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D E C I S I O N
of 8 November 1995

Case Number: T 0923/92 - 3.3.4

Application Number: 83302501.8

Publication Number: 0093619

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Human tissue plasminogen activator, pharmaceutical compositions containing it, processes for making it, and DNA and transformed cell intermediates therefor

Patentee:
GENENTECH, INC.

Opponents:
01 KabiVitrum AB
02 The Wellcome Foundation Limited
03 Celltech Limited
04 Toyo Boseki Kabushiki Kaisha
06 Behringwerke Aktiengesellschaft
07 Boehringer Mannheim GmbH

Headword:
human t-PA/GENENTECH

Relevant legal provisions:
EPC Art. 123, 87, 88, 54, 56, 83, 84

Keyword:
"Main request - entitlement to priority (no) - differences in sequences"
"Main request - novelty (no)"
"Subsidiary requests 1 and 2 - lack of clarity (yes)"
"Lack of sufficient disclosure (yes)"
"Subsidiary request 3 - formal admissibility (yes)"
"Subsidiary request 3 - reformatio in peius (no)"
"Entitlement to priority (yes)"
"Sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive step (yes) - no reasonable expectation of success"

Decisions cited:
T 0292/85, T 0161/86, T 0281/86, T 0081/87, T 0269/87, T 0301/87, T 0073/88, T 0212/88, T 0816/90, T 0184/91, T 0409/91, T 0435/91, T 0626/91, T 0065/92, T 0223/92, T 0296/93, T 0412/93, G 0011/91, G 0009/92, G 0004/93

Headnote:

I. The skilled person considers a reference to a particular amino acid sequence in a claim as a true technical feature characterizing the invention. Such a claim is not under Article 87 entitled to priority from an earlier application in which that amino acid sequence was **not** disclosed (cf. points 8 and 16 of the Reasons).

II. A claim to a process which comprises the preparation of a protein which has human tissue plasminogen activator (t-PA) function, without further indication which of the many functions of human t-PA are meant, is not allowable under Articles 83 and 84 EPC. This is firstly because the skilled addressee would be left guessing whether or not a derivative which fulfils only one of the functions typical of this molecule falls under the scope of the claim. Moreover, the requirement of Article 83 EPC is not fulfilled if the claim, on the basis of the broadest possible meaning of the functional definition contained in it, relates to an invention which, having regard to the examples and the information given in the patent specification, cannot be performed in the **whole** area claimed by a person skilled in the art, using common general knowledge, without undue burden (cf. point 27 of the Reasons).

III. Given a description that contains adequate information how to produce human t-PA, and a claim directed to derivatives of human t-PA with an indication of the functions to test for, the skilled person can be expected to be able to prepare without application of inventive skill or undue burden, derivatives of human t-PA by way of amino acid deletion, substitution, insertion, addition or replacement and test which of the derivatives satisfy the functional requirements, so that the claimed invention is adequately described for the purpose of Article 83 EPC [cf. points 44 and 45 of the Reasons].

Case Number: T 0923/92 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 8 November 1995

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Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office dated 1 September 1992 concerning maintenance of European patent No. 0 093 619 in amended form.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: L. Galligani
S. C. Perryman

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Headnote:
(follows)

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Case Number: T 0923/92 - 3.3.4

D E C I S I O N
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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office dated 1 September 1992 concerning maintenance of European patent No. 0 093 619 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: L. Galligani
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 93 619 (application No. 83 302 501.8) relating to "human tissue plasminogen activator, pharmaceutical compositions containing it, processes for making it, and DNA and transformed cell intermediates therefor" was granted on 13 September 1989 for ten Contracting States with eighteen claims and for Austria with seventeen claims. The priority of three earlier applications was claimed, namely of 5 May 1982 (P1), 14 July 1982 (P2), 7 April 1983 (P3).

II. Claims 1, 2, 3, 4, 16 and 18 as granted for all designated states except Austria read:

"1. A process which comprises preparing cDNA from mRNA extracted from the Bowes melanoma cell line and isolating from it a DNA sequence having the restriction pattern shown in Fig. 4 hereof for the putative mature tissue plasminogen activator sequence and which encodes a 527 amino acid polypeptide having human tissue plasminogen activator function."

"2. A process which comprises preparing one or more cDNA libraries from mRNA extracted from cells producing human tissue plasminogen activator, probing the library or libraries with one or more hybridisation probes selected from the sequences:

(i) 5'-TCACAGTACTCCCA-3'

(ii) 5'-TTCTGAGCACAGGGCG-3'

(iii) a 4.2kb Pvu II fragment of human genomic DNA which hybridises under high stringency with the HpaII-RsaI DNA fragment located downstream from amino acid No. 30 in Fig. 5 hereof;

sequencing the cDNA from strongly hybridising colonies, and using said cDNA to obtain a DNA sequence encoding a polypeptide of 527 amino acids from N-terminal serine to C-terminal proline which has human tissue plasminogen activator function."

"3. A process which comprises the preparation of a protein which has human tissue plasminogen activator function and which comprises the 527 amino acid sequence as encoded by the DNA product of claim 1 or claim 2, wherein the protein is prepared by expression in a recombinant host organism of transforming DNA encoding the protein."

"4. A process which comprises the preparation of a protein which comprises an allele or derivative, by way of amino acid deletion, substitution, insertion, inversion, addition or replacement, of the 527 amino acid sequence as encoded by the DNA product of claim 1 or claim 2, and which has human tissue plasminogen activator function, wherein the protein is prepared by expression in a recombinant host organism of transforming DNA encoding the protein."

"16. A protein having human tissue plasminogen activator function and which comprises a derivative by way of amino acid deletion, substitution, insertion, inversion, addition or replacement of the 527 amino acid sequence as encoded by the DNA product of claim 1 or claim 2."

"18. A protein as prepared by the process of claim 3 or claim 4 which is unaccompanied by glycosylation native to human tissue plasminogen activator."

III. Notices of opposition were filed against the European patent by seven parties (Opponents 01 to 07). Opponent 05 later withdrew the opposition.

Revocation of the patent was requested on the grounds of Article 100(a), (b) and (c) EPC. During the procedure before the Opposition Division thirty five documents were relied upon by the parties. Of these, the following are referred to in the present decision (the numbering used by the Opposition Division is adhered to):

(4) Wallace et al., Nucl. Ac. Res., 1981, Vol. 9(4), pages 879 to 894;
(7) Rijken et al., J. Biol. Chem., 10 July 1981, Vol. 256, No. 13, pages 7035 to 7041;
(9) Weimar et al., The Lancet, 7 November 1981, pages 1018 to 1020;
(11) Suggs et al., Proc. Natl. Acad. Sci. USA, November 1981, Vol. 78, No. 11, pages 6613 to 6617;
(12) EP-B1-0 041 766;
(13) Opdenakker et al., Eur. J. Biochem, 1982, Vol. 121, pages 269 to 274;
(17) Edlund et al., Proc. Natl. Acad. Sci. USA, January 1983, Vol. 80, pages 349 to 352;
(18) Pennica et al., Nature, 20 January 1983, Vol. 301, pages 214 to 221;
(33) Noda et al., Nature, 21 January 1982, Vol. 295, pages 202 to 206.

IV. The Opposition Division issued on 1 September 1992 an interlocutory decision within the meaning of Article 106(3) EPC whereby the patent was maintained in amended form on the basis of fifteen claims filed during oral proceedings held on 2 and 3 June 1992 in the two versions for all non-AT States and Austria. Claims 1, 2 and 9 for the non-AT States therein were as follows:

"1. A process which comprises the preparation of a protein which has human tissue plasminogen activator function and which comprises amino acid sequence 1-527 as depicted in Fig. 5 hereof, wherein the protein is

prepared by expression in a recombinant host organism of transforming DNA encoding the protein."

"2. A process which comprises the preparation of a protein which comprises an allele or derivative, by way of amino acid deletion, substitution, insertion, addition or replacement, of the amino acid sequence 1-527 as depicted in Fig. 5 hereof, and which has human tissue plasminogen activator function, wherein the protein is prepared by expression in a recombinant host organism of transforming DNA encoding the protein."

"9. A DNA isolate encoding a said protein as prepared by the process of claim 1 or claim 2."

V. The Opposition Division considered the said claims to be allowable under Article 123(2) and (3) EPC and to comply with Article 84 EPC. As regards the priority right, the Opposition Division held that the nucleotide and amino acid sequences of Figure 5 were entitled to the first priority date in spite of the admitted differences (3 nucleotides ---> 3 amino acids) with respect to the sequences as reported in first priority document (P1). In their opinion, although it was true that a sequence identical to that of Figure 5 was reported only in the third priority document (P3), three discrepancies could be considered as tolerable errors within the statistical imprecision, especially in view of the length of the sequence (about 2415 nucleotides) and of the fact that the nature and/or character of the obtained product was not affected (citing decisions T 212/88, OJ EPO 1992, 28 and T 73/88, OJ EPO 1992, 557).

