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D E C I S I O N
of 6 November 2001

Case Number: T 0218/97 - 3.3.4

Application Number: 88906476.2

Publication Number: 0365597

IPC: A61K 37/547

Language of the proceedings: EN

Title of invention:

Improved processes for the treatment of vascular disease

Patentee:

GENENTECH, INC.

Opponents:

Roche Diagnostics GmbH
YAMANOUCHI PHARMACEUTICAL CO. LTD.

Headword:

t-PA deletion mutants/GENENTECH

Relevant legal provisions:

EPC Art. 123(2)(3), 111(1), 114

Keyword:

"Admissibility of late - filed documents (no)"
"Remittal to first instance (yes)"

Decisions cited:

T 0534/98, T 0017/91, T 0013/97, T 0426/94, T 0982/94,
T 0898/91, T 0433/86, T 0073/88

Catchword:

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Case Number: T 0218/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 6 November 2001

Appellant I: GENENTECH, INC.
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 23 December 1996
revoking European patent No. 0 365 597 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairwoman: U. M. Kinkeldey

Members: A. L. L. Marie
V. Di Cerbo

Summary of Facts and Submissions

I. European Patent EP 0 365 597 has been granted on the basis of 33 claims, claims 1 to 4, 8, 11, 21, 25 and 33 of which read:

"1. The use of an amino acid deletion variant human t-PA protein in the preparation of a medicament for the treatment of vascular disease in a patient for which t-PA plasma half-life longer than that exhibited by natural t-PA and/or clearance rates less than the clearance rate exhibited by natural t-PA is advantageous, wherein said deletion variant provides human t-PA protein exhibiting plasma half-life longer than that exhibited by natural t-PA and/or clearance rates less than the clearance rate exhibited by natural t-PA protein."

"2. The use of a variant t-PA of claim 1, such longer half-life and/or lower clearance rate resulting from a deletion which comprises at least a portion of the finger or Kringle 1 domain."

"3. The use of a variant t-PA protein of claim 2 wherein the deletion includes at least a portion of the growth factor domain."

"4. The use of variant t-PA of claim 1 wherein said t-PA variant is devoid of at least a portion of the finger domain."

"8. The use of variant t-PA of claim 1, wherein said t-PA variant is devoid of at least a portion of the Kringle 1 domain."

"11. The use of variant t-PA of any of the preceding claims wherein said variant t-PA additionally has Glu at amino acid 275."

"21. The use of variant t-PA of any one of the preceding claims wherein the t-PA variant has been prepared by expression in a suitable host of a recombinant vector which encodes the variant."

"25. A method for providing a variant human t-PA protein exhibiting an enhanced half-life or decreased clearance rate relative to natural t-PA, the method comprising the steps of:

(a) obtaining a t-PA variant comprising t-PA modified by deletion which comprises at least a portion of the finger or Kringle 1 domain;

(b) comparing the pharmacokinetics of said variant to that of natural t-PA; and

(c) selecting a variant t-PA so obtained which exhibits a longer half-life and/or decreased clearance rate relative to the natural t-PA."

"33. Des 1-44 Glu 275 t-PA."

II. It has been revoked by the opposition division because of lack of novelty (Article 54 EPC) in view of document (B) (cf infra) and an oral disclosure made at the International Symposium on "Biotechnology in Clinical Medicine" held on April 13 to 15, 1987 in Rom.

III. The decision of the opposition division has been based

on a main and an auxiliary request submitted during the oral proceedings, both containing 24 claims. Claims 1, 7, 11, 12, 13 and 24 of the main request read:

"1. The use of an amino acid deletion variant human t-PA protein produced in a recombinant host cell in the preparation of a medicament for the treatment of vascular disease in a patient for which t-PA plasma half-life longer than that exhibited by natural t-PA and/or clearance rates less than the clearance rate exhibited by natural t-PA is advantageous, wherein said deletion results in said variant human t-PA protein exhibiting plasma half-life longer than that exhibited by natural t-PA made in the same host cell and/or clearance rates less than the clearance rate exhibited by natural t-PA protein made in the same host cell."

