DECISION
of 26 July 2000

Case Number: T 0743/97 - 3.3.4
Application Number: 87902884.3
Publication Number: 0293394
IPC: C12N 15/12
Language of the proceedings: EN

Title of invention:
Novel thrombolytic proteins

Patentee:
GENETICS INSTITUTE, INC.

Opponent:
Boehringer Ingelheim GmbH

Headword:
Thrombolytic proteins/GENETICS INSTITUTE

Relevant legal provisions:
EPC Art. 84, 123(2), 83, 56

Keyword:
"Main request - added subject-matter (no)"
"Clarity (yes)"
"Sufficiency of disclosure (yes)"
"Inventive step (yes)"

Decisions cited:
G 0009/92, T 0409/91, T 0019/90, T 0128/92, T 0694/92,
T 0939/92

Catchword: -
Case Number: T 0743/97 - 3.3.4

DECISION
of the Technical Board of Appeal 3.3.4
of 26 July 2000

Appellant: GENETICS INSTITUTE, INC.
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Respondent: Boehringer Ingelheim GmbH
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Decision under appeal: Interlocutory decision of the Opposition Division
of the European Patent Office posted 15 April
1997 concerning maintenance of European patent
No. 0 293 394 in amended form.

Composition of the Board:
Chairman: U. M. Kinkeldey
Members: L. Galligani
C. Holtz
Summary of Facts and Submissions

I. An appeal was lodged by the proprietors of the patent against the interlocutory decision of the opposition division issued on 15 April 1997 by which the European patent No. 0 293 394, which had been opposed under Article 100(a) and (b) EPC, was maintained in amended form on the basis of claims 1 to 14 of the first auxiliary request, and an adapted description.

Claim 1 read as follows:

"A thrombolytic protein having tissue plasminogen activator-type activity characterized by a peptide sequence of human t-PA, wherein at least one of the consensus N-linked glycosylation sites is modified to other than a consensus N-linked glycosylation site and wherein the amino acids Cys-6 through Ile-86 are deleted."

The patent had been granted on the basis of claims 1 to 23 for all the designated Contracting States except Austria (non-AT states) and claims 1 to 22 for Austria.

Claims 1 and 14 as granted for the non-AT states were as follows:

"1. A thrombolytic protein having tissue plasminogen activator-type activity characterized by a peptide sequence of human t-PA, wherein one or more amino acids are deleted within the region Gly-(-3) through Thr-91, and either

(a) Arg-275 is deleted or is replaced by a different amino acid, or
(b) at least one of the consensus N-linked glycosylation sites is modified to other than a consensus N-linked glycosylation site, or

(c) both (a) and (b)."

"14. A thrombolytic protein having tissue plasminogen activator-type activity characterized by a peptide sequence of human t-PA, wherein one or more amino acids within the region Gly-(−3) through Thr-91 are replaced with different amino acids."

II. The opposition division, while not allowing the claims of the main request then on file for lack of inventive step, decided that the subject-matter of the auxiliary claim request, the novelty of which was not contested, was sufficiently disclosed and involved an inventive step, having regard in particular to the following documents:

(6) EP-A-0 178 105;

(14) FEBS, Vol. 189, 1985, pages 145 to 149;


III. With the statement of grounds of appeal, the appellants filed a new main request, and new documents (28) to (32).

IV. In their reply to the statement of grounds of appeal, the respondents (opponents) submitted that the newly filed claim 1 contravened Article 123(2) EPC, that it was not entitled to any of the four priority dates and that it was not based on an inventive step. They
further expressed the opinion that the subject-matter of the claim was not sufficiently disclosed.

V. The appellants replied to the submissions of the respondents.

VI. On 25 April 2000, the board issued a communication with an outline of the points to be discussed and a provisional view on some of the issues.

VII. In reply thereto, submissions were made both by the appellants and the respondents. The appellants filed a new main request. The respondents filed new evidence in relation to the public availability of following citation:


VIII. As regards the latter citation, the board, having sought independent information from the National Academy of Sciences, was informed that, according to the records, the issue of July 1986 had been mailed to subscribers on 30 June 1986. This information was communicated to the parties during oral proceedings which took place on 26 July 2000. It was accepted by the parties that document (11) had been available to the public before 3 July 1986.

IX. At the oral proceedings, the appellants submitted as a new main request claims 1 to 14 for all non-AT States and claims 1 to 13 for AT.

Claim 1 for the non-AT States read as follows:
"A thrombolytic protein having tissue plasminogen activator-type activity and having an improved fibrinolytic profile relative to native human t-PA characterized by a peptide sequence of human t-PA that retains both kringle regions, wherein at least one of the consensus N-linked glycosylation sites is modified to other than a consensus N-linked glycosylation site and wherein

(a) one or more amino acids are deleted within the region Val-4 to Val-72; or

(b) one or more amino acids are replaced within the region Arg-23 to Val-72; or

(c) features (a) and (b) are combined; or

(d) the amino acids Cys-6 through Cys-51 are deleted; or

(e) the amino acids Cys-51 through Asp-87 are deleted; or

(f) the amino acids Cys-6 through Ile-86 are deleted."

Claims 2 to 4, 7 to 11 concerned embodiments of a thrombolytic protein according to claim 1 (f); claims 5 to 6 were directed to embodiments of a thrombolytic protein according to claims 1 to 4; claim 12 was directed to a DNA molecule encoding said protein; claim 13 was directed to the protein thereby expressed and claim 14 was directed to a therapeutic composition containing said protein.

Claims 1 to 13 for AT were in the form of process
The appellants argued essentially that the post-published documents (cf. documents (22),(28)-(31)) provided many examples of variants falling under the scope of the claims which had advantages and unexpected properties in comparison with the t-PA of the prior art, thus demonstrating a general advantage and unexpected effect linked to the teaching of the patent, including synergistic effects. This teaching was that
for obtaining a t-PA with improved properties a deletion and/or substitution of at least one or more amino acids in the indicated regions at the N-terminal end of the molecule had to be combined with a modification of a glycosylation site. Such a teaching was not obvious vis-à-vis any combination of prior art documents, in particular vis-à-vis the combination of document (6) with either document (5) or (14). The patent specification not only enabled the person skilled in the art to produce the claimed variants but also to select those which had a positive technical effect.

XII. The respondents considered that the admission into the proceedings of the additional documents (28) to (32) filed by the appellants (cf. Section III supra) was not justified because the said documents were not in relation to the rationale of the decision of the opposition division and, moreover, they were not relevant in respect of the issues under discussion. They suggested to the board, in case it should be inclined to reverse the opposition division's decision on the basis of the said documents, to remit the case to the first instance in order to enable consideration of the new evidence at two levels of jurisdiction.

As regards the formal requirements, the respondents submitted essentially that:

- The amendments in the claims contravened Rule 57a EPC and offended against Article 123(2) EPC. In particular, in claim 1 the features (a), (b), and a fortiori also feature (c) were newly created specific combinations from the group of the twelve distinct contiguous subregions within the region
from -3 to +91 reported in table on page 3 of the application as filed. This table and the preceding paragraphs of the description, which referred rather to "more conservative modifications", could not support the broadly claimed substitutions or/and deletions of one or more amino acids in the arbitrarily selected areas now referred to in items (a) to (c) of the claim;

- Claim 1 lacked clarity because: (i) it did not allow the reader to establish whether deletions encompassing those specifically mentioned were also covered, and (ii) the meaning of the feature "having an improved fibrinolytic profile relative to native human t-PA" could not be properly understood in view of the many ways, including a "more homogeneous form", whereby, as indicated in the description of the patent specification (cf. on page 3, lines 7 to 12), an improvement could manifest itself.

As regards the substantive requirements, the respondents argued essentially as follows:

- Claim 1, in particular in items (a) to (c), proposed modifications in a broad general way. The patent specification listed on page 1, lines 1 to 12, the benefits allegedly resulting therefrom. However, neither results were given, nor indications whatsoever were reported of any actual effects to be inferred from the proposed modifications. No instructions were given in view of the achievement of any particular stated effect. In view of the extent of the modifications proposed, it was highly probable that most of the
wealth of compounds falling under the scope of the claim would not provide any effect at all. It was simply not credible, for example, that any kind of substitution within a large area of the t-PA molecule could provide an improved fibrinolytic profile. Under these circumstances, the patent specification was merely a vague invitation to make deletions and/or substitutions, large or small or in-between, within the first 91 amino acids of t-PA in the vague hope that it might produce some unspecified advantageous effect classifiable under the general description of "an improved fibrinolytic profile". The concept of a sufficient disclosure had not to be interpreted as meaning merely the ability to produce a compound out of idle curiosity, but as requiring also the ability to make compounds which exhibited the technical effect upon which the alleged invention was based. In this sense, the claimed subject-matter was not sufficiently disclosed. The claims thus requested an extent of protection which was not justified in the light of the contribution to the art, if there was any (cf. T 939/92 OJ EPO 1996, 309).

It was known from the prior art that t-PA variants lacking either the N-terminus and first kringle region (cf. document (19)) or having modified consensus glycosylation sites (cf. document (6)), while retaining the fibrinolytic activity, had the advantage of a longer half-life or reduced clearance. It was also known that variants with deleted finger or growth factor domains, which were expressed in E. coli and consequently lacked glycosylation, retained their activity (cf.
documents (5), (11) and (14)). Moreover, document (18), which dealt with the production of human t-PA by recombinant DNA techniques, had already contemplated modifications including deletions, substitutions, insertions and additions of amino acids to the native t-PA. In view of such knowledge, no inventive step could be acknowledged to claims directed to a broad group of "contemplated" compounds for which no particular properties could be inferred from the patent specification other than, possibly, those already predictable from the prior art. As a matter of fact, the speculation in the patent in suit was no better than that in document (18) and it merely invited the reader to try it out. This could hardly be seen as an inventive contribution to the art (cf. T 939/92 supra). The appellants could not base an inventive step on alleged surprising effects which were discovered after the filing date in relation to some specific members of a large groups of compounds. Inventive step had to be assessed on the basis of what was claimed and of what could be predicted from the prior art. The invention could not be created by the subsequent work of others. For these reasons, the claims lacked an inventive step.

XIII. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request as submitted in the oral proceedings.

The respondents requested that the appeal be dismissed.
Reasons for the Decision

Procedural matters

1. Documents (28) to (32) were filed by the appellants with the statement of grounds of appeal as further evidence in support of their main request. In consideration of the fact that (i) the documents were submitted at the very onset of the appeal proceedings, thus giving to the respondents enough time for submitting, if deemed necessary, counter-evidence; (ii) they concerned the fibrinolytic profile of variant t-PA molecules falling within the scope of the appellants' main request; and (iii) were meant as expert evidence supporting the main claim request in response to the decision under appeal, the board decided to admit the documents into the proceedings.

2. As the said documents, although being useful for providing an overall picture on protein engineering of t-PA-type molecules, were per se not decisive for the outcome of the appeal, the board deemed it not to be necessary to remit the case to the first instance for further consideration of their contents.

The main request

The formal requirements:Articles 84 and 123 EPC.

3. No objections under Article 123(3) EPC were raised by the respondents. Nor does the board have any objections in this respect since the extent of protection conferred by the amended claims is narrower than that of the claims as granted, being the amendments of a restrictive nature.
4. As regards the issue under Article 123(2) EPC, no objections are seen by the board based on the following considerations:

(i) The application as filed provides unambiguous support for embodiments (a) to (c) of claim 1 (and of the claims which refer thereto) which concern modifications (deletions and/or substitutions of one or more amino acids) in the region from either Val-4 or Arg-23 through Val-72. This conclusion is based on the following observations:

(a) The application as filed deals essentially with amino acid modifications (deletions and/or substitutions) in the N-terminus region from Gly(-3) to Thr(91) of the t-PA protein (cf. eg claims 5 and 10 as filed);

(b) All modifications in this region can be in combination with modifications of the glycosylation sites, in particular with the modification of "at least one of the consensus N-linked glycosylation sites" to "other than a consensus N-linked glycosylation site" (cf. claims 6 and 16 as filed);