As regards the compliance with the requirements of Article 83 EPC, the Opposition Division observed that the Respondents had been the first to disclose the nucleotide and amino acid sequences of t-PA and decided

that the disclosure of the impugned patent was enabling since it provided the skilled person with all the information which was necessary for the expression of a protein with human tissue plasminogen activator (t-PA) function, for its purification and for the preparation of its "derivatives". Although t-PA had several functions, the skilled person would have taken the notion of "function" in a large sense and would have included therein the already known immunologic function of t-PA.

Furthermore, the Opposition Division acknowledged both novelty and inventive step in respect of the claimed subject-matter. As for inventive step, the Opposition Division considered that the closest prior art was represented by Opdenakker et al. (13) which disclosed the partial purification of mRNA coding for human t-PA from the Bowes melanoma cell line and its translation using oocytes from Xenopus laevis. The technical problem was seen in the preparation of large amounts of human t-PA by recombinant DNA technology. The solution proposed in the claims resulted from the sum of several intermediary steps which were not common practice at the priority date and/or were uncertain in their outcome so that the skilled person could not have assumed that success in cloning and expressing t-PA could have been reasonably expected.

VI. Appeals were lodged by three Appellants (Opponents 02, 03 and 07 referred to as Appellants II, III and VII) against the decision of the Opposition Division.

VII. The Respondents filed a response to the statements of grounds of the Appellants on the basis of the claims as maintained by the Opposition Division.

VIII. The Board sent a first communication pursuant to Article 110(2) EPC with a preliminary analysis of the case, in particular of the issues of the formal admissibility of the claims on file under Article 123(2) and (3) EPC and of the entitlement to priority.

The Respondents and the Appellants sent responses to this communication from the Board.

IX. The Board issued then a communication pursuant to Article 11(2) of the rules of procedure of the Boards of Appeal with a brief outline of the points to be discussed at oral proceedings.

X. In reply thereto, the Respondents filed six subsidiary claim requests in replacement of the then existing subsidiary claim requests.

XI. In a further communication pursuant to Article 11(2) of the rules of procedure of the Boards of Appeal, the Board made a review of the requests on file and expressed the preliminary opinion that of them only the main request, namely the claims as maintained by the Opposition Division, could be admitted into the proceedings.

XII. The Respondents replied to the Board's communication and submitted "possible" subsidiary claim requests A and B for advance consideration by the Board.

XIII. Oral proceedings were held on 2 and 3 August 1995 and it was announced by the Board the final decision would be issued in writing.

After the initial submission of nine subsidiary requests, not wholly identical to the previously filed requests in substitution for all previously filed

subsidiary requests, the main request was discussed. After the Board had announced the decision that the main request was not allowable, and had indicated that several of the subsidiary requests were likely to be refused for the same reasons, the Respondents were given a choice of either proceeding on the basis of the already submitted nine subsidiary requests, or submitting not more than three new subsidiary requests in substitution of all previous subsidiary requests. After a recess, the Respondents then submitted three new subsidiary claim requests in substitution of all previous subsidiary requests.

Claims 1 and 2 for the non-AT States in **new subsidiary claim request 1** read as follows:

"1. A process which comprises the preparation of a protein which has human tissue plasminogen activator function by expression in a recombinant host organism of transforming DNA encoding the protein; wherein said protein comprises a sequence of 527 amino acids from N-terminal serine to C-terminal proline encodable by cDNA derived from mRNA extracted from the Bowes melanoma cell line, and which

(a) has the restriction pattern shown in Fig 4 hereof for the putative mature tissue plasminogen activator sequence, and

(b) hybridises strongly with the sequences:

(i) 5'-TCACAGTACTCCCA-3'

(ii) 5'-TTCTGAGCACAGGGCG-3'

(iii) a 4.2kb Pvu II fragment of human genomic DNA which hybridises strongly with the sequence: CGG GTG GAA TAT TGC TGG TGC AAC AGT GGC AGG GCA CAG TGC CAC TCA GTG CCT GTC AAA AGT TGC

AGC GAG CCA AGG TGT TTC AAC GGG GGC ACC TGC
CAG CAG GCC CTG T."

"2. A process which comprises the preparation of a protein which has human tissue plasminogen activator function by expression in a recombinant host organism of transforming DNA encoding the protein, wherein the protein comprises an allele or derivative, by way of amino acid deletion, substitution, insertion, addition or replacement, of said 527 amino acid sequence as defined in claim 1."

Claims 1 and 2 for the non-AT States in **new subsidiary claim request 2** read as follows:

"1. A DNA isolate as obtainable by preparing one or more cDNA libraries from mRNA extracted from the Bowes melanoma cell line, probing the library or libraries with one or more hybridisation probes selected from the following sequences:

(i) 5'-TCACAGTACTCCCA-3'

(ii) 5'-TTCTGAGCACAGGGCG-3'

(iii) a 4.2kb Pvu II fragment of human genomic DNA which hybridises under high stringency with the human tissue activator cDNA sequence:
CGG GTG GAA TAT TGC TGG TGC AAC AGT GGC AGG GCA CAG TGC CAC TCA GTG CCT GTC AAA AGT TGC AGC GAG CCA AGG TGT TTC AAC GGG GGC ACC TGC CAG CAG GCC CTG T

and isolating and sequencing cDNA from strongly hybridising clones, and using said cDNA to produce a DNA sequence isolate which has the restriction pattern shown in Fig 4 hereof for the putative mature tissue plasminogen activator sequence, and which encodes a polypeptide of 527 amino acids from N-terminal serine to

C-terminal proline which has human tissue plasminogen activator function."

"2. A process which comprises expressing in a host organism recombinant transforming DNA to produce the 527 amino acid polypeptide as encodable by said DNA sequence isolate of claim 1, or an allele or derivative of said polypeptide by way of amino acid deletion, substitution, insertion, addition or replacement and which has human tissue plasminogen activator function."

Claims 1 and 2 in **new subsidiary claim request 3** read like Claims 1 and 2, respectively, of new subsidiary request 1 except for the fact that the human tissue plasminogen activator function was specified as follows: "in particular, it is capable of catalyzing the conversion of plasminogen to plasmin, it binds to fibrin, and is classified as a t-PA based on immunological properties".

XIV. The Appellants objected to the formal admissibility of all requests under Article 123(2) EPC or under Article 123(3) EPC or both. The relevant arguments in this respect are given in the Reasons for the decision, infra. In respect of the main request, the Appellants insisted that the subject-matter therein was not entitled to the first priority date because of the substantial differences in the nucleotide and amino acid sequence data between the first priority and the patent in suit. They submitted that, consequently, the said subject-matter lacked novelty having regard to Pennica et al. (18). They made reference in particular to decisions T 81/87 (OJ EPO 1990, 250), T 269/87 of 24 January 1989 (not published in the OJ EPO), T 301/87 (OJ EPO 1990, 335), T 161/86 of 25 June 1987 (not published in the OJ EPO) and T 184/91 of 4 April 1986 (not published in the OJ EPO), which in their opinion were of relevance as they all dealt with the problem of

the entitlement to priority for nucleotide or amino acid sequences. It was suggested that, if necessary, the Board could refer to the Enlarged Board of Appeal the question of what was the correct approach to be taken in determining the priority date of a claim.

The Appellants considered that none of the requests complied with the requirements of Article 84 EPC, especially in view of the expressions "human plasminogen activator function" and "derivative" which lacked clarity and support by the description and argued also that the patent in suit did not satisfy the requirements of Article 83 EPC because the disclosure in the specification was insufficient. In particular, the embodiments related to the t-PA derivatives and the expression of human t-PA in E.coli were disputed. With respect to this latter, the Appellants submitted as expert's opinions the following additional documents:

(36) Sarmientos et al., Bio/Technology, Vol. 7, May 1989, pages 495 to 501;
(37) Krause J., Fibrinolysis, Vol. 2, 1988 pages 133 to 142;
(38) Rothstein et al., Gene, Vol. 61, 1987, pages 41 to 50,

which, in their opinion, demonstrated that even at a later date the production of human t-PA in E.coli was still not feasible.