"7. The use of variant t-PA of any one of the preceding claims wherein said t-PA variant is devoid of at least a portion of the finger domain"

"11. The use of an amino acid deletion variant human t-PA protein in the preparation of a medicament for the treatment of vascular disease by bolus administration in a patient for which t-PA plasma half-life longer than that exhibited by natural t-PA and/or clearance rates less than the clearance rate exhibited by natural t-PA is advantageous, wherein said deletion results in said variant human t-PA protein exhibiting plasma half-life longer than that exhibited by natural t-PA and/or clearance rates less than the clearance rate exhibited by natural t-PA protein,

said t-PA variant being devoid of at least a portion of the kringle 1 domain; but excluding variant t-PAs which consist only of the 527 amino acid sequence of mature t-PA but with a deletion within the region Glu85-Asp179 and with the sequence 275 to 277 either absent or consisting of 1 to 3 amino acids."

"12. The use of variant t-PA of claim 11, wherein said t-PA variant comprises natural t-PA devoid of amino acids 92-179."

"13. The use of variant t-PA of claim 11, wherein the deletion includes at least a portion of the growth factor domain."

"24. Des 1-44 Glu275 t-PA."

Claims 1 to 24 of the auxiliary request were identical to the corresponding claims of the main request, except for the mention in claims 1 and 2 of the fact that the t-PA variant is brought to the patient **by bolus administration**.

- IV. An appeal has been introduced against this decision by the patentee/appellant I.
- V. Opponent 2/appellant II has introduced an appeal against the **reasons** having led to this decision.
- VI. Opponent 1/respondent had indicated in his letter of 1 September 2000 his intention no longer to actively participate to the appeal procedure.

VII. The Board issued a communication pursuant to Article 11(2) of the rules of procedure of the boards of appeal giving its preliminary, non-binding opinion on *inter alia* the priority assessment of the claims and the admissibility of the appeal by opponent 2/appellant II in view of the requirement mentioned in Article 107 EPC for an appellant to be adversely affected by the decision under appeal, whereby the concept of "adversely affected" does not relate according to decision T 73/88 (EPO OJ 1992, 557) to the reasons of the decision.

VIII. Oral proceedings were held on 6 November 2001.

IX. During the oral proceedings, his attention having been drawn by the Board to a possible contradiction between claim 12 and the disclaimer of claim 11 of the main and auxiliary requests, on which the opposition division based its decision, the appellant I/patentee submitted a new main and a new auxiliary request, both with 22 claims. Claim 1, 10 and 11 of the main request read:

"1. The use of an amino acid deletion variant human t-PA protein produced in a recombinant host cell in the preparation of a medicament for the treatment of vascular disease in a patient for which t-PA plasma half-life longer than that exhibited by natural t-PA and/or clearance rates less than the clearance rate exhibited by natural t-PA is advantageous, wherein said deletion **includes all or a portion of the finger region**, and results in said variant human t-PA protein exhibiting **a plasma half-life of at least 12 minutes or at least 2 times longer** than that exhibited by natural t-PA made in the same host

cell and/or **clearance rates less than 2 ml/min/kg or half or less** the clearance rate exhibited by natural t-PA protein made in the same host cell, **with the exclusion of t-PA lacking functionally and structurally intact finger, growth factor and kringle 1 domains and where the catalytic site essential for fibrinolytic activity is blocked by a removable blocking group.**"

"10. The use of an amino acid deletion variant human t-PA protein in the preparation of a medicament for the treatment of vascular disease by bolus administration in a patient for which t-PA plasma half-life longer than that exhibited by natural t-PA and/or clearance rates less than the clearance rate exhibited by natural t-PA is advantageous, wherein said deletion **includes at least a portion of the kringle 1 domain**, and results in said variant human t-PA protein exhibiting a **plasma half-life of at least 12 minutes or at least 2 times longer** than that exhibited by natural t-PA made in the same host cell and/or **clearance rates less than 2 ml/min/kg or half or less** the clearance rate exhibited by natural t-PA protein made in the same host cell, **with the exclusion of t-PA lacking functionally and structurally intact finger, growth factor and kringle 1 domains and where the catalytic site essential for fibrinolytic activity is blocked by a removable blocking group**, and ~~excluding also variant t-PAs which consist only of the 527 amino acid sequence of mature t-PA but with a deletion within the region Glu85-Asp179 and with the sequence 275-277 either absent or consisting of 1-~~

~~3 amino acids."~~

"11. The use of variant t-PA of claim 10, wherein said t-PA variant comprises natural t-PA devoid of amino acid 92-179."

