

EXHIBIT I



PATENT
Attorney Docket No.: A54515-16/WHD

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#6
Rep. Tom
Lecon. w/attach
12/20/96

In re application of:)	Examiner: D. Jacobsen
)	
Goeddel et al.)	Group Art Unit: 1814
)	
Serial No. 08/472,549)	
)	
Filed: 6 June 1995)	
)	
For: Human Tissue Plasminogen)	
Activator)	
)	
)	

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CERTIFICATE OF MAILING

I hereby certify that this correspondence, including listed enclosures, is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, DC 20231 on November 21, 1996.

Signed: Maria Ciganovich
Maria Ciganovich

AMENDMENT

Assistant Commissioner of Patents
Washington, DC 20231

Sir:

This response is directed to the remarks of the Office Action dated 21 June 1996. This response is accompanied by a petition for a two month extension of time and the required fee, making this a timely response. Consideration of the following remarks is respectfully requested.

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REMARKS

The Commissioner is authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-54515-16/WHD).

Claims 3, 11 and 16 are rejected under 35 U.S.C. § U.S.C. §102(a) as anticipated by, or in the alternative, under 35 U.S.C. § U.S.C. §103, as obvious over, Rijken et al., or Collen et al. (U.S. Patent No. 4,752,603).

Rijken et al. (1981) purified plasminogen activator from a human melanoma cell line, resulting in about 1 mg of protein with a specific activity of 90,000 units/mg. Collen et al. is the patent resulting from the Rijken et al. (1981) work, of t-PA from a human melanoma cell line.

The applicants note that relevant arguments and exhibits previously made in related cases are not yet of record; accordingly, we submit with these remarks a number of exhibits and comments as follows:

Attached Exhibit A is a declaration by Dr. Michael Spellman, originally filed in U.S.S.N. 07/012,694, which is listed on the official filing receipt in the lineage of the present case. Dr. Spellman outlines his experiments which demonstrate a distinction between the recombinant human t-PA of the present invention prepared in CHO cells from the t-PA of Collen et al. and Rijken et al. These distinctions are based on the glycosylation of

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the native t-PA and t-PA produced in CHO cells. As shown in Dr. Spellman's declaration, the t-PA isolated by Collen et al. contained fucose, mannose, galactose, N-acetylglucosamine, N-acetylgalactosamine and sialic acid. The t-PA isolated from CHO cells contained fucose, mannose, galactose, N-acetylglucosamine and sialic acid; N-acetylgalactosamine was absent. Thus, Dr. Spellman concludes that the glycosylation structure of CHO-expressed recombinant human tPA is different from the structure of native human tPA, and thus demonstrates that the Collen et al. material was different from the CHO material.

Thus, neither Rijken nor Collen anticipate the tPA of the present claims, and the rejections under 35 U.S.C. § U.S.C. §102(a) should be withdrawn.

As regards the rejections under 35 U.S.C. § U.S.C. §103, the applicants respectfully remind the Examiner that the standard for obviousness is that the claimed invention, taken as a whole at the time the invention was made, would not have been obvious to a person skilled in the art.

The applicants submit that at the time the invention was made, and even today, it would not have been predictable whether such glycosylation differences would, in fact, produce intact, functionally biologically active glycoprotein. In support of this position, the applicants submit remarks made

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in originally filed in U.S.S.N. 07/012,694 (attached Exhibit B). These remarks include arguments, based on three subsequent publications (attached Exhibits C, D and E), concerning the pronounced unpredictability of glycosylation on the biological activity of a particular glycoprotein. These articles are not prior art, but rather are powerfully instructive as to the contemporary state of the art, emphasizing the patentable difference glycosylation makes, especially in 1982 when this application was effectively filed).

In the first article (Exhibit C), the authors report on differences found in the glycosylation structure between tPA from a human colon fibroblast cell line and from a Bowes melanoma cell line. The last two paragraphs emphasize that even as of 1989, seven years after the original filing, there was substantial uncertainty on what effects, if any, differences in carbohydrate structure impose upon a given glycoprotein.

[D]oes each cell within the population express all glycoforms, a unique subset, or just one? Should the N-glycosylation of one polypeptide change under external influences, is there a similar and concomitant change in the N-glycosylation of all the other glycoproteins being expressed by the cellular population in question? If not, how is such a change avoided? Why do such changes in the N-glycosylation of a polypeptide not lead to immune rejection?

[T]hese results have significant implications for the genetic engineering of mammalian glycoproteins, including tPA. Expression of the desired polypeptide in recombinant form in a cell type in which it is not normally expressed would probably lead to the production of

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a nonphysiological set of glycoforms. Irrespective of changes in any functions of that glycoprotein which are normally mediated directly by oligosaccharide, these glycoforms may have unusual additional properties arising from novel N-glycosylation. These may include new circulatory properties, changes in tropism and immunogenicity (Page 7661, emphasis supplied).

In the second paper authored by Wittwer et al. (Exhibit D), the authors report the conclusion that both “qualitative and quantitative differences in tPA N-glycosylation influence its in vitro enzymatic activities”. (Page 7663, left column, lines 9 to 11).

Similarly, the third paper (Exhibit E) further highlights the unpredictable effect of glycosylation:

Altered N-glycosylation could disturb functions normally influenced by oligosaccharides, as well as conferring new ones, or even render the recombinant glycoprotein immunogenic by creating novel epitopes or raising the levels of ones that were previously subimmunogenic. (page 7670, right column, lines 15-19).

[Our] result implies that a recombinant glycoprotein expressed in a cell type in which it is not normally expressed would not constitute a “natural” product. (Page 7677, right column, first complete paragraph).

Thus, at the time this invention was made, it could not have been predicted with reasonable certainty that the recombinant tPA products having glycosylation structure different from that disclosed by the prior art, or native material, would be useful in the manner that they have proved to be, namely, in therapeutic application in a safe manner to human beings.

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The applicants submit that the novelty of the present invention is certainly established, and, for the reasons elaborately propounded over the decade-plus of prosecution history of this case, the unobviousness as well. The glycosylation differences which have clearly been demonstrated, as outlined in the Spellman declaration summarized above and attached hereto, coupled with the uncertainty associated with the biological effects of glycosylation differences, render the t-PA of the present invention non-obvious. As further evidence of non-obviousness, the applicants submit evidence concerning commercial success.

The Supreme Court of the United States has stated that "such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origins of the subject matter sought to be patented." Graham v. John Deere Co., 148 USPQ 459 (1966). The Federal Circuit has emphatically and repeatedly held that objective evidence of nonobviousness must be taken into account always and not just when the decision maker is in doubt (see, for example, Hybridtech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81 (Fed. Cir. 1986); Bausch & Lomb, Inc. v. Barnes Hindes, Inc., 230 USPQ 416 (Fed. Cir. 1986); Jones v. Hardy, 220 USPQ 1021 (Fed. Cir. 1984)).

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First of all, applicants submit that the t-PA of the claims is being sold by Genentech, Inc., the assignee of the present invention, as Activase®. The applicants respectfully draw the Examiner's attention to the declaration of Dr. William F. Bennett, as submitted previously on September 29, 1994 in U.S.S.N. 08/264,134 and attached hereto as Exhibit F. Dr. Bennett is the Staff Scientist and Director of Recovery Process Sciences at Genentech, Inc. This declaration establishes the required "nexus" between the claimed invention and the evidence offered, since Activase® is commercially successful, and the t-PA of Claims 3, 11 and 16 is sold as Activase®.

The applicants submit that Activase® is commercially successful. Introduced in 1987, Activase sales in 1989 were \$196.4 million dollars, representing two-thirds of the market for thrombolytic agents. Sales in 1990 reached \$210.0 million, again capturing approximately two thirds of the market. Sales in 1991 were \$196.5 million, representing 50-55% of the market. Sales in 1992 were \$182.1 million dollars, representing roughly 50% of the market (see relevant pages of the Genentech Annual Reports for 1989 (Exhibit G), 1990 (Exhibit H), 1991 (Exhibit I) and 1992 (Exhibit J)).

The report of the GUSTO trial, discussed below, released in 1993, caused an increase in 1993 sales to \$236.3 million dollars, which again returned the market share to roughly two-thirds. Sales in 1994 were \$280.9

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million, and sales in 1995 were \$301.0 million dollars (see the relevant pages of the Genentech Annual Reports for 1993 (Exhibit K), 1994 (Exhibit L) and 1995 (Exhibit M)).

Applicants point out that this rises to the level of "tremendously commercially successful", as outlined by the Federal Circuit (see Symbol Technologies Inc. v. Opticon, Inc., 19 USPQ 2d 1241, 1249 (Fed. Cir. 1991), wherein total sales of \$150 million were classified as "tremendously commercially successful").

t-PA has repeatedly been shown to be a superior thrombolytic agent for the treatment of heart attacks, contributing materially to its success in the marketplace. The GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trials, the results of which were released in 1993, showed a significant benefit of t-PA over streptokinase, resulting in its clinical superiority and thus its commercial success. As reported in the New England Journal of Medicine, "the findings of this large-scale trial indicate that accelerated t-PA [a dosage regimen] given with intravenous heparin provides a survival benefit over previous standard thrombolytic regimens" (see New England Journal of Medicine, 329(10):673 (1993), conclusion of abstract, a copy of which is enclosed as Exhibit N). This benefit is apparently due to a more rapid and complete

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restoration of coronary flow through the infarct-related artery, which leads to improved ventricular performance and lower mortality rates. (See New England Journal of Medicine, 329(22):1615 (1993), conclusion of abstract, a copy of which is enclosed as Exhibit O).

A graphic representation of the superiority of t-PA as shown by the results of the GUSTO trials is depicted in the graph enclosed as Exhibit P. These results clearly show a significant benefit of t-PA over streptokinase-based treatments.

This benefit has recently been acknowledged by the Food and Drug Administration (FDA). As reported in the Wall Street Journal, the FDA has recommended the labeling changes associated with the accelerated dosage regimen, and "by permitting a more rapid dosage of t-PA, the panel effectively endorsed trial results indicating that t-PA opens arteries of heart-attack patients faster than its rival, and thus saves significantly more lives" (See the Wall Street Journal, June 13, 1994, page B3, a copy of which is enclosed as Exhibit Q, emphasis added). The article also confirms the 70% market share currently enjoyed by t-PA, again doubtless attributable to its superiority as a thrombolytic therapeutic in practice.

Applicants maintain that the t-PA product itself has been repeatedly shown to be superior in the marketplace. It is superior to streptokinase, the

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alternative treatment; it is this superiority which is the primary basis of its market share, i.e., commercial success. To this end, applicants submit that t-PA is commercially successful, as outlined above, and that the product that is successful is the invention disclosed and claimed in the patent, i.e. t-PA. Thus, a prima facie case of the required nexus between the merits of the claimed invention and the evidence offered has been made, and the t-PA of the present invention, Activase®, is commercially successful.

In conclusion, the applicants submit that the commercial success of Activase®, the t-PA of the present invention, weighs heavily towards a finding of non-obviousness, and the rejection under 35 U.S.C. § U.S.C. §103 as based on either Rijken et al., or Collen et al., should be withdrawn.

Claims 3, 11 and 16 are provisionally rejected under the judicially created doctrine of obviousness type double patenting over claim 1 of copending application Serial No. 08/487,456. Since this is a provisional rejection, the applicants respectfully request that the rejection be held in abeyance until otherwise allowable claims are found.

Finally, we note that the foregoing was found persuasive of patentability in companion application, U.S. Serial No. 08/264,134, which is proceeding to issuance. We petition the same result here.

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It is the position of the applicants that the claims are now in condition
for allowance and an early notification of such is solicited.

Respectfully submitted,

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