(c) All modifications at the N-terminus can be in combination with the replacement or deletion of Arg 275 (cf. claims 6 and 16 as filed)

(d) The modifications in question can be carried out on t-PA analogs containing at position 245 either Met or Val (cf. page 41);
(e) On page 3 and on page 26 of the application as filed, the same table indicates twelve discrete subregions in which the modifications (one or more deletions or substitutions) can be made. These subregions are contiguous and span Gly(-3) through Thr(91) without any interruption. They include: a subregion starting from Val-4 (subregion 2), a subregion starting at Arg-23 (subregion 5), and a subregion ending at Val 72 (subregion 10). The accompanying passage of the description before the table makes reference to "one or more amino acid deletions or substitutions within one or more" (emphasis added) of the subregions. This statement, in the light of the contiguity of the subregions, provides direct support for the combination of subregions 2 through 10 (embodiment (a)) and 5 through 10 (embodiment (b)).

(f) On page 40, the first sentence of the third paragraph of the application as filed makes reference to "a combination of deletion and substitution". This provides direct support for embodiment (c).

(ii) Support for embodiment (d) of claim 1 (and of the claims which refer thereto) is given in particular by claim 7 as filed which refers to the deletion of amino acids Cys-6 through Cys-51.

(iii) Support for embodiment (e) of claim 1 (and of the claims which refer thereto) is given in
particular by claim 8 as filed which refers to the deletion of amino acids Cys-51 through Asp-87.

(iv) Embodiment (f) of claim 1 (and of the claims which refer thereto) corresponds to the subject-matter of the claims as maintained by the opposition division (cf. Section I supra) and is not open to discussion as it is not subject to the appeal revision not having been challenged by the respondents by means of an appeal (cf. G 9/92 OJ EPO 1994, 875).

(v) The features "having an improved fibrinolytic profile relative to native human t-PA" and "that retains both kringle regions" are found, respectively, on page 1, second paragraph, first sentence and on page 1, last paragraph, first sentence of the application as filed.

5. As regards the objections under Rule 57a EPC to the amendments, the board sees no problems as they were occasioned by a ground of opposition because the appellants, having had the main request before the opposition division refused for lack of inventive step and only the auxiliary request accepted, amended upon appeal their request in an attempt to obtain a larger protection than that offered by the latter request.

6. As regards the clarity issues under Article 84 EPC, no objections are seen by the board for the following reasons:

(a) The respondents' view point that, it not being known whether the list of modifications (a)-(f) is
exhaustive, claim 1 is unclear, is not shared by the board because the claim defines in an explicit manner, on the one hand, the modifications which characterise the claimed thrombolytic protein in comparison with human t-PA ("wherein at least one..." and "wherein (a)-(f)"), and, on the other hand, the regions which are retained ("that retains..."). Thus, the area for which protection is sought is clearly defined: any thrombolytic t-PA variant which fulfils said features falls under the scope of the claim;

(b) The feature "having an improved fibrinolytic profile relative to native human t-PA" is sufficiently clear for a person skilled in the art who is told on page 1, second paragraph of the description of the patent specification how such an improvement can manifest itself, ie as an increased affinity to fibrin, a decreased reactivity with inhibitors of t-PA, a faster rate of thrombolysis, an increased fibrinolytic activity and/or a prolonged biological half-life. These are all activities which the skilled person can unambiguously identify, routinely test and compare with that of native human t-PA. The respondents referred in particular to the subsequent sentence of the same paragraph of the description where "a more homogeneous form" is mentioned. However, in the board's judgement, this has nothing to do with the fibrinolytic profile, but is related with the preparation of the proteins in question, and introduces no elements of ambiguity.

Allocation of priority
7. The embodiments (a) to (d) of claim 1 were described for the first time in the International application upon with the patent in suit is based, which was filed on **30 January 1987**. Thus their effective date is the latter, as they are not entitled to any of the four priority dates claimed. The embodiments (e) to (f) of claim 1 were described for the first time in the fourth priority document and are thus entitled to its priority date, ie **3 July 1986**. Both the appellants and the respondents agreed with this finding.

