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D E C I S I O N
of 2 July 2003

Case Number: T 0351/01 - 3.3.8

Application Number: 88301190.0

Publication Number: 0278776

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Language of the proceedings: EN

Title of invention:
Methods and deoxyribonucleic acid for the preparation of tissue factor protein

Patentee:
GENENTECH, INC.

Opponent:
The Scripps Research Institute

Headword:
Tissue Factor Protein/GENENTECH

Relevant legal provisions:
EPC Art. 123(2)(3), 84, 83, 87, 88, 54, 56

Keyword:
"Main request - entitlement to priority - no"
"Main request - novelty - no"
"Auxiliary request - formal admissibility - yes"
"Auxiliary request - sufficiency of disclosure - yes"
"Auxiliary request - priority - yes"
"Auxiliary request - novelty - inventive step - yes"

Decisions cited:
G 0002/98, T 0019/90, T 0379/93, T 0923/92, T 0223/96, T 0060/89, T 0816/90, T 0207/94

Catchword:
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Case Number: T 0351/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 2 July 2003

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 29 January 2001 concerning maintenance of European patent No. 0278776 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
M. B. Günzel

Summary of Facts and Submissions

I. European patent No 0 278 776 with the title "Methods and deoxyribonucleic acid for the preparation of tissue factor protein" was granted with 26 claims based on European patent application No.88 301 190.0, claiming priority from US 13743 of 12 February 1987, from US 35409 of 7 April 1987 and from US 152698 of 5 February 1988.

Granted claims 1, 11 and 20 read as follows:

"1. A polynucleotide as defined in Figure 2, or a variant thereof, encoding a biologically active tissue factor protein or a biologically active variant or fragment of the said tissue factor protein wherein at least one amino acid has been selectively inserted, deleted or substituted."

"11. A biologically active tissue factor protein capable of being encoded by a polynucleotide as defined in claim 1 or a biologically active variant or fragment of said tissue factor protein which either lacks glycosylation, or has non-mammalian glycosylation."

"20. A nucleotide sequence encoding a biologically active tissue factor protein or variant or fragment as defined in any one of Claims 11 to 17."

Claims 2 and 3 defined further features of the polynucleotide of claim 1. Claims 4 to 8 were directed to methods for producing the tissue factor protein (TFP) encoded by the polynucleotide of claims 1 or 2. Claims 9 and 10, 12 to 19 were directed to various

biologically active TFPs encoded by a polynucleotide as defined in claim 1. Claim 21 related to an expression vector comprising a nucleotide sequence according to any one of claims 1 to 3 or 20; claims 22 to 25 respectively related to cells comprising this vector and to a method for producing TFP from these cells. Claim 26 was directed to a method for obtaining a polynucleotide encoding a biologically active TFP.

II. Two notices of opposition were filed. Opponents 1 withdrew their opposition when the case was pending before the Opposition Division. By a decision within the meaning of Article 102(3) EPC dated 29 January 2001, the Opposition Division maintained the patent on the basis of the auxiliary request then on file.

Claims 1, 9, 11, 12 and 20 of the said auxiliary request read as follows:

"1. A polynucleotide as defined in Figure 2, or a variant thereof, encoding a biologically active tissue factor protein or a biologically active variant or fragment of the said tissue factor protein *which induces coagulation* wherein at least one amino acid has been selectively inserted, deleted or substituted." (*emphasis added by the Board)*

"9. A biologically active tissue factor protein or a biologically active variant or fragment of said tissue factor protein which induces coagulation obtainable by the method of claim 4."

"11. A biologically active tissue factor protein capable of being encoded by a polynucleotide as defined in claim 1 or a biologically active variant or fragment of said tissue factor protein which induces coagulation which either lacks glycosylation, or has non-mammalian glycosylation."

"12. A biologically active tissue factor protein variant which induces coagulation capable of being encoded by a polynucleotide as defined in claim 1 wherein the transmembrane domain of native tissue factor protein is not present."

"20. A nucleotide sequence encoding a biologically active tissue factor protein or variant or fragment as defined in any one of Claims 11 to 17."

The expression "which induces coagulation" was also inserted in claims 2, 4, 6, 10, 13, 16 to 18 as a feature of the biologically active TFP, TFP variant or fragment.