As regards inventive step, the Appellants observed that possible **potential** difficulties would not have prevented the skilled person from starting on the task of applying routine cDNA cloning techniques on t-PA. In practice **actual** difficulties were not found. The Appellants emphasized in particular that it was obvious for the

skilled person to combine the teaching of Opdenakker et al. (13), which related to the preparation of t-PA mRNA from Bowes melanoma cells, with that of Noda et al. (33), which described a cloning strategy essentially identical to the one followed by the Respondents. The Appellants held that, in the light of said references and of other prior art references such as documents (7), (9), (17), the person skilled in the art would have had a reasonable expectation of success in cloning a t-PA cDNA. They observed that the Respondents themselves had admitted that once the cDNA encoding t-PA was obtained, its expression in bacteria, yeast and mammalian cells involved no inventive effort.

XV. In reply to the above objections, the Respondents essentially argued in favour of the formal admissibility of the claims both under paragraphs (2) and (3) of Article 123 EPC. For the sake of conciseness, the relevant arguments in respects of this issue as well as of the other issues are reported in the Reasons for the decision, infra.

In respect of the objections of lack of clarity, the Respondents maintained that the "function" of t-PA was known in the art and the skilled person would have taken it in a large sense to include the known immunological function. As for the term "derivative", this was qualified in relation to the function and also as to the nature of the derivative, so it was clear enough in the context.

Concerning the reproducibility of the invention, the Respondents observed that Article 83 required the reproducibility of the **invention**, not of the **examples** and argued that, in any case, the specification sufficiently demonstrated the first cloning and expression of human t-PA in E.coli and its production in

mammalian cells. The patent in suit provided detailed information about the structure and properties of the molecule. The work described therein had found confirmation worldwide.

With respect to the priority issue, the Respondents submitted that the rationale of decisions T 73/88 (supra) and T 65/92 of 13 June 1993 (not published in OJ EPO) applied to the present case as the differences between the sequence reported in Figure 5 of the patent in suit and that of the first priority document were not substantive. The molecule disclosed and enabled in the two documents was in substance the same. Thus, in their opinion, the main request was entitled to the first priority date and, consequently, Pennica et al. (18) was not prior art.

As for inventive step, the Respondents observed that the present invention was the result of a long and arduous enterprise full of uncertainties which involved the use and the adaptation of techniques which were not routinely available at the priority date. The combination of Opdenakker et al. (13) with Noda et al. (33) was inappropriate. From Opdenakker et al. (13) one could not derive information on the quality and purity of the t-PA mRNA or make predictions on the possibility of using the said mRNA to isolate clones of t-PA DNA. As for Noda et al. (33), the cloning task described therein was much easier. In the Respondents' submissions, no predictions could be made about the possibility to successfully use the said approach for cloning t-PA DNA.

XVI. The Appellants requested that the decision under appeal be set aside and the patent be revoked.

The Respondents requested as a main request that the appeal be dismissed and, as auxiliary requests 1 to 3, that the decision under appeal be set aside and the patent be maintained on the basis of one of the new subsidiary claim requests 1 to 3 submitted at the end of the first day of oral proceedings.

Reasons for the Decision

1. The appeals are admissible.

The main request: Claim 1

Formal admissibility under Article 123(2) and (3) EPC

2. Claims 1 finds formal support in the application as originally filed so that no objection under Article 123(2) EPC arises.

In the Board's judgement, Claim 1 of this request does not have a broader scope than the scope of Claims 3 and 4 as granted. In fact, the reference to the "amino acid sequence 1-527 as depicted in Fig. 5 thereof" confines this claim 1 to a precisely defined embodiment, namely the process of preparation of a human t-PA protein with the recited amino acid sequence by expression in a recombinant host organism of transforming DNA encoding it. The candidate transforming DNA encoding said protein falls within the large group of DNA sequences encoding "a 527 amino acid polypeptide having human tissue plasminogen activator function" of Claims 3 and 4 as granted. Thus, the requirements of Article 123(3) EPC are met.

Entitlement to priority (Articles 87 and 88 EPC)

3. The right to priority is governed by Article 87 EPC, which requires that the European patent (application) and the application whose priority is claimed relate to the **same invention**. Article 88(3) EPC further specifies that, if one or more priorities are claimed in respect of a European patent application, the right of priority shall cover only those elements of the application which are included in the respective priority application(s).

4. The subject-matter of Claim 1 is defined by means of a reference to the amino acid sequence of Figure 5. The sequence reported in Figure 5 of the patent in suit differs from that reported in Figure 5 of the first (P1) and second (P2) priority documents in respect of three amino acids in positions 175, 178 and 191. The former sequence is disclosed for the first time in the third priority document (P3). The corresponding nucleotide triplets are also different.

The Appellants' position

5. Claim 1 is not entitled to the first or second priority date, but only to the third date because the sequence of Figure 5 to which reference is made is only disclosed in the third priority document. The amino acid sequence is an essential part of the invention as differences in one or more amino acids (here: three) could bring about differences in folding or activity of the protein. Decision T 73/88 (supra) referred to by the Respondents is concerned with a different situation and with a different technical field and thus is not applicable here. Rather decisions T 81/87, T 269/87, T 301/87, T 161/86 and T 184/91 (supra), which all deal with the problem of the entitlement to priority for nucleotide or

amino acid sequences, or decision G 11/91 (OJ EPO 1993, 125), which relates to the problem of the correction of errors, are of relevance to the present case. In particular, it was observed that this was not a case where a specific DNA sequence had been deposited or where one inevitably would have arrived at the specific DNA sequence of Figure 5 of the patent in suit from Bowes melanoma cells.

The Respondents' position

6. The differences between the sequence reported in Figure 5 of the present application and that of the first priority document are informational, not substantive. The sequence in question is essential only for determining the scope of protection. The molecule referred to in the two documents is in substance the same. The said molecule is enabled already by the description in the first priority document because a skilled person by following the DNA isolation protocol given therein would arrive at the identification of the correct sequence, i.e. to the sequence reported in Figure 5 of the patent in suit. The three errors in question do not relate to critical features of the invention because - as shown by the experimental reports submitted - they have no effect whatsoever on the activity of the molecule and, therefore, they do not change the essential nature of the invention. Decisions T 81/87, T 269/87 and T 301/87 (supra) do not apply here because they all relate to cases in which either an essential feature was missing or no sufficient information on the sequence had been given. In the present case the DNA sequence encoding human t-PA is fully identified. One has rather to rely on decisions T 73/88 (supra) and T 65/92 (supra). The first decision indicates that the strict application of Article 123(2) EPC is not the proper, or at least not the ultimate,

test for the determination of priority. As for decision T 65/92 (supra), the situation was analogous to that of the present case because a difference in the reported upper limit of the molecular weight range of a polypeptide between the European patent application and the priority application was not considered to change the substance of the invention because - just like in the present case - the experimental protocols given in the two documents for the isolation and characterisation of the product were identical.

The Board's conclusions

7. The Board observes that it is undisputed that there are differences between the amino acid and nucleotide sequences reported in Figure 5 of the first or second priority document and those of Figure 5 of the patent in suit and that the sequences of Figure 5 of the patent in suit are found for the first time in the third priority document. The controversial point here is whether this is the same invention as disclosed in the first or second priority document.

8. In the Board's judgement, the skilled person considers the primary amino acid structure of a protein as an essential feature thereof because it represents its chemical formula. The skilled person knows that the secondary, tertiary and quaternary structures of a protein are determined by the amino acid structure of the primary polypeptide chain and that these structural features in turn determine the physico-chemical and biological properties of the molecule, for example, its activity, immunological properties, glycosylation, cleavage by proteases, in vivo half-life etc.. The skilled person, while being aware on the one hand of the fact that allelic variations or other modifications of a given primary structure of a protein can result in

molecules whose essential physical and biological characteristics remain unaffected, knows on the other hand that even a small structural modification (e.g. the substitution or deletion of one amino acid) can produce dramatic functional changes. For these reasons, the skilled person would consider the reference to the chemical formula, i.e. to the amino acid sequence, of a protein as having not merely an informational character, but as being a primary technical feature linked to the character and nature of the product.

9. In the present case, both in the patent in suit and in the first (or second) priority document, the reported full nucleotide sequence encoding human t-PA (and, consequently, the deduced amino acid sequence of human t-PA) of Figure 5 is said to be that determined from the two clones pPA25E10 and pPA17. The language of the documents in this respect is identical. However, when comparing the sequences reported in the respective Figures 5, the skilled reader observes the following differences at the level of three deduced amino acids (and of the corresponding triplets), namely:

- in position 175 the **basic** amino acid (Lys) reported in Figure 5 of P1 is replaced by an **acidic** amino acid (Glu),

- in position 178 the **aliphatic** amino acid (Gly) reported in Figure 5 of P1 is replaced by a **hydroxylic** amino acid (Ser),

- in position 191 the **aliphatic** amino acid (Ala) reported in Figure 5 of P1 is replaced by a **hydroxylic** amino acid (Thr).

When comparing the technical content of the P1 (or P2) document with that of the patent in suit, the skilled

reader, while realising that possibly some errors were made in reporting the sequences, is not in a position to establish which one of the two reported sequences of human t-PA is the correct one. Nor can the skilled reader know therefrom whether the two polypeptides, in spite of the differences in their primary structure, are identical in their physical and biological characteristics. At least on paper the quoted replacements of amino acids, due to their nature, are not irrelevant and could, therefore, imply important structural and functional differences. Thus, the skilled person would regard the two respective polypeptides of Figures 5 as being two specific, **distinct** variants of human t-PA possibly with similar, but not necessarily identical characteristics.

10. The Respondents filed evidence (cf. affidavit of D. V. Goeddel dated 4 April 1988) to show that the sequence errors were the result of errors in the assignment of three individual nucleotides during DNA sequencing and that at any rate, when reproduced experimentally, they did not have a substantial effect on the production or activity of human t-PA. In fact, the corresponding transfected cells produced about the same amount of immuno-recognisable t-PA as the wild-type transfectants, with only a small reduction in specific activity. However, in this respect, the Board observes that the quoted evidence, which is understandably restricted to the testing of a limited number of parameters, namely immunorecognition and activity in a clot lysis assay, constitutes at most a proof of similarity, not of identity of the two polypeptides. Even if displaying similar biological and/or immunological activity, the two polypeptides could differ in one or more of the hundreds of properties of the protein, e.g. stability, folding, susceptibility to proteases, glycosylation, in vivo half-life etc.. In any

case, they differ in one essential characteristic, i.e. the primary amino acid sequence.

11. As regards the case law referred to by the parties, in the Board's judgement, the points of law with which decisions T 73/88 (supra) and T 65/92 (supra) were concerned are not relevant to the present case. Nor does the Board see any need to refer the question, which is of technical nature, to the Enlarged Board of Appeal.

12. In decision T 73/88 (supra), at issue was the entitlement to priority of a claim to a snack food product, said claim including in the pre-characterising portion a technical feature ("at least 5% by weight of oil or fat") which was not included in the priority document. Since in the view of the Board, this feature, although necessary for limiting the extent of protection, had nothing to do with the essential character and nature of the invention as such, the claimed invention was considered to be the same as disclosed in the priority document. Contrary to that, in the present case the primary amino acid sequence of the polypeptide - for the reasons given above - is considered to have to do with the essential character and nature of the invention.

13. In decision T 65/92 (supra), the Board decided that a difference in the reported upper limit of the molecular weight of the glycosylated form of a polypeptide between the priority document and the European patent application (all other measured parameters being identical) did not reflect a true structural difference between the products of the two applications, especially in view of the fact that the molecular weight is able to be determined only approximately. Contrary to that, in the present case the primary structure of human t-PA is not a parameter which is determined approximately,

unless one relies on a general formula, which is not the case here.

14. In the Board's view, more relevant to the present case is decision T 301/87 (supra). In this decision, it was not accepted that the mere reference to a specific DNA sequence fully contained in a deposited plasmid could establish by implication priority for a component part of the sequence, because this could not be envisaged directly and unambiguously as such, and required considerable investigation to reveal its identity. For similar reasons, in the present case it is considered that, contrary to the Respondents' view, the disclosure of the two clones pPA25E10 and pPA17 in P1 (or P2) document does not establish - by implication - priority for the "correct" sequences of Figure 5 of the patent in suit. In fact, the latter cannot be derived directly and unambiguously from the P1 (or P2) document, in which different sequences are reported in Figure 5, and a large amount of investigation is required in order to reveal their true identity.

15. The other decisions relied upon by the parties are considered to concern quite different situations to that here or to deal with issues (e.g. correction of errors) not arising here and so do not need to be dealt with in detail here.

16. Thus, the primary amino acid sequence of a protein (or the nucleotide sequence of a DNA) constitutes a true technical feature and relying on a given sequence rather than on another one for the definition of the subject-matter of an invention in a claim makes a critical difference. Thus, Claim 1 is not entitled to the first or to the second priority date because it does not relate to the same invention as disclosed in the

respective priority documents. It is only entitled to the priority date of P3, i.e. 7 April 1983.

Novelty (Article 54 EPC)

17. In view of the conclusion in point 16. supra, Pennica et al. (18), published on 20 January 1983, constitutes prior art under the meaning of Article 54(2) EPC. This document discloses the cloning and expression of human t-PA cDNA in E.coli and reports in Figure 3 the nucleotide sequence and the deduced amino acid sequence of the full-length human t-PA cDNA insert of the expression plasmid pt-PAtrp12 which corresponds to that of Figure 5 of the patent in suit. The expressed polypeptide has the fibrinolytic properties characteristic of human t-PA. Thus, the subject-matter of Claim 1 of the patent in suit is not novel having regard to document (1) and the main request of which Claim 1 is part is not allowable under Article 54(1) and (2) EPC.

Subsidiary claim requests 1 and 2

18. The Board examines here first the compliance of these requests with the requirements of Article 84 EPC (clarity and support by the description) and 83 EPC (sufficiency of disclosure), in particular in the light of the rationale laid down in decisions T 409/91 (OJ EPO 1994, 653), T 435/91 (OJ EPO 1995, 188) and T 626/91 of 5 April 1995 (not published in the OJ EPO). The two requests are examined in conjunction as the question at issue is the same for both.

The Appellants' position

19. The Appellants object in particular that the extent of patent monopoly demanded by Claim 2 in respect of human t-PA derivatives is by far too large in consideration, firstly, of the limited amount of examples and information provided by the description and, secondly, in view of the vague and unclear definition of the parameter "has human tissue plasminogen activator function".

The Respondents' position

20. The Respondents contend that Article 84 EPC cannot be relied upon as a legal basis for refusing the requests because the objections based upon this article do not arise out of amendments deemed to be vague or indefinite, but out of definitions which were already present in the claims as granted.

The Board's conclusions

21. The Board observes that Article 84 EPC is a proper basis for rejecting a claim request if this objection arises out of amendments made to the granted claims. Further questions of clarity may affect the decision on issues under Article 100 EPC, for example novelty, inventive step or sufficiency of disclosure. In decision T 626/91 (supra), which concerned a case inter-partes, the clarity of one of the features used for defining the claimed subject-matter was taken into consideration within the framework of the examination of novelty and sufficiency of disclosure. This feature had not arisen out of amendment. It was decided that, since the patent in suit did not provide any relevant information as to

the determination of the said feature, the disclosure was to be considered insufficient for the corresponding subject-matter.

22. Decision T 409/91 (supra) concerned an ex-parte case which was thus open to objections under Article 84 EPC. In this decision, the Board, with reference to the general legal principle that the extent of the patent monopoly, as defined by the claims, should correspond to the technical contribution to the art in order for it to be supported or justified, established a link between the requirements of Article 83 and 84 EPC. In the Board's view, in order to fulfil the requirement of Article 83 EPC, the application as filed must contain sufficient information to allow a person skilled in the art, using common general knowledge, to carry out the invention within the whole area that is claimed. Claims which by omission of an essential feature extend to subject-matter which, after reading of the description, would still not be at the disposal of the person skilled in the art, are objectionable both under Article 83 and 84 EPC.

23. In decision T 435/91 (supra), which concerned an inter-partes case, it was considered that a claim directed to a detergent composition in which an "additive" was defined in functional terms could not be allowed under Article 83 EPC because the patent did not disclose a self-sufficient technical concept which adequately corresponded to the said functional definition of the "additive". This definition was considered to be not more than an invitation to perform a research programme in order to find other "additives" which met the "functional" requirement set out in the claim (cf. point 2.2.1 of the Reasons).

24. In the present case, Claim 2 of both requests is concerned inter alia with the preparation in a recombinant system of derivatives of the 527 amino acid sequence "as defined in claim 1" (subsidiary request 1) or "as encodable by said DNA sequence isolate of claim 1" (subsidiary claim request 2), said derivatives having "human tissue plasminogen activator function". It is observed that in these requests, differently than in the main request discussed above, neither the 527 amino acid sequence nor the nucleotide sequence encoding it are defined by reference to specific sequences. They are rather defined by means of other parameters such as the restriction pattern and the hybridisation properties of the encoding cDNA. Thus, no reference structure of human t-PA (neither in terms of an amino acid sequence nor of a nucleotide sequence) is provided in the claims for the derivatives, as it was in the case of the main request.

25. Furthermore, it is observed that the feature "has human tissue plasminogen activator function" is quite vague and ambiguous. Although this feature was not amended during opposition proceedings, its significance and thus its clarity have to be reconsidered within the framework of the amendments to the claims in view of its influence on the decision on the issue of the sufficiency of disclosure (cf. T 626/91 supra).