**Novelty**

8. The novelty of the subject-matter of the main request was no longer contested by the respondents. Nor does the board have any objection in this respect.

**Sufficiency of disclosure and support by the description (Articles 83 and 84 EPC)**

9. The relevant question under Article 83 EPC is whether the description of the patent specification is sufficiently clear and complete for the skilled person who wishes to prepare the claimed products (cf. claim 1). The extent to which the subject-matter of the invention is sufficiently disclosed is closely linked with the issue of support of the claims by the description since claims may not be considered allowable if they encompass subject-matter which in the light of the disclosure provided by the description can be performed only with undue burden or application of inventive skill (cf. T 409/91 OJ EPO 1994, 653, see points 3.3 to 3.5 of the reasons).

Claimed here is a broad group of t-PA variants which
are functionally characterised by having tissue plaminogen-type activity and having an improved fibrinolytic profile relative to native human t-PA, and which are structurally characterized by a peptide sequence of human t-PA that retains both kringle regions, wherein at least one of the consensus N-linked glycosylation sites is modified to other than a consensus N-linked glycosylation site and wherein additional deletions and/or substitutions in specific subregions as indicated in (a) to (f) are made. The latter are all modifications in the N-terminal region of the t-PA molecule.

10. The respondents expressed no doubts as to the possibility of making the said t-PA variants. Nor does the board have any doubts in this respect as the description of the patent specification, although not reporting data on the actual fibrinolytic profile, provides sufficient technical details for preparing and testing the variants falling within the scope of the claim (cf. also point 6, item b) above).

11. However, the respondents maintain that making t-PA variants out of idle curiosity without providing a credible basis of their technical effect is not sufficient for the purposes of Article 83 EPC. In particular, they submit that it is not credible that improvements of any kind will result from all the types of modifications claimed because the patent specification does not give any evidence of any improvement for any such variant.

12. The respondents' objection amounts in fact to a lack of support objection, ie to the objection that what is claimed is not supported by experimental data in the
description. However, according to the rationale of T 939/92 (supra), such an objection cannot be validly raised for the sole reason that the description does not contain sufficient information which makes credible that an improvement in the fibrinolytic profile can be achieved by all the products claimed. This question may of relevance for the issue of inventive step, if the achievement of an improvement is the decisive factor for non-obviousness, not for the issue of sufficient disclosure and support by the description because there are no doubts about the possibility of preparing and testing them with undue burden or application of inventive skill (cf. point 10 supra).

13. At any rate, the board notes that, while there is evidence on file (in the form of later documents) showing that t-PA variants falling under the scope of the claim had an improved fibrinolytic profile as defined in the patent in suit (cf. documents (22), (23), (28) to (31)), no evidence was produced to show that any significant area covered by the claim is unworkable or displays a deterioration of the fibrinolytic profile. Nor was it demonstrated that the claim fails to recite any technical feature essential for the definition of claimed products (cf. eg T 409/91 supra).

14. While it is an established principle of the case law of the boards of appeal that the scope of the claims shall correspond to its technical contribution to the state of the art (cf. also T 409/91, T 939/92, supra; T 694/92 OJ EPO 1997, 408; T 128/92 of 30 November 1994), it is equally an accepted principle that an objection of lack of sufficient disclosure presupposes that there be serious doubts, substantiated by
verifiable facts. As stated eg in T 19/90 (OJ EPO 1990, 476), the mere fact that a claim is broad is not in itself a ground for considering the application as not complying with the requirement of sufficient disclosure (ibid., see point 3.3 of the reasons).

15. In sum, the board concludes that the requirements of Articles 83 and 84 EPC are met.

Inventive step (Article 56 EPC)

The background art

16. The modification of human t-PA proteins, in particular of t-PAs produced by recombinant DNA technology, was known in the art. For example, in chronological order:

- Document (18) (published in 1983) proposed in a very general manner modifications of t-PA by single or multiple amino acid substitutions, deletions, additions or replacements, including the preparation of derivatives retaining the kringle region and the serine protease region (cf. page 9, second paragraph).

- Document (14) (published in 1985) described the expression in E. coli of an unglycosylated t-PA which lacked the finger domain (ie amino acids 1 to 44) but retained fibrin affinity.