(Emphasis in bold or italics and bold and deletion by strikeout made by the Board).

The claims of the auxiliary request were identical to those of the main request, except for the mention of a "***bolus administration***" in claims 1 and 2 and the addition of "***...more particularly myocardial infarction following reperfusion, deep vein thrombosis, peripheral vascular disease, or patients requiring t-PA but who are not in life-threatening situations,...***" in claims 1, 2 and 10.

X. Appellant II/opponent 2 at the onset of the oral proceedings withdrew his appeal and thereby became respondent.

XI. The following documents are cited in the present decision:

(A) EP 0 386 240

(B) EP 0 196 920

(BM1a) P. Cambier et al., Journal of Cardiovascular Pharmacology, 1988, Volume 11, pages 468-472

XII. In view of the admissibility under Article 114 EPC of the declarations of Drs. Kresse and Albert

appellant I/patentee argued that their relevance was highly questionable and that their submission at the oral proceedings before the opposition division by opponent I was an abuse of the procedure, because said evidence had been in the possession of opponent I since April 1987. Decisions T 534/89 (OJ EPO 1994, 464) and T 17/91 (26 August 1992) were mentioned in this context.

In view of Article 123(2) EPC appellant I/patentee justified the deletion of the disclaimer in new claim 10 by the fact that document (A) in its first priority only disclosed a single mutant with a deletion between Cys84 and Cys180 which did not conflict with the mutant of the patent in suit devoid of amino acids 92-179. The introduction of the numerical values for the half-life and the clearance of the variant t-PA was an answer to the objection raised by appellant II/opponent 02 in view of Figure 2 of document (B).

XIII. Appellant II/opponent 2 pleaded in favour of the admittance of the declarations of Drs. Kresse and Albert into the proceedings because of their relevance, since they disclosed t-PA deletion mutants with an increased half-life.

He further submitted that the deletion of the disclaimer of new claim 10 resulted in a new technical and factual framework, which had not been considered by the first instance, this justifying a remittal of the case to the opposition division under Article 111(1) EPC.

No objection under Article 123(2) EPC against the

amendments of the new main and auxiliary requests had been raised.

- XIV. Appellant I/patentee, who had no objection against a remittal to the first instance, requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main or auxiliary requests filed during oral proceedings.
- XV. Appellant II/opponent 2 requested that the appeal be dismissed.
- XVI. A few days after the decision of the Board has been announced and the oral proceedings closed, submissions from both appellants were received.

Reasons for the Decision

Late submissions made by the appellant and respondent

1. Since these submissions have been made after the Board has pronounced its decision and closed the oral proceedings, they are not taken into consideration.

Article 114 EPC

2. The relevance of the declarations and evidence of Drs. Kresse and Albert does not justify their introduction into the proceedings. Indeed, this evidence ("Bericht" dated 1.4.87) indicates that the first phase (the "alfa phase") of the biphasic clearance of a t-PA mutant deleted in the finger and growth factor domains is very rapid ("sehr schnell"). However, since no numerical

value is given for the "alfa phase" of the mutant, a direct comparison with the natural t-PA, showing an alfa-phase of 0.8 min, is not possible. This first phase is said to be responsible for the clearance of 80% of the molecule and is therefore from a pharmacological point of view the most important one of this biphasic phenomenon, as far as the treatment of patients in need of t-PA is concerned. Thus, it seems highly doubtful whether such a mutant, 80% of which is cleared very rapidly, can be compared with the t-PA mutants of the patent in suit in its suitability as an ingredient for the preparation of a medicament for patients suffering under cardiovascular diseases. Furthermore, the rapid clearance seems to be in relation with a mechanism ("Desialidierung") different from that described in the patent in suit (deletion mutation).

As a consequence, the declarations of Drs. Kresse and Albert are disregarded under Article 114(2) EPC.

Article 123(2)(3) EPC

3. The disclaimer of claim 11 of the main and auxiliary requests, on which the opposition division based its decision, has been deleted from corresponding claim 10 of the new main and auxiliary requests (cf section IX above; emphasis by ~~strikeout~~).