26. Human t-PA is a molecule with multiple functions, some of which are in common with other molecules like, for example, urokinase (cf. description of the patent in suit, page 1, lines 42 to 58). Therefore, a reference which fails to characterise the precise function(s) meant is of no assistance to the skilled addressee. The patent in suit contains at least four definitions in this respect:

(a) on page 5, lines 24 to 27, human t-PA denotes human extrinsic (tissue type) plasminogen activator, produced by microbial or cell culture systems, in bioactive forms comprising a protease portion and corresponding to those tissue plasminogen activators otherwise native to human tissue;

(b) on page 5, lines 59 to 61, reference is made to the serine protease function plus the fibrin binding;

(c) on page 5, lines 62 to 65, reference is made to products comprising only the serine protease portion;

(d) on page 6, lines 1 to 3, reference is made to a product which is capable of catalyzing the conversion of plasminogen to plasmin, binds to fibrin and is classified as a t-PA based on immunological properties.

Thus, the skilled addressee is left in doubt as to the exact meaning of the expression "which has human tissue plasminogen activator function".

27. In view of the above, the Board attributes to the feature "has human tissue plasminogen activator function" the broadest possible meaning, i.e. any of the functions of human t-PA. This definition shows that the subject-matter of Claim 2 relates to a vast catalogue of derivatives of human t-PA of unspecified structure having any unspecified function of human t-PA. There is no dispute that the present description provides a disclosure of the production of human t-PA in a recombinant system. However, in the Board's judgement, the examples and the information given are not sufficient to allow a person skilled in the art, using

common general knowledge, to perform the invention without undue burden in the whole area claimed, especially in consideration of the broad functional meaning attributed to the quoted parameter. Claim 2 leaves the skilled addressee guessing as to whether any derivative of human t-PA which fulfils only one of the functions typical of this molecule is a derivative meant by the claim. In this respect the Board, in line with the quoted case law, considers the patent in suit to be insufficient and thus to contravene the requirements of Article 83 EPC. Furthermore, the area covered by the claim is not clearly defined, which is contrary to the provisions of Article 84 EPC.

28. For these reasons, subsidiary requests 1 and 2 must be refused under the provisions of Articles 83 and 84 EPC.

Subsidiary claim request 3

29. As stated in Section XIII., last paragraph, supra, this subsidiary claim request differs from subsidiary claim request 1 merely in that in Claims 1 and 2 the "human t-PA function" is specified by means of the expression "in particular, it is capable of catalyzing the conversion of plasminogen to plasmin, it binds to fibrin, and is classified as a t-PA based on immunological properties". In the context of the claims at issue this amendment means that present Claims 1 and 2 concern the process of preparation of a protein which displays at least the functions of human t-PA that are indicated. In the Board's judgement, this amendment clarifies the feature "has human tissue plasminogen activator function" objected to in subsidiary requests 1 and 2 (cf. points 25 to 28 supra) so that the reasons which brought to their rejection do not apply to the

present request. In fact, although also in this request no reference structure of human t-PA (cf. point 24 supra) is given in the claims for the derivatives of human t-PA, at least an indication is given as to the biological activities which have to be tested for when carrying out the modifications on the protein produced according to Claim 1. This reduces to an acceptable level the amount of burden which the skilled person has in performing the invention in the whole area claimed. Furthermore the area covered by the claim is now sufficiently precisely defined to meet the requirements of Article 84 EPC.

Admissibility of the request

30. The Appellants' objections to the formal admissibility of this request are essentially two-fold:

(i) it contravenes the provisions of Article 123(2) and (3) EPC; and

(ii) it extends the scope of protection beyond that conferred by the claims as maintained by the Opposition Division, which, in the light of the fact that the Respondents did not file an appeal, is against the view taken in decision G 4/93 of 14 July 1994 (to be published in the OJ EPO) whereby in such situation a Respondent is primarily limited to defending the claims as maintained.

Formal admissibility under Article 123(2) and (3) EPC

The Appellants' position

31. As regards objection (i) (cf. point 30 supra), the Appellants object that several changes in the claim language in comparison with the claims as granted

introduce modifications which either extend the scope of protection conferred by the patent as granted [Article 123(3) EPC] and/or are beyond the contents of the application as filed [Article 123(2) EPC]. In particular:

(a) the wording "a DNA sequence .... which **encodes** a 527 amino acid polypeptide..." of Claim 1 as granted (emphasis added) or "a DNA sequence **encoding** a polypeptide of 527 amino acids..." of Claim 2 as granted (emphasis added) has now been changed in Claim 1 to "a sequence of 527 amino acids...**encodable** by cDNA" (emphasis added);

(b) while Claim 2 as granted referred to "preparing one or more cDNA libraries..." and to the "probing the library or libraries", present Claim 1 merely refers to "cDNA... which hybridises strongly with the sequences", no reference being made to the preparation and probing of cDNA libraries;

(c) the wording "which hybridises under high stringency" used in Claim 2 as granted in relation to probe (iii) has been changed to "which hybridises strongly" in present Claim 1;

(d) the reference to "the HpaII-RsaI DNA fragment located downstream from amino acid No. 30 in Fig. 5 hereof" in Claim 2 as granted has been replaced by the recitation of a specific sequence of 112 nucleotides. In the description of the patent in suit the quoted fragment was said to consist of 230 bp (cf. page 14, line 8).

The Respondents' position

32. The Respondents reply essentially that the use of "encodable" reflects the fact that more than one DNA encodes the same protein and refer to Claim 3 as granted in which the expression "transforming DNA encoding the protein" was used. They further argue that there is a substantial equivalence between "hybridising strongly" and "hybridising under stringent conditions" because what the skilled person looks for are the clones that lit up strongly and in order to achieve this "high stringency" conditions are used. As regards the characterisation of probe (iii), the Respondents submit that the recited nucleotide sequence is derivable directly and unambiguously from the information given in the patent application as originally filed [cf. pages 34 to 37, in particular point E.1.H items (b) to (d)], in spite of the historical error made in the description of the probe used to identify the 4.2 Kb PvuII fragment (the HpaII-RsaI fragment was in fact a 230bp RsaI-PstI fragment; cf. affidavit of Dr Pennica).

The Board's conclusions

33. As regards the Appellants' objection outlined in point 31, **item (a)** supra, the Board observes that the term "encodable" in the context of present Claim 1 cannot be interpreted in a different manner than the term "as encoded" in the context of Claim 3 as granted. In the latter claim, the protein is "**as encoded** by the DNA product of claim 1 or claim 2" (emphasis added), Claims 1 and 2 being directed to the preparation of cDNA from mRNA from human t-PA producing cells, in particular from Bowes melanoma cells. Just like in the present case, what is meant is any protein having the same properties as that "encoded by cDNA from mRNA...". Thus,

the contested term does not result in an extension of the protection conferred by the claim or in new matter.

34. As for the objection outlined in point 31, **item (b)** supra, the omission of a reference to the preparation and probing of libraries in present Claim 1 does not result in an extension of the protection conferred in comparison with the claims as granted because these refer broadly to the preparation and isolation of cDNA from the Bowes melanoma cell line (cf. Claim 1) and to its use in the preparation of human t-PA protein (cf. Claim 3).

35.1 With regard to the objection outlined in point 31, **item (c)** supra, the relevant question is whether the change of the expression "which hybridises under high stringency" to "which hybridises strongly" modifies the definition of the candidate probe (iii) so as to include in its meaning probes other than that (or those) originally meant, thereby opening the whole of the Claim 1 to objections under Article 123(2) and (3) EPC.

35.2 The Board observes that neither of the two expressions is explicitly used in the application as originally filed for describing the conditions of the reaction between the HpaII-RsaI DNA fragment of pPA25E10 and the 4.2kb PvuII fragment of human genomic DNA. The application as originally filed makes reference either to prior art reference Fritsch et al., Cell, Vol. 19, 1980, page 959 ff. (cf. page 35, lines 14 to 16) or to the actual conditions used (cf. page 35, line 32 to page 36, line 18). In both cases, the skilled person derives from this information that hybridisation is carried out "under high stringency conditions". Thus, the expression "which hybridises under high stringency", which was introduced during the substantial examination phase and is found in the claims as granted, can indeed

be derived from the application as filed and is in conformity with the requirements of Article 123(2) EPC. The question here is whether or not its change to "hybridises strongly" in the request at issue is objectionable under the terms of Article 123(2) EPC because it introduces new matter, or under the terms of Article 123(3) EPC because it enlarges the extent of protection conferred by the claims as granted.

35.3 There is indeed a difference between the two expressions because in a hybridisation reaction, depending on the conditions used, be these of low stringency or high stringency, strong or weak hybridisation, i.e. a strong or weak signal, can be measured. The use by the Respondents in Claim 2 as granted under item (iii) of the wording "which hybridises under high stringency" and further down of the wording "strongly hybridising colonies" is seen by the Board as a confirmation of the fact that there is a difference. The expression "hydridises strongly" has a more general meaning since it is not restricted to any particular conditions of stringency.

35.4 In situations in which a specific synthetic oligonucleotide probe or mixture of probes of 15-30 nucleotides in length, representing possible coding sequences of parts of a protein, is used to screen by hybridisation cDNA or genomic libraries in order to identify DNA fragments encoding said protein, the finding of appropriate DNA fragments is dependent upon the stringency of the reaction conditions. This is because the said conditions influence the formation of duplexes of nucleic acids, in that under stringent conditions only long sequences with nearly perfect complementary matching will securely anneal, while, by relaxing the conditions, shorter and/or less well matching sequences will hybridise. In such situations, a

change of the qualification of the reaction from "which hybridises under high stringency" to "which hybridises strongly" would indeed imply a relevant change in the conditions of operation and thus the possibility of a different final result. However, in the present case, the candidate probe (iii) is a fragment of human genomic DNA of a specific size, namely 4.2kb, obtainable by digestion of the said DNA with the specific restriction enzyme PvuII. This distinct fragment is further identified and isolated by means of hybridisation with the recited, defined sequence of 112 nucleotides, this latter sequence being derived from DNA encoding human t-PA that has been previously isolated and sequenced. It is thus expected that this latter oligonucleotide probe matches perfectly with its target 4.2Kb PvuII fragment. Moreover, the said oligonucleotide probe is sufficiently long to allow the use of conditions of hybridisation that can guarantee discrimination between the target DNA sequence and other unrelated sequences. In the particular technical situation of the present case, in the Board's judgement, it makes no matter whether the interaction between the oligonucleotide probe and the target probe is qualified by means of "strong hybridisation" or "hybridisation under high stringency", as both qualifications lead the skilled person - who is told to look for a strong signal - to the same probe (iii). Therefore, the use of the expression "which hybridises strongly" in place of "which hybridises under high stringency" in the particular circumstances of the present case does neither result in the introduction of new matter nor in the broadening of the extent of protection and is thus not objectionable under Article 123(2) and (3) EPC.

36. As to the objection outlined in point 31, **item (d)** supra, the Board observes that the 4.2 kb fragment of human genomic DNA referred to as probe (iii), is now

identified in Claim 1 in terms of the explicit sequence of the HpaII-RsaI fragment used for probing it, i.e. the 112 nucleotide sequence recited in the claim. This sequence can be exactly identified by the skilled reader from Figure 5 on the basis of the information given in the patent application as originally filed as follows: the HpaII site (C'CGG) is found 34 bp from the 5'end of clone 25E10 (cf. page 35, lines 34 and 35), this 5'end starting with the third base of the codon for His (T)'at residue 18. This clone encodes 508 amino acid and lacks the N-terminal coding sequence (cf. page 32, lines 23 to 26). The sequence of the probe (ii) hybridises 13 bp from the N-terminal of clone 25E10 (cf. page 34, lines 30 to 32). The first RsaI site (GT'AC) is found downstream around the Tyr residue 67 (T being the first base of the corresponding codon). The fact that another RsaI site is found further downstream around the Tyr residue 163 may initially cause the skilled reader to hesitate having regard to the erroneous information provided in the specification about the size of the probe (230 bp) because neither of the two HpaII-RsaI fragments has that size. However, the whole of the information reported above together with the sequence information of Figure 5 unmistakably leads the skilled reader to the first of the fragments, i.e. to the sequence CGG...CTGT. Thus, the feature which characterises the probe (iii) in present Claim 1 results from making explicit the sequence of "the HpaII-RsaI DNA fragment located downstream from amino acid No. 30 in Fig. 5 hereof" referred to in Claim 2 as granted, said sequence being unambiguously derived from the application as originally filed. The fact that, as admitted during opposition proceedings, historically not this HpaII-RsaI fragment, but the adjacent RsaI-PstI fragment was used (this is at the origin of the error in reporting the size of the probe), is irrelevant for the question of admissibility under Article 123 EPC, which

relates to the contents of the disclosure as originally filed, not to its technical value for reproducing the teaching of the claimed invention, and need not to be discussed here (cf., however, point 44 iv. infra).

37. In summary, the Board does not consider that the amendments in subsidiary claim request 3 are such as to extend the protection conferred in comparison with the claims as granted or that they result in the addition of subject-matter extending beyond the content of the application as filed. Thus, there are no objections under Article 123(2) and (3) EPC to this request.

The question of "reformatio in peius"

The Appellants' position

38. As regards objection **(ii)** (cf. point 30 supra), the Appellants argue essentially that subsidiary request 3, by omitting a reference to the specific sequence of Figure 5, has now a much broader scope than the claims as maintained by the Opposition Division (main request) wherein the said reference constituted a key feature. In this respect, Appellants VII put forward a calculation showing that this omission results in a reduction of the number of reference nucleotides in the present request (probes, restriction sites) to only 13.5% of the total number of nucleotides referred to in the main request by way of Figure 5 (214 out of 1581). In their submission, this demonstrates the enormous difference in the extent of protection conferred between the two requests. Thus, in the light of decision G 4/93 (supra; cf. G 9/92, OJ EPO 1994, 875), this request should not be admitted into the proceedings because, if accepted, the Appellants would be put in a worse position than if they had not appealed ("reformatio in peius").

The Respondents' position

39. In response thereto, the Respondents argue that the request at issue, the main request and the claims as granted, although using different language, all have the same broad scope, this being the preparation of any human t-PA and functional derivatives thereof in a recombinant host organism. Thus, the different versions of the claim requests have the same scope. Under these circumstances, the prohibition enunciated in G 4/93 (supra) has no relevance.

The Board's conclusions

40. In decision G 4/93 (supra), the Enlarged Board of Appeal held that "if the opponent is the sole appellant against an interlocutory decision maintaining a patent in amended form, the patent proprietor is primarily restricted during appeal proceedings to defending the patent in the form in which it was maintained by the Opposition Division in its interlocutory decision. Amendments proposed by the patent proprietor as a party to the proceedings as of right under Article 107, second sentence, EPC, may be rejected as inadmissible by the Board of Appeal if they are neither appropriate nor necessary." (cf. Order, point 2). In the present case, the Respondents, having had their main request accepted, were not adversely affected by the decision of the Opposition Division and thus could not lodge an appeal (cf. Article 107 EPC). However, as the said main request is now successfully challenged by the Appellants (cf. the Board's conclusions supra), the Respondents can be expected to put forward amendments in order to defend their case by trying to overcome the objections raised in respect of the main request. However, in accordance with decision G 4/93 (supra), amended claim requests which, if accepted by the Board, would put the

Appellants in a worse position than if they had not appealed must be rejected.

41. It must therefore be examined whether the extent of protection conferred by the subsidiary claim request at issue is larger than that conferred by the main request (claims as maintained by the Opposition Division; cf. Section IV. supra). This main request was constructed around "the amino acid sequence 1-527 as depicted in Figure 5" and its alleles and derivatives. As the latter request failed for lack of novelty in consequence of the Board's negative finding in respect of the question of the entitlement to the first priority date (cf. points 3 to 17 supra), the Respondents legitimately attempt in the present request a definition of the protein which avoids a reference to Figure 5. The protein is now defined in terms of the DNA encoding it as well as of its function. The DNA encoding the protein is not defined in terms of a sequence, but in terms of its origin ("cDNA derived from mRNA extracted from Bowes melanoma cell line"), its restriction pattern ("shown in Fig 4") and its capability to hybridise strongly with sequences (i) to (iii). The description in the patent specification demonstrates that such a DNA indeed encodes the amino acid sequence 1-527 as depicted in Figure 5.

42. The Board observes that, although it is true that the definition "said protein comprises a sequence of 527 amino acids from N-terminal serine to C-terminal proline encodable by cDNA..." referred to in Claim 1 of the present request is broader in scope than "a protein... which comprises amino acid sequence 1-527 as **depicted in Fig. 5**" (emphasis added), it is also true that Claim 2 of the main request (cf. Section IV. supra) already referred to alleles and derivatives "of the amino acid sequence 1-527 depicted in Fig. 5". The

Appellants, though during oral proceedings asked by the Board to do so, were unable to give any example that was within the claims now put forward, but not within the claims accepted by the Opposition Division. For this reason, in the Board's view the total scope of each request is the same. Moreover, it should be remarked that the vague expression "human t-PA function" of the main request has been clarified in the present request (cf. point 29 supra). Thus, in the Board's judgement, should the present claim request be allowed, the Appellants would not be in a worse position than if they had not appealed. Therefore, the said request can be admitted.