- Document (6), published on 16 April 1986, described amino acid substitutions in t-PA at one or more N-glycosylation sites by way of site-specific mutagenesis in order to prevent glycosylation (cf. passage bridging pages 30 and
The partially and non-glycosylated t-PAs produced in eukaryotic cells were stated to display a longer half-life (cf. page 3, lines 14 to 17), no actual data being provided.

Document (19), published on 8 October 1986 (thus, prior art under Article 54(2) only for the embodiments (a) to (d), cf. point 7 supra), described a fibrinolytically active variant lacking the N-terminus and the first kringle region, and indicated that it had a reduced clearance.

Document (11), which was available to the public before 3 July 1986 (cf. Section VIII supra), described inter alia t-PA variants with deletions at the N-terminus, in particular deletions of the finger domain, the epidermal growth factor domain (region 45 to 91) and/or the kringle regions. It was concluded that the fibrin-binding characteristics of t-PA were mediated by the finger domain and by the kringle 2 domain, the latter contributing most to the binding (in respect of this finding reference was made also to document (14); cf. note at the end of the discussion, ref. 23). Moreover, the document confirmed that the carbohydrate moieties of t-PA were not involved in its biological activity.

Document (5) (published on 7 January 1987; thus, prior art under Article 54(2) only for the embodiments (a) to (d), cf. point 7 supra) described fibrinolytically active t-PA variants modified in the growth factor domain (ie the amino acid region 44 to 91) by removal or deletion of
certain amino acid residues, in particular the
deletion of the region from amino acid residue 57
to amino acid residue 87, with expression taking
place eg in E. coli (no glycosylation) or in other
hosts ensuring varying degrees of glycosylation.

The closest prior art and the underlying technical problem

17. In the board's judgement, the closest prior art - among
the above citations - is represented by document (6)
because it describes one of the structural
modifications proposed by the claims at issue, namely
the modification of one or more N-glycosylation sites,
and it puts said modification in relation to an
improvement in a fibrinolytic property of the t-PA
molecule, ie the half-life. Of the other documents,
only document (19) establishes a relationship between a
structural modification and an improvement in a
property of the t-PA molecule. However, the said
structural modification involves the deletion of the
first kringle region, which is contrary to the
requirement of the claims at issue (cf. feature
"retains both kringle regions" in claim 1). The
remaining documents merely recognise that the modified
molecules retain fibrin affinity.

18. In the light of document (6), the problem to be solved
can be defined as being the provision of further t-PA
variants with an improved fibrinolytic profile, this
being defined as in the patent specification (cf.
point 6, item (b) above).

19. As a solution, the claims propose the group of t-PA
variants referred to in point 9, second paragraph
above, and methods and means for making them, as well
as compositions containing them.

20. The patent in suit, although giving examples of the preparation of t-PA variants according to the claims, provides no actual data in respect of the effects of the proposed structural changes on the fibrinolytic profile. Later evidence on file shows, however, that the rationale provided by the patent specification, ie to combine the deletion and/or substitution of one or more amino acids within specified regions at the N-terminal end (finger and/or growth factor domain) with a modification of (a) N-glycosylation site(s), proved to be successful in achieving a longer half-life (cf. eg documents (22), (23) as well as (28)-(30)). In particular, documents (22) and (23) relate to the variants of Examples 4 and 5. As already stated in point 13 above, there is no evidence on file that for any significant area of the claims the rationale provided by the patent specification produced a deterioration of the fibrinolytic profile. In view of the broad range of proposed modifications within the N-terminal region of the molecule, it can, of course, not be excluded that some potential t-PA variant(s) covered by the claims will be unsuitable or not particularly suitable. However, this possibility, which is recognised by the skilled reader, is per se not sufficient to undermine the rationale on which the claims are based because, firstly, occasional failure is part of any scientific work, and, secondly, no evidence is available showing that the claimed technical effect can definitely not be achieved within the whole range of application or that it can be achieved only with undue burden.