4. This disclaimer had no basis in the application as filed and was introduced as an attempt to overcome a novelty objection raised in view of Document (A), which discloses a t-PA mutant having the sequence between amino acids 85 and 179 partly or totally deleted and the sequence 275 to 277 either absent or consisting

of 3 amino acids. This disclaimer fulfilled the requirements of Article 123(2) EPC. It was in agreement with the established board of appeal practice concerning the support of disclaimers in prior art documents, as exemplified in decisions T 426/94 (22 May 1996), T 982/94 (16 September 1997), T 898/91 (18 July 1997) and T 433/86 (11 December 1987). However, since it had no support in the application as filed, its deletion does not contravene the requirements of Article 123(2) EPC.

5. This disclaimer was also absent from the claims as granted, so that its deletion does not contravene the requirements of Article 123(3) EPC.

Article 111(1) EPC

6. The claims of the main and auxiliary requests submitted during the oral proceedings before the Board do not only differ from those, on which the opposition division based its decision, by the deletion of the disclaimer to document (A)(cf points 2 to 5 above and section IX, emphasis by ~~strikeout~~).
7. They also differ by the introduction of precise numerical values for the half-life and clearance rate of the t-PA mutants (cf section IX above, emphasis in bold letters) and a disclaimer to document (B) (cf section IX above, emphasis in bold letters and italics) in new claims 1, 2 and 10.
8. This may considerably change the importance of the documents cited in view of the novelty objection raised under Article 54 EPC and may also have an impact on the assessment of priority (Articles 87 to 89 EPC).

9. Further, the formulation of the claims of both the new main and auxiliary requests also justifies a thorough reconsideration of the priority enjoyed by the claims. For instance, the verb "*to include*" as used in claims 1, 2 and 10 has no limiting meaning, so that the extent of the mentioned deletion is not necessarily restricted to the domain mentioned. Therefore, it has to be determined within this context, which priority (if any) the various embodiments of said claims may enjoy.

10. This may again result in the necessity of a completely new analysis of the documents on file in view of their relevance for the novelty objection (Article 54 EPC) raised. In this context, it is necessary to precisely determine the publication date of eg document (BM1a), on which a publication date has been mentioned in handwriting apparently during the opposition procedure, although no confirming document from the publisher can be found in the file.

11. The deletion of the disclaimer to document (A) (cf section IX above, emphasis by ~~strikeout~~) was found to be in agreement with the requirements of Article 123(2)(3) EPC (cf points 2 to 5 above). However, it still remains to be determined, in the new context resulting from the introduction of the precise numerical values mentioned above (cf point 7), whether this disclaimer is unnecessary for assessing novelty (Article 54 EPC) over document (A).

12. As far as the disclaimer to document (B) (cf section IX above, emphasis in bold letters and italics) is concerned, it should be kept in mind that disclaimers are only admissible to delete from the scope of the

claims an accidental novelty-destroying disclosure which has no relevance for any further examination of the claimed invention, in particular for inventive step (Decision T 13/97 of 22 November 1999). The disclaimer to document (B) in new claims 1 and 10 has not been considered by the opposition division. The Board, taking into consideration the legal framework of the decision of the first instance, **which has made no decision on Article 56 EPC**, is reluctant to consider whether this disclaimer to document (B) is in agreement with Decision T 13/97 mentioned above as far as inventive step is concerned. In terms of economy of the procedure, it does not appear appropriate for the Board to further consider the novelty of claims containing a disclaimer, which may later prove not to be admissible during the examination for inventive step.

13. Therefore, due to the quantitative and qualitative importance of the amendments introduced by the appellant, the claims of the main and auxiliary requests submitted during the oral proceedings before the Board define a factual framework different from that one, which has been considered by the first instance for reaching its decision.

14. The Board is thus of the opinion that opportunity should be given to the parties to possibly have this new factual framework considered by two instances and therefore makes use of its power under Article 111(1) EPC to remit the case to the opposition division for further prosecution on the fulfilment of the requirements of the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside
2. The case is remitted to the first instance for further prosecution on the basis of the main or auxiliary requests both filed during the proceedings.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey