal domain in the activation, proteolytic activity, and tissue inhibitor of metalloproteinase interactions of gelatinase B," Journal of Biological Chemistry, Vol. 269, No. 21, pp. 14967-14973 (May 27, 1994).

Claim 3 stands rejected under 35 U.S.C. § 103 as unpatentable over Goldberg, O'Connell, Murphy and Liotta. Claim 4 stands rejected under 35 U.S.C. § 103 as unpatentable over Goldberg, O'Connell, Murphy, Liotta, Hirel and Thomas. We reverse both rejections.

## DISCUSSION

Matrix metalloproteinases comprise a family of enzymes collectively capable of degrading all components of extracellular matrix. Members of the family include several collagenases, a 92 kDa gelatinase, a 72 kDa gelatinase, three stromalysins, macrophage metalloelastase, matrilysin, etc.<sup>2</sup> The 92 kDa gelatinase consists of five structural domains: the amino-terminal and zinc-binding catalytic domains shared by all members of the secreted metalloproteinase gene family, the collagen binding fibronectin-like domain shared with the 72 kDa gelatinase, a carboxyl-terminal hemopexin-like domain shared by all matrix metalloproteinases except matrilysin, and a unique 54 amino acid proline-rich domain homologous to the  $\alpha$ -2 chain of type V collagen. The metalloproteinases are secreted as zymogens,<sup>3</sup> and undergo activation extracellularly through amino-terminal proteolytic processing. Once activated, the 92 kDa gelatinase, as its name indicates, has the ability to degrade gelatin (denatured collagen); it also degrades insoluble elastin. There are three other metalloproteinases with the ability to degrade insoluble elastin: the 72 kDa gelatinase, matrilysin and macrophage metalloelastase. Specification, pages 2 and 3; Goldberg, columns 1 and 2, and Figure 6.

Claim 3 is directed to cDNA encoding the zinc-binding catalytic domain of the 92 kDa gelatinase, but lacking the three fibronectin-like type II repeats normally present in the

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<sup>2</sup> The 92 kDa gelatinase is also known in the art as gelatinase B, and as MMP-9; the 72 kDa gelatinase is also known as gelatinase A, and as MMP-2.

<sup>3</sup> A zymogen is an inactive enzyme precursor, also known as a proenzyme.

catalytic domain of the parent enzyme. The protein encoded by the claimed cDNA consists of amino acid residues 106-216 fused to residues 391-443 of the parent molecule. In other words, the truncated protein is distinguished from the parent enzyme by three separate deletions: amino-terminal residues 1-105, internal residues 217-390, and carboxy-terminal residues 444-707. According to the specification, the protein encoded by the claimed cDNA is catalytically active against gelatin, but, unlike the parent enzyme, inactive against insoluble elastin. Specification, page 3.

Goldberg discloses the full length 92 kDa gelatinase proenzyme, and cDNA encoding it. The 92 kDa gelatinase is structurally related to the 72 kDa gelatinase, but is unique among matrix metalloproteinases in having a 54 amino acid proline-rich domain homologous to the  $\alpha$ 2 chain of type V collagen. Figure 6 shows the structural domains shared by the 92 kDa and 72 kDa gelatinases in alignment; the two enzymes share some sequence similarity but the 92 kDa gelatinase contains three potential N-glycosylation sites not found in the 72 kDa gelatinase and is fully glycosylated.

O'Connell assesses the role of the carboxyl-terminal collagen- and hemopexin-like domains of the 92 kDa gelatinase. Deletion of these domains, which correspond to carboxy-terminal amino acids 444-707, does not affect the catalytic activity of the enzyme, but does affect the rate of activation in the presence of the inhibitor TIMP-1.<sup>4</sup> O'Connell

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<sup>4</sup> Tissue Inhibitor of Metalloproteinase-1.

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also discloses activation of the carboxy-terminal truncated protein to delete various portions of the amino-terminal, including a deletion corresponding to amino acids 1-105.

Murphy assesses the role of the fibronectin-like domain of the 72 kDa gelatinase. A deletion mutant lacking the fibronectin-like domain was unable to bind collagen or gelatin; once activated, the deletion mutant exhibited markedly impaired ability to degrade gelatin. Page 6634, left-hand column, and page 6635, left-hand column.

Liotta teaches that a region of the amino terminus of the 72 kDa gelatinase acts as an intrinsic enzyme inhibitor when the enzyme is in a latent state.

Claim 3 stands rejected as unpatentable over the combined disclosures of Goldberg, O'Connell, Murphy and Liotta. According to the examiner:

It would have been obvious to one of ordinary skill in the art using the 92 kDa gelatinase of [Goldberg] at the time of the invention, to make truncations in it to delete the carboxyl terminal collagen-like and hemopexin-like domains, as taught by [O'Connell] in order to reduce sensitivity to the TIMP-1 inhibitor; to delete the internal fibronectin domain, as taught by [Murphy] in order to reduce binding to collagen; and to delete the amino terminal at least up to Phe<sup>88</sup> as taught by [O'Connell] and [Liotta] in order to reduce intrinsic inhibition. Motivation to make a multiply truncated 92 kDa gelatinase is provided by the teachings of [Goldberg, O'Connell, Murphy and Liotta], who teach the various improvements in gelatinase activity as described above. (Examiner's Answer, page 6, emphasis added).

We disagree. The reason proposed by the examiner for deleting the amino- and carboxy-terminal regions of the 92 kDa gelatinase is plausible as far as it goes: to minimize inhibition of enzyme's ability to degrade gelatin (i.e., denatured collagen). Indeed, O'Connell discloses a truncated mutant with both of these deletions. The reason

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given for the further deletion of the internal fibronectin-like domains, however, is an entirely different matter. To the extent that manipulation of the 72 kDa gelatinase is relevant to the 92 kDa gelatinase, Murphy shows that deletion of the fibronectin-like domains, by eliminating the ability of the mutant to bind collagen, markedly impairs the ability of the truncated mutant to degrade gelatin. Thus, the combination of deletions proposed by the examiner would seem, based on the references cited, to operate at cross-purposes.

It is well settled that the initial burden of establishing unpatentability rests on the examiner, In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). As stated in Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ 1626, 1629, (Fed. Cir. 1996) (citation omitted):

[B]efore 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.

In our judgment, the only reason or suggestion to modify the references to arrive at the claimed truncation mutant comes from appellants' specification. Accordingly, we find that the examiner's initial burden of establishing a prima facie case of obviousness has not been met. The rejection of claim 3 under 35 U.S.C. § 103 is reversed.<sup>5</sup>

Claim 4, directed to the truncation mutant of claim 3 containing two additional amino acids at the amino-terminus, stands rejected as unpatentable over Goldberg,

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<sup>5</sup> Having determined that a prima facie case of obviousness has not been established, we find it unnecessary to comment on appellants' arguments regarding the unexpected properties of the claimed truncation mutants.

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O'Connell, Murphy, Liotta, Hirel and Thomas. The underlying rationale of the rejection corresponds to that of claim 3, and suffers from the same infirmity. Again, we find that the examiner's initial burden of establishing a prima facie case of obviousness has not been met, and the rejection of claim 4 under 35 U.S.C. § 103 is reversed.

REVERSED

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