III. The Appellants (Opponents) lodged an appeal against the decision of the Opposition Division, paid the appeal fee and filed a statement of grounds of appeal.

IV. Submissions in response to the appeal were filed by the Respondents (Patentees).

V. The Board sent a communication pursuant to Article 11(2) of the Rules of Procedure of the Boards of Appeal, conveying its preliminary non-binding opinion on some of the issues to be decided.

VI. Both parties answered the communication. With their letter dated 2 June 2003, the Respondents filed auxiliary requests 1 to 5 for consideration by the Board.

VII. At oral proceedings which took place on 2 July 2003, the Respondents made the auxiliary request 5 their auxiliary request 1, the other requests being renumbered accordingly. Claim 1 of said auxiliary request 5 read as follows:

"1. A polynucleotide encoding a biologically active tissue factor protein *whose sequence is given in Figure 2* or a biologically active variant or fragment of the said tissue factor protein *which induces coagulation* wherein at least one amino acid has been selectively inserted, deleted or substituted." (*emphasis added by the Board)*

The other claims remained identical to the claims of the request accepted by the Opposition Division (section II, supra).

VIII. The following documents are referred to in this decision:

(N1): Bach, R., documents in relation to the oral presentation at the 7th National Conference on Thrombosis and Hemostasis, The American Heart Association's 59th scientific sessions, November 19, 1986;

(N2): Morrissey, J. et al., abstract Nr. 1632 from the American Heart Association's 59th Scientific sessions. Circulation Supplement, Part 2, Vol. 74, No. 4, October 1986;

(N4): Fisher, K.L. et al., Thrombosis Research, Vol. 48, pages 89 to 99, 1987;

(N15): Broze, G.J. et al., The Journal of Biological Chemistry, Vol. 260, No. 20, pages 10917 to 10920, 1985;

(N16): Guha, A. et al., Proc.Natl.Acad.Sci.USA, Vol. 83, pages 299 to 302, January 1986;

(N29): Giercksky, K-E., Scand.J.Haematol., Vol.19, pages 385 to 395, 1977;

(N32): Paborsky, L.R. et al., The Journal of Biological Chemistry, Vol. 266, No. 2, pages 21911 to 21916, 1991;

(N38): EP-A-0 266 993;

(N41): Old, R.W. et al., "Principles of Gene Manipulation", N.G. Carr, J.L. Ingraham and S.C. Rittenberg Eds, Blackwell Scientific Publications, Third Edition, pages 38 to 44, 1985;

(N46): Neuenschwander, P.F. et al., The Journal of Biological Chemistry, Vol. 267, No. 20, pages 14477 to 14482, 1992;

(N47): Wildgoose et al., Blood, Vol. 80, No. 1, pages 25 to 28, 1992;

(N49): Declaration by Dr J.H. Morrissey dated 30 May 2003.

IX. The Appellants' arguments in writing and during oral proceedings can be summarized as follows:

Main request; claims accepted by the Opposition Division

Article 123(2)(3) EPC in relation to claim 12

In the application as filed, the general part of the description taught that the term "tissue factor protein" covered molecules which had coagulation activity and others which had not (pages 12 to 18). Nothing was said about the activity of a TFP deleted for the transmembrane domain (page 16, lines 11 to 18). Thus, the combination in claim 12 of the two features: "wherein the transmembrane domain...is not present" and "which induces coagulation" constituted hitherto undisclosed subject-matter. Moreover, this combination conferred to the claimed subject-matter a scope of protection different from that conferred by granted claim 12. The requirements of Article 123(2)(3) EPC were, thus, not fulfilled.

Article 84 EPC; clarity of claim 1

Claim 1 was unclear because it did not specify which assay was to be used to measure coagulating activity whereas the two assays proposed in the description, namely, the chromogenic assay and the one stage

clotting assay, could give different results. For example, the TFP variant lacking the transmembrane domain would not exhibit coagulating activity in the first assay whereas some activity would be seen in the second assay. This could be explained by the fact that Factor VIIa which was needed for coagulation to occur was not present in the chromogenic assay whereas it was present to some extent in the plasma used to measure coagulating activity by the one stage clotting assay. The relevant documents to illustrate this point were documents (N32) and (N49).