Sufficiency of disclosure (Article 83 EPC)

The Appellants' position

43. The Appellants object that the disclosure of the present invention is not sufficiently clear and complete for it to be carried out by the skilled person. In particular, they submit that:

(i) The Bowes melanoma cell line, although available in some laboratories, was not generally available to the public in a form (deposition with a recognised institution) which could ensure unlimited access thereto throughout the life-time of the patent in suit. In this respect, reference was made to the European patent EP-B1-0 041 766 [document (12)] which, following opposition by third parties, was revoked for lack of sufficient disclosure due to the non-availability of the Bowes melanoma cell line.

(ii) As shown by experimental reports submitted by Appellants VII during the opposition and appeal proceedings, the examples concerned with the expression in E.coli are not workable. This is also supported by later evidence [cf. documents (36) to (38)] which shows that long after the priority date the production of human t-PA in E.coli was still problematic. Thus, the Respondents are not entitled at least to claims directed to this specific embodiment.

(iii) The description of the patent specification does not contain enough information with respect to the fibrin-binding and immunological assays which are important for distinguishing human t-PA from urokinase (cf. description, page 3, lines 44 to 52).

(iv) The information in respect of probe (iii) of Claim 1 is misleading as it is known that not the HpaII-RsaI fragment, but the RsaI-PstI fragment was used for its isolation [cf. Pennica et al. (18)].

(v) Not a single example of a functional derivative is provided in the description of the patent in suit. Though, a wealth of possible derivatives are claimed. This is nothing more than an invitation to carry out a research programme in order to find suitable derivatives of human t-PA (cf. decision T 435/91 supra).

The Board's conclusions

44. In respect of the above objections, the Board's view is as follows:

(i) a large body of evidence shows that Bowes melanoma cells were generally available and freely exchanged in the scientific community among all those engaged in a research programme on t-PA [cf., for example, documents (7), (13), (17)] and that neither secrecy agreements nor contractual obligations among the research workers restricted the use or dissemination of the cells. Further, no evidence was produced that the cells would be available only to some selected laboratories for a limited time period. Thus, in the Board's judgement, the Bowes melanoma cells were part of the state of the art already at the priority date. Under these circumstances the Board cannot agree to the Appellants' position that it would have been the Respondents' obligation to ensure their availability for the life-time of the patent in suit by means of a deposition under Rule 28 EPC.

(ii) According to the established case law (cf., for example T 281/86 OJ EPO 1989, 202; T 301/87, supra, and T 292/85, OJ EPO 1989, 275), the question under Article 83 EPC is not whether or not a specifically described example is exactly repeatable, but whether the overall teaching of a patent in respect of a claimed embodiment can reliably lead the skilled person to put it into practice. In the present case, the Appellants do not dispute that the teaching of the patent in suit as regards expression of human t-PA in mammalian cells (cf. Claims 5 and 6) is

sufficient. They dispute sufficiency of disclosure in respect of the expression in E.coli which is the subject of Claim 4. In this respect, the Board observes that the later evidence submitted by the Appellants does not prove that it was impossible to obtain expression of a human t-PA molecule in E.coli, but that expression of active t-PA "at a significant level" [cf. Sarmientos et al. (36)] was not shown, or that "**most** of the protein accumulates in the cytoplasm in an inactive form" [cf. Krause (37)], or that "expression is **poor**" [Rothstein et al. (38)]. It should be remembered that at issue here is whether the teaching of the patent in suit is sufficient in order to achieve expression of human t-PA in E.coli at any level. In this respect, the quoted later evidence is rather confirmatory because it demonstrates that a DNA sequence encoding human t-PA can indeed be expressed in an E.coli recombinant system. Even if the specifically described example is not exactly repeatable as allegedly shown by the experimental reports submitted by Appellants VII, it does not invalidate the teaching of the patent in suit as a whole. This must be seen from the wider perspective of the overall disclosure (full nucleotide sequence encoding human t-PA and amino acid sequence of the latter), not from the narrow angle of a single example which after all outlines only how the Respondents arrived at the final result. In the Board's view, the skilled person, given the stated sequence information and the results of its expression in a mammalian host, does not have to apply inventive skill or undue experimentation in order to achieve expression in the E.coli system.

(iii) Immunological and fibrin-binding assays of human t-PA were part of the state of the art at the priority date [cf., for example, Rijken et al. (7), in particular "Experimental procedures"] and needed not to be addressed in detail in the description of the patent specification as their performance involved nothing out of the ordinary for a skilled person.

(iv) The fact that the isolation of probe (iii) referred to in Claim 1 historically involved not the stated HpaII-RsaI fragment of pPA25E10, but the adjacent fragment RsaI-PstI is irrelevant with respect to the question of sufficiency of disclosure because the former fragment, due to its structure, is equally capable of hybridisation with a 4.2kb PvuII fragment of human genomic DNA (cf. also point 36 supra). This is also confirmed by the Pennica's notebooks - see Notebook 6 pages 90 to 95 filed by the Respondents with letter dated 7 May 1991 - in which it is indicated that the 110bp HpaII-RsaI probe was in fact used for rescreening positive clones obtained by screening with the 230bp RsaI-PstI fragment.

(v) When given a basic molecular structure (here: the nucleotide sequence and deduced amino acid sequence of human t-PA) and an activity to be tested (here: capability of catalyzing the conversion of plasminogen to plasmin, binding to fibrin, and t-PA's immunological properties), the average skilled person can be expected to be able to prepare without application of inventive skill or undue experimentation generic functional derivatives of the molecule by way of amino acid deletion, substitution, insertion,

addition or replacement within the framework of routine trials.

45. In summary, in the Board's judgement, none of the objections put forward by the Appellants can lead to the conclusion that the disclosure of the claimed subject-matter is not sufficiently clear and complete for it to be carried out by a person skilled in the art. Consequently, the requirements of Article 83 EPC are met by the patent in suit.

Entitlement to priority (Articles 87 and 88 EPC)

46. In the Board's opinion, the claimed subject-matter of this request is entitled to the priority date of P1 because all elements which characterise it are found in the P1 document and thus is the **same** invention. In particular, P1 relates to a process for the preparation of human t-PA protein by expression in a recombinant host organism, such as E.coli or mammalian cells, of a transforming DNA (cf. pages 1 to 8), said protein comprising a sequence of 527 amino acids from N-terminal serine to C-terminal proline (cf. Figure 5) as encoded by cDNA derivable from mRNA extracted from Bowes melanoma cells (cf. page 21) which has the restriction pattern shown in Figure 4 and hybridises strongly with the same probes (i) to (iii) referred to in Claim 1 of the present request (cf. page 27, line 3; page 29, third line from the bottom; pages 30 to 32 in connection with Figure 5, in particular the nucleotides corresponding to the amino acid residues No. 30 to 67 which are identical with the corresponding ones of Figure 5 of the patent in suit). Document P1 makes also reference to the preparation of variants of the said protein, these being either natural allelic variants or variants derived from amino acid deletions, substitutions, insertions, inversions or additions (cf. page 38). Thus, subsidiary

request 3 is entitled to the priority date of 5 May 1982 (P1).

Novelty (Article 54 EPC)

47. None of the cited documents made available to the public before the P1 priority date discloses the claimed subject-matter which is, therefore, novel under Article 54(1) and (2) EPC.

Inventive Step (Article 56 EPC)

48. Opdenakker et al. (13) represents the closest prior art for the claims at issue. This document discloses the isolation from the Bowes human melanoma cell line of mRNA for t-PA, its fractionation and the isolation of a single fraction corresponding to 19-S RNA which was translated in oocytes into measurable protease activity as tested by the fibrin-plate method (cf. page 271, under "Results"). The document points out that the presence of a 70 Kd product revealed by autoradiogram and immunoprecipitation studies was highly suggestive of a protein identical with human t-PA, but that the identity of the translated proteins remained to be determined. The stated purpose of the study in Opdenakker et al. (13) was "to isolate and purify the mRNA for extrinsic plasminogen activator as a starting material and probe for cloning the extrinsic plasminogen activator gene into a prokaryotic vector" (cf. page 273, left-hand column, second paragraph). In this respect, the document points to the variability in the mRNA preparations and to the difficulties in the accurate estimation of the amount of specific mRNA present (cf. page 273, left-hand column, last paragraph).

49. In the light of Opdenakker et al. (13), the technical problem to be solved can be seen in the provision of qualitatively and quantitatively adequate amounts of DNA for the production of human t-PA in a recombinant host organism.

50. This problem is solved by the patent in suit by providing cDNA suitable for transformation of a recombinant host organism and by elucidation of its structure as well as of the structure of the human t-PA encoded thereby. In view of the detailed information contained in the patent in suit, the Board is satisfied that the above-stated technical problem has been solved.