For these reasons, the board is satisfied that the
claims at issue provide indeed a solution to the underlying technical problem. In this respect, the board considers the rationale provided by the patent in suit on which the claims at issue are based not to be a mere intellectual exercise for designing compounds out of idle curiosity, but a plan for achieving a technical result which was devised and developed starting from a series of prior art observations (cf. introductory part of the patent specification). In the board's view, the provision of this plan constitutes the further step contributed by the patent in suit to the art for which the question has to be asked whether or not it was inventive.

21. In this respect, the essential question is what measures would have been adopted by the skilled person faced with the stated technical problem, in consideration of other relevant prior art findings and/or common general knowledge, and whether these would indeed have included further modifying the known t-PA variants described in document (6) by introducing deletions and/or substitutions of one or more amino acid residues in the specific N-terminal regions referred to in claim 1 (a) to (e) (embodiment (f) cannot be challenged, cf. point 4, item (iv) supra).

22. The respondents' answer to these questions is in essence that it was obvious for the skilled person to combine the features derivable from document (6), ie a modification of at least one N-glycosylation site, which resulted in a prolonged half-life, with the features derivable from document (19), ie deletion at the N-terminal end, which also resulted in a prolonged half-life, or from documents (5), (11) or (14), ie deletions at the N-terminal end which caused no change
in the fibrinolytic activity, or from document (18).

23. The proposed solution might prima facie seem obvious in its simple and broad outline. However, as repeatedly emphasized in the case law of the boards of appeal, in the assessment of inventive step it is important to avoid any ex-post-facto analysis which, especially in cases where the proposed solution is simple, represents a high risk.

24. It is thinkable that the skilled person, in the light of the observation that both a modification of at least one N-glycosylation site (cf. document (6)) and the deletion of the N-terminus and the first kringle region (cf. document (19)) independently resulted in a prolonged half-life, would have readily adopted the two measures in combination in designing further variant t-PAs. It is not known whether such a step would indeed have resulted in variant molecules retaining an increased half-life property. However, such variant t-PAs are outside the claims at issue, which require the presence of both kringle regions. Thus, the combination of the teaching of documents (6) and (19) would not have led the skilled person to the claimed subject-matter.

25. The question remains whether the skilled person would have introduced in modified t-PAs according to document (6) the further modifications taught by the other documents (5), (11), (14) or (18). Of them, document (18) was too general to suggest any specific changes in the direction of the claims at issue.
The majority of the modifications described in document (11), which was mainly preoccupied with establishing the impact of the deletion of one or more structural domains on fibrin-binding activity, involved also the kringle domains (thus, contrary to the requirement of the claims at issue), no particular emphasis being placed on the deletions involving only a smaller part of the N-terminal end, eg those of variant LEK1-2. Therefore, this document would not have provided any direct hints in the direction of the claims at issue.

As for the remaining documents, in the board's judgement, the finding therein that modifications, in particular amino acid deletions, at the level of either the growth factor or finger domain of t-PA molecules did not particularly affect fibrin-binding activity was not sufficient to readily encourage the skilled person to combine them with the modifications already carried out according to the teaching of document (6) and to do this in the expectation of keeping the advantage (prolonged half-life) achieved in the latter or of a further improvement in the fibrinolytic profile.

26. The board notes that later document (26), taken as an expert opinion, confirms that in 1987 there were still some uncertainties surrounding the functional significance of the various structural domains, and in particular the role played by the N-terminal finger, growth factor or kringle 1 domain of natural t-PA. In this respect, the document discusses inter alia documents (11) and (14). It is stated that it was indeed surprising and unexpected to find that removal of amino acids at the N-terminal end resulted in improved pharmacokinetic properties, in particular the prolonged half-life (cf. eg page 5, lines 24 to 29, and
This supports the boards' view that the rationale upon which the claims at issue are based, which relies upon the combination of two kinds of modifications, constituted a valid contribution to the art for which, in the light of the above considerations, the question of inventive step can be answered in the affirmative.

27. In sum, the board judges that the subject-matter of the claims at issue involves an inventive step.

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 the main request as submitted in the oral proceedings and a description to be adapted thereto.

The Registrar: The Chairperson:

U. Bultmann U. Kinkeldey