Article 83 EPC in relation to Article 84 EPC

The skilled person would be unable to carry out the assays measuring coagulating activity on the basis of the information given in the patent in suit, which was unclear and, therefore, he/she could not obtain the claimed TFPs without undue burden: for the chromogenic assay to be repeatable, it would be necessary that the molecular amounts of each of the reagents be disclosed; one could not repeat the one stage clotting assay as described since the origin of the plasma (eg from patients suffering from hemophilia A or B) was not adequately identified. In both cases, the incubation time was not mentioned, which was an essential feature of the assay (document (N46)).

Article 83 EPC; sufficiency of disclosure

– Document (N32) provided evidence that RFP deleted in the transmembrane domain had no coagulating activity when tested by the same chromogenic assay as described in the patent in suit. This

demonstrated that the subject-matter of claim 12 could not be reproduced.

– The claims encompassed a myriad of compounds, yet no teachings were made available in the specification as to which TFP regions should be kept in order to retain coagulating activity. Very few examples were shown which were not even qualitatively satisfactory since they concerned, in particular, the whole TFP or a variant deleted in the cytoplasmic domain, a region which was of no interest. The scope of the claim was not commensurate with the contribution to the art.

– The present case was alike to that dealt with in decision T 923/92 (OJ EPO 1996, 564) where a claim considered to relate to a vast catalog of tPA derivatives of unspecified structure and vaguely defined function was refused. The then competent Board decided that the examples and information given in the patent were not sufficient to allow the skilled person to perform the invention without undue burden over the whole area claimed.

Articles 87 and 88 EPC: priority rights, Article 54 EPC: novelty of claim 1

The sequence shown in Figure 2 of the priority documents I and II differed from the sequence shown in Figure 2 of the patent in suit by five nucleotides. To assess priority, it was irrelevant that these nucleotides were not in the TFP coding region because, on the one hand, the claimed polynucleotide was larger than the coding region and, on the other, in accordance

with the Enlarged Board of Appeal's opinion G 2/98 (point 9, OJ EPO 2001, 413), it was inappropriate and prejudicial to a proper exercise of priority rights to make a distinction between technical features related to the function and effect of the invention and technical features which were not.

The claimed polynucleotide did not enjoy priority rights from the filing dates of priority documents I or II. Document (N4), the scientific article disclosing the claimed invention was, thus, part of the prior art and destroyed the novelty of, in particular, the subject-matter of claim 1.

Auxiliary request 1

Article 123(3) EPC; claim 1

The scope of claim 1 was larger than that of granted claim 20 when dependent on claim 11. Indeed, in contrast to claim 1, granted claim 20 did not comprise, for example, the polynucleotide encoding full-length natural TFP since it related to a nucleotide sequence encoding unglycosylated TFP, ie to a nucleotide sequence which did not comprise the codons encoding the amino acids which were the sites where glycosylation occurred.

Articles 87 and 88 EPC; priority rights, Article 83 EPC; sufficiency of disclosure

The subject-matter of claim 1 did not enjoy priority rights from the dates of filing of priority documents I or II nor was it sufficiently disclosed for the same

reasons as given for claim 1 of the main request because the added feature " whose sequence is given in Figure 2" related to the polynucleotide and not to the tissue factor protein.

Article 54 EPC; novelty: claims 9 and 11

The subject-matter of claims 9 and 11 was not novel over the teachings of document (N2), which enabled a 100.000 fold purification of TFP and its subsequent deglycosylation. Document (N2) was enabling as it mentioned Factor VII-affinity chromatography as the key step in the purification method, the other steps being directly derivable from the teachings of documents (N15) or (N16).

It also lacked novelty under Article 54(3)(4) EPC over the teachings of document (N38). Moreover, the human TFP described in documents (N15) and (N16) fell within the scope of claim 11.

Article 56 EPC; inventive step: claim 1

There were three prior art documents which described a protein identified as TFP or portions thereof, characterized by partial amino acid sequences: (N15), (N16) and (N1). It was not disputed that the sequences shown in document (N1) had been presented by Dr Bach at the 59th scientific sessions of the 7th National Conference on Thrombosis and Hemostasis before the first priority date. Since the oral disclosure of Dr Bach represented the latest development, it would be considered by the skilled person as the most reliable teaching: it was the closest prior art.