51. The relevant question in respect of inventive step is whether the skilled person, starting from the disclosure of Opdenakker et al. (13), would have attempted the preparation of cDNA encoding human t-PA with a reasonable expectation of success. In respect of this question, the statement in decision T 296/93 (OJ EPO 1995, 627) that "a reasonable expectation of success" should not be confused with the understandable "hope to succeed" (cf. loc.cit., point 7.4.4 of the Reasons) is of relevance. This is because in the light of Opdenakker et al. (13), the preparation of cDNA from the mRNA extracted from Bowes melanoma cell line was "obvious to try" for the skilled person and his or her hope was to succeed. The explicit suggestion to try is indeed given therein. However, the question here is whether the skilled person was in a position to reasonably predict, on the basis of the existing knowledge, before the starting of this research project, a successful conclusion to the project within acceptable time limits (cf. loc. cit., supra). For answering this question, avoiding any hindsight, account should be taken also of the fact that, as stated in decision T 816/90 of 7 September 1993 (not published in the OJ EPO), "even

when it is possible to theoretically conceive a straightforward approach to solve a specific technical problem, the skilled person might be confronted with unexpected difficulties when trying to put the conceived strategy into practice." (cf. loc. cit. point 5.2.7 of the Reasons). Similar considerations were taken into account in other decisions concerned with inventions in the genetic engineering field [cf., for example, T 223/92 of 20 July 1993, see point 5.15 of the Reasons and T 412/93 of 21 November 1994, see point 142 (iv) of the Reasons, both not published in the OJ EPO].

The Appellants' position

52. With respect to this question, the Appellants maintain that t-PA research was not an unexplored technical area because sufficient amounts (up to 4 mg) of human t-PA isolated from the Bowes melanoma cell line were available for amino acid analysis [cf. Rijken et al. (7), in particular page 7037 as well as Weimar et al. (9), in particular page 1018] and a number of possible routes was known for the straightforward preparation of cDNA from mRNA. In particular, they point out that Noda et al. (33) had taught a screening strategy useful for isolating cDNA clones when mRNA sequences were present in low abundance (cf. loc. cit., page 202, right-hand column) which was based on the preparation of a mixture of probes representing all degenerate sequences deduced from a pentapeptide sequence. Suggs et al. (11) and Wallace et al. (4) had also taught a general approach for the preparation of hybridisation probes suitable for use in a mixture for the isolation of cDNA sequences. The skilled person, following the hint given in Opdenakker et al. (13), would have prepared without any difficulty effective hybridisation probes according to known methods (cf. Suggs et al. (11) or Wallace et al. (4)] on the basis of the accessible knowledge of the

amino acid sequence of human t-PA. In their view, the determination of the latter would have been easy enough, due to the availability of human t-PA in large amounts. The Appellants consider that, after having established the amino acid sequence of human t-PA, the skilled person, by following in an analogous manner the strategy indicated in Noda et al. (33), would have prepared probes for screening cDNA clones derived from the highly purified mRNA fraction known from Opdenakker et al. (13). Thus, the skilled person would have arrived at the claimed subject-matter without inventive effort.

The Respondents' position

53. The Respondents emphasise all the uncertainties and problems that the skilled person had to face (low abundance of mRNA, size of mRNA, unknown amino acid sequence of human t-PA etc.) and maintain that evidence (cf. the various affidavits and declarations of various distinguished scientists submitted during the opposition proceedings) shows that more than ordinary skill was required in order to achieve a solution to the underlying technical problem and that the teams involved in this project were rather skeptical about the possibility of succeeding.

The Board's conclusions

54. In 1982 the synthesis and cloning of cDNA was not yet routinely established because genetic engineering had not yet made all the technical and theoretical advances which nowadays (thirteen years later) are available to a competent laboratory. Contamination of the reagents (e.g. enzymes), for example, was still one important problem. Moreover, many methods, vectors, screening procedures had just been established or were in the trial phase. This should be taken into account when

making an objective analysis of the degree of confidence that the skilled person would have had at the time that he or she would have succeded in solving the underlying technical problem.

55. Before embarking on the cloning and expression of cDNA encoding human t-PA, the skilled person would have considered carefully which methods would have offered the best chance of success. In doing that, the skilled person, being aware inter alia of the probable low abundance of mRNA encoding human t-PA, would have considered in particular the cloning strategy described in Noda et al.(33) which was based on the approach already known from Suggs et al. (11) and Wallace et al. (4), and which was presented as "useful for isolating cDNA clones that carry mRNA sequences present in low abundance". This strategy made use in the screening of recombinant clones of a mixture of probes representing codon combinations for a portion of the amino acid sequence of the desired protein, said sequence displaying possibly a low degree of degeneracy. The skilled person would have selected this mixed probes hybridisation method to screen cDNA libraries knowing that other methods of selection such as hybrid selection or expression screening would have been more problematic because the first was feasible only when dealing with few colonies and the second was more appropriate for small protein products, neither of which was the case here. It is accepted by the parties that according to the common general knowledge at the priority date in 1982 the said approach would have been the "method of choice". This is reflected by the document "Points of agreement between W.Brammar and G.Stark" dated 5 August 1986 which was introduced into the opposition proceedings (cf. point 12 therein). Thus, at least on paper, the skilled person would have indeed been in a

position to conceive a protocol for cloning and expressing a DNA sequence encoding human t-PA.

56. However, when trying to reasonably predict the successful conclusion of this research endeavour within acceptable time limits, the skilled person would have had to take the following facts into account:

(a) the procedure for screening recombinant clones described in Suggs et al. (11) and Wallace et al. (4) was stated to be suitable for proteins for which the amino acid sequence was **known** [cf. document (11), page 6613, left-hand column, paragraph in the middle and document (4), abstract).

(b) In Noda et al. (33) the said procedure was indeed applied to the cloning and sequence analysis of a protein the sequence of which was partly **known** and which had a **smaller** molecular weight than human t-PA.

(c) Human t-PA has a large size [about 72Kd, cf. Rijken et al. (7)]. Although its amino acid **composition** had been determined [cf. Rijken et al. (7), Table II], no information whatsoever was available on its primary structure. Thus, protein sequencing of human t-PA, which in itself was already a cumbersome and challenging task for a molecule of that size, was a prerequisite to being able to prepare hybridisation probes and one could not say in advance whether any sequences of low redundancy useful for this purpose were present in the molecule.

(d) The corresponding large size of mRNA [cf. Opdenakker et al. (13)] was expected to influence the degree of difficulty in establishing a cDNA library because of the ever-present danger of degradation or fragmentation of the molecule and of the possibility that reverse transcriptase would not transcribe it to its 5'end. Moreover, accurate estimations about the amount of specific mRNA present were lacking, it was not known whether the amount of mRNA could be increased by induction and whether one or more t-PA genes were present. Furthermore, Opdenakker et al. (13) had reported high variability of individual preparations.

57. All the above factors would have influenced the degree of confidence of the skilled person in the successful conclusion of cloning and expressing human t-PA. Knowing that a cDNA library could not be better than the mRNA from which it was derived and faced with the various uncertainties depicted above, the skilled person would not have expected the theoretically straighforward route (cf. point 55 supra) to be easily put into practice. On the contrary, although hoping to succeed, the skilled person embarking on this project would have known that its successful conclusion depended not only on the technical skill in putting into practice the sequence of precise steps of the theoretical experimental protocol, but importantly also on the ability of taking the right decisions along the way whenever a difficult experimental situation would have required it. Under these circumstances, in the Board's judgement, it cannot be said that the skilled person had a reasonable expectation of success in the sense set out in the case law (cf. point 51 supra).

58. The various affidavits and declarations of prominent scientists who, on different sides, were involved in this research endeavour confirm that, while there was a considerable interest in arriving - possibly before everybody else - at the cloning and expression of human t-PA in a recombinant host, the task was regarded as tough, the prospects of success were considered thin and the announcement of the isolation by the Respondents of a full-length clone encoding human t-PA was received in the interested milieux as a pleasant surprise (cf. in particular the affidavit of Dr. Pennica, points 52 to 57).

59. No objections arise on the other dependent claims or on the formulation of the claims for AT. For these reasons, the Board concludes that the subject-matter of the request at issue involves an inventive step. Thus, the subsidiary claim request 3 (Claims 1 to 15 for non-AT States and Claims 1 to 15 for AT) is allowable.

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 with the order to maintain the patent on the basis of Claims 1 to 15 (non-AT States) and Claims 1 to 15 (AT) of new subsidiary request 3 as filed in the oral proceedings.

The Registrar: The Chairwoman:

L. McGarry U. Kinkeldey