Starting from document (N1) which disclosed 55% of the TFP protein sequence, the problem to be solved could be defined as obtaining the full length protein.

Based on the partial amino acid sequences and using common general knowledge such as that found in document (N41) or mentioned in document (N49), it would have been a matter of routine work in 1987 to clone the TFP encoding cDNA. In fact, no special difficulties were mentioned either in Example I of the patent in suit or in the corresponding scientific publication, document (N4):

– It could be seen in Example 1 that the cDNA library was prepared according to a known technique.

– It was known that tissue factor could be found in all tissues and, besides, the Respondents' choice of adipose tissue was obvious in view of the teachings of document (N29).

– The scarcity of the mRNA was no problem as millions of clones could be screened with the probe known from document (N1). Its large size was also of no consequence since libraries were commercially available at the priority date which contained cDNAs of an average length of 2000 to 3000 bases. If only part of the cDNA was obtained, one could as a matter of routine, use this part as a primer to isolate the rest.

– The situation was quite different from that encountered in case T 223/96 of 29 January 1999 relied upon by the Respondents. There, inventive step was acknowledged since there existed real cloning difficulties, in particular, only one tissue could be the source of the relevant mRNA. In the present case, no such difficulties existed, thus inventive step had to be denied.

X. The Respondents' arguments in writing and during oral proceedings can be summarized as follows:

Main request; claims accepted by the Opposition Division

Article 123(2)(3) EPC in relation to claim 12

A basis for the subject-matter of this claim could be found in the application as filed on page 12, lines 5 to 7 where it was stated that variants which demonstrated tissue factor protein activity were comprised within the scope of the claim. Amongst these variants were those lacking the transmembrane domain (page 16). In contrast, derivatives which were not coagulating were only mentioned for the first time on page 18. The requirements of Article 123(2) EPC were, thus, fulfilled.

Article 84 EPC; clarity of claim 1

Claim 1 was clear although not mentioning the assay used to measure coagulation. It was mere speculation in the Appellants' statement that the two assays described in the patent in suit would give different results. They both relied on the same biological effect and both

depended on Factor VIIa being present. In the chromogenic assay, the presence of Factor VIIa was insured by the presence of Factor VII and Factor IXa, Factor IXa being able to convert Factor VII into Factor VIIa (document (N47)). The plasma used in the one stage clotting assay could contain different amounts of Factor VIIa, yet, it did not mean that coagulation would not be seen but only that, as shown in document (N46),(Figure 2, page 14479), a little more incubation time was necessary in order to see it when the levels of Factor VIIa were low.

Article 83 EPC in relation to Article 84 EPC

In order to establish which amounts of Factor IXa and X were needed to carry out the chromogenic assays, it would suffice to establish a standard curve. Document (N38) showed that it was perfectly possible to perform the assay starting from a commercially available mixture of the two factors. The one stage clotting assay was described in document (N47) as exquisitely sensitive to trace amounts of Factor VIIa, which meant that it could be made to work irrespective of the origin of the plasma chosen to carry it out with. The average incubation time necessary for coagulation to take place was 120 seconds ie. much less than the incubation times contemplated in the patent in suit.

Article 83 EPC; sufficiency of disclosure

– Document (N32) did not provide evidence that TFP deleted in the transmembrane domain did not show coagulating activity when tested by the chromogenic assay as described in the patent in

suit because it did not make use of this assay but of an alternative assay where Factor IXa was not present, ie where Factor VIIa could not have been produced from Factor VII.

– Claim 1 was not an overly broad claim. It would be within the skilled person's ability to obtain the correct variants with a reasonable amount of trial and errors.

– The present case was alike to that dealt with in decision T 923/92 (see supra) where sufficiency of disclosure was recognized to derivatives of tPA as long as adequate information was given on how to produce human tPA and the functions to be tested were clearly indicated. In fact, the situation was even better than in this earlier case since several examples of how to produce TFP variants were provided and at least two such variants were shown to be functional in the chromogenic assay.

Articles 87 and 88 EPC; priority rights; claim 1

The formulation of claim 1 as being directed to **"a** polynucleotide as defined in Figure 2" implied that said polynucleotide needed not have the whole sequence shown in claim 2. On the contrary, the polynucleotide was that which encoded TFP ie, the coding portion of the sequence of Figure 2. This interpretation of the claim was consistent with the thrust of the disclosure. On page 2, the invention was defined as "the coding portion". In the legend to Figure 2, no emphasis was put on the non-coding part of the sequence. In claim 12

as originally filed, the invention was defined as the DNA sequence which encoded tissue factor protein.

The skilled person wanting to reproduce the invention would never attempt to obtain the DNA of Figure 2 as a whole but only the coding region. In addition, it had to be taken into account that the five differences between the sequences shown in Figure 2 of priority documents I and II and Figure 2 of the patent were irrelevant for the subject-matter of the invention. It would be going too far to apply the opinion G 2/98 (see *supra*) so strictly that irrelevant differences would jeopardize the right to priority.

Auxiliary request 1

Article 123(3) EPC; claim 1

The subject-matter of claim 1 did not go beyond that of granted claim 20 when dependent on granted claim 11. Granted claim 11 comprised, in particular, full length **unglycosylated** TFP (or full length TFP carrying non-mammalian glycosylation) as being produced in hosts incapable of glycosylation. Granted claim 20 related to a nucleotide sequence encoding the TFP of granted claim 11, which sequence was the same as that of the polynucleotide which encoded full length **natural** TFP as comprised in claim 1. Thus, granted claim 20 had the same scope as claim 1. The requirements of Article 123(3) EPC were satisfied.

Articles 87 and 88 EPC; priority rights, Article 83 EPC; sufficiency of disclosure

There was no doubt that the expression "whose sequence is given in Figure 2" in claim 1 was meant to apply to the TFP protein and not to the polynucleotide encoding it. The TFP amino acid sequence disclosed in the priority documents I and II was the same as that disclosed in Figure 2 of the patent in suit. Said documents also disclosed polynucleotides encoding said amino acid sequence. Priority rights could be acknowledged from the filing date of the first priority document.

Sufficiency of disclosure could be acknowledged for the same reasons as given in relation to the main request.

Article 54 EPC; novelty: claims 9 and 11

While reporting the purification and subsequent deglycosylation of natural TFP, document (N2) was not enabling insofar as the purification was concerned, as it only briefly mentioned one of the steps in the process. Document (N38) was also not enabling with regard to the production of human TFP by recombinant means as it merely mentioned this possibility on page 5, lines 31 to 35 without providing any further technical details. Documents (N15) and (N16) disclosed purified preparations of proteins which had partial amino acid sequences different from that of TFP and which were glycosylated. None of these documents destroyed the novelty of the subject-matter of claims 9 or 11.

Article 56 EPC; claim 1

Document (N1) was the report of an oral disclosure of partial TFP amino acid sequences which took place at the 59th Scientific Sessions of the Conference on Thrombosis and Hemostasis. It did not make the disclosed sequences available to the public in the way required by the case law. In particular, evidence from some members of the audience was missing, which would have been necessary to ascertain what had really been said.

Even if the disclosure in document (N1) was taken at its face value, there was no reasons why the person skilled in the art wanting to clone the TFP cDNA would have isolated a probe from the amino acid sequences given therein. Seeing the discrepancies between said sequences and those disclosed in documents (N15) or (N16), the skilled person would rather have chosen to re-isolate the natural protein and partially sequence it, which was a very difficult task.

Starting with the amino acid sequences shown in document (N1), the cloning of TFP cDNA involved many difficulties which could not be solved without inventive skills.

– Brain tissue and placenta were the tissues from which TFP was commonly isolated . The TFPs from both these sources were known to have different N-terminal sequences (document (N2)) and this would leave the skilled person uncertain as to which tissue was to be chosen as an mRNA source. The Respondents had shown that attempts at cloning

the cDNA from placenta mRNA would not succeed. To obtain it, they had to start from adipose tissue which, although having been identified as a source of TFP in a document dating from 1977 (document (N29)), was not an obvious source of the factor.

– The mRNA was in very low abundancy and of a high size (2350bp). Reverse transcription of the full length molecule would, thus, not be expected to occur, the average length of cDNA obtainable by the then available methods being of about 600 bp.

– This cloning was at least as difficult as the one performed in the patent on appeal under the number T 223/96 (see *supra*) where at least a partial cDNA sequence had already been disclosed.

XI. The Appellants requested that the decision under appeal be set aside and that the European patent No. 0 278 776 be revoked.

As main request, the Respondents requested that the appeal be dismissed. As auxiliary request 1, the Respondents requested that the decision under appeal be set aside and that the patent be maintained with the claims of auxiliary request 5 filed on 3 June 2003. As auxiliary requests 2 to 5, the Respondents requested that the patent be maintained with the claims of auxiliary requests 1 to 4 filed on 3 June 2003, taken in their numerical order.

Reasons for the Decision

Main request

Article 123(2)(3) EPC; claim 12

1. This claim relates, in particular, to a TFP deleted in the transmembrane domain and having coagulation activity. After defining various forms of full-length TFP (pages 10 and 11), the application as filed (page 12, line 4 onwards) discloses "derivatives of tissue factor protein that demonstrate tissue factor protein activity". Amongst these derivatives, the variant which lacks the transmembrane domain is mentioned on page 16, lines 20 to 31. "Tissue factor protein derivatives that are not coagulation inducing" are described starting from page 17, line 33 onwards. In the Board's judgment, the application as filed, thus, clearly discloses TFP deleted in the transmembrane domain as falling within the category of variants with coagulating activity.

2. The scope of the claim is narrower than that of granted claim 12 since it no longer includes TFP deleted in the transmembrane domain and **not** having coagulation activity.

3. The requirements of Article 123(2)(3) EPC are therefore fulfilled.

Article 84 EPC in relation to the expression "which induces coagulation"

4. The expression "which induces coagulation" was added as a feature characterising the tissue factor protein in each claim which related to or mentioned this protein. Yet, the claims do not specify which assay should be used to measure coagulating activity. Two methods are described in Example 9 of the patent in suit: the chromogenic assay and the one stage clotting assay.

5. The Appellants pointed out to document (N32) as evidence that the variant of claim 12 did not induce coagulation when tested by the chromogenic assay whereas, in their view, it would score positive in the one stage clotting assay. In their opinion, this implied that a reference to the method of determination was essential for a clear definition of the claimed subject-matter.

6. A careful study of document (N32) shows that the chromogenic assay used therein is carried out in the absence of Factor IXa. Yet, this factor is an efficient activator of the conversion of Factor VII in Factor VIIa which is itself indispensible for coagulation to occur. On the contrary, Factor IXa is present in the chromogenic assay according to Example 9. Therefore, the teaching of document (N32) is not adequate to prove that the chromogenic assay would provide results different from those obtained in the one stage clotting assay. In the absence of any factual evidence on file, of the existence of such a difference, the Board has to assume that "the induction of coagulation" is an activity which the skilled person can measure with

either of the methods referred to. Thus, the requirements of Article 84 EPC are considered to be fulfilled.

Article 83 EPC in relation to Article 84 EPC

7. It was argued that the coagulation assays disclosed in the patent in suit were not described in a sufficiently precise manner for the skilled person to be able to reproduce them ie. to be able to obtain the claimed TFPs. In accordance with the case law (T 19/90, OJ EPO 1990, 476), an argument for lack of sufficient disclosure may only be raised if there are serious doubts **substantiated by verifiable facts** that the claimed subject-matter is not reproducible on the basis of the information provided. No such facts are forthcoming in the present case.

8. In the Board's judgment, the amounts of Factor IXa or Factor X necessary to carry out the chromogenic assay may be determined as a matter of routine by establishing a standard curve of the level of coagulation observed for a given amount of a TFP preparation as a function of varying amounts of said factors. In this context, reference is made to document (N47) (to be taken as an expert document) which teaches that coagulation is "exquisitely sensitive to trace amounts of Factor VIIa", which teaching suggests that little amounts of Factor IXa may be needed to activate Factor VII in order to trigger coagulation.

9. With regard to the one stage coagulation assay, the objection was raised that the description failed to indicate the source of plasma to be used (from

hemophilia A or B patients). Yet, document (N47), Figure 2a shows that coagulation times do not exceed 120 seconds irrespective of the kind of plasma used. The information, thus, does not seem to be critical.

10. For these reasons and while accepting that different levels of coagulation will be obtained after different amounts of time depending on the TFP variant which is characterised, the Board is nonetheless unable to follow the Appellants' arguments as to a lack of reproducibility resulting from a lack of clarity in Example 9.

Article 83 EPC

11. Claim 12 is directed to a TFP variant lacking the transmembrane domain. The characterisation of this molecule as being capable of inducing coagulation was that which was objected to for lack of sufficient disclosure. Yet, no factual evidence was provided that the variant could not be characterised as having this property by the chromogenic assay (where Factor VII is activated in the presence of Factor IXa), nor by the one stage clotting assay (where Factor VIIa is present in the plasma). The objection is thus rejected.

12. Claim 1 indeed comprises a very high number of polynucleotides encoding TFPs with coagulating activity. In accordance with the case law (T 19/90, point 3.3, *supra*), the mere fact that a claim is broad is not in itself a ground for considering the application as not complying with the requirements of Article 83 EPC. In the present case, the starting point for making the variant sequences is the sequence of Figure 2 which is

fully disclosed. In the Board's judgment, at the priority date (1987), it would not have required from the skilled person more than routine work involving a reasonable amount of trial and errors, to obtain the claimed variants or fragments starting from said sequence. In addition, testing the biological activity of these variants is enabled by the patent in suit (see point 10, *supra*).

13. In fact, the situation is very similar to that encountered in the case T 923/92 (supra) relating to a much earlier invention (1983). The then competent Board denied sufficiency of disclosure in relation to a claim to a process for the preparation of variants or fragments of a protein of a given sequence having a vaguely and ambiguously defined "human tPA function". Yet, a claim to a process for the preparation of tPA, tPA variants or fragments was accepted once the said tPA function had been more precisely defined so as to reduce to an acceptable level the burden of testing it. In this respect, it was stated: "although... no reference to the structure of human tPA ... is given in the claims for the derivatives of human tPA, 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 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." (cf. point 29 of the reasons).

14. For the above reasons, clarity and sufficiency of disclosure are acknowledged.

Articles 87 and 88 EPC, priority rights; Article 54 EPC, novelty

15. The polynucleotide which is the subject-matter of claim 1 is characterised in structural terms ("as defined in Figure 2) as well as by its function ("encoding a biologically active tissue protein factor which induces coagulation"). The priority documents I and II disclose a polynucleotide having the same function. However, its structure differs from that of the polynucleotide of claim 1 by five bases, all found in the part of the sequence which does not relate to the function ie. outside of the coding region.

16. The requirement for claiming priority of the same invention has been treated in the Enlarged Board's opinion G 2/98 (*supra*). In this opinion, it is stated that "the concept of the same invention must be given a narrow or strict interpretation equating it with the concept of the same subject-matter ... An extensive or broad interpretation ... making a distinction between technical features which are related to the function and effect of the invention and technical features which are not, with the possible consequence that a claimed invention is considered to remain the same even though a feature is modified...is inappropriate and prejudicial to a proper exercise of priority rights."

17. Following this opinion, the Board concludes that the Respondents' arguments (Section X, *supra*) to the avail that the claimed invention was the TFP coding sequence which was the same in all the documents and that the differences observed in the non-coding portion were irrelevant, are not found convincing. Claim 1 is

directed to a polynucleotide as defined in Figure 2, ie to a polynucleotide which has the sequence from the first to the last nucleotide depicted in the Figure. This sequence like the one reported in Figure 2 of the first and second priority documents encodes a TFP. However, it is structurally different. Thus, it cannot be seen as the **same subject-matter**. For this reason, claim 1 does not enjoy priority rights from the filing dates of either of priority documents I or II.

18. Document (N4) belongs to the state of the art. It discloses in Figure 1 exactly the same polynucleotide as described in Figure 2 of the patent specification. It shows that the encoded TFP exhibits coagulation activity in the chromogenic assay (Figure 4). These teachings are novelty-destroying for the subject-matter of claim 1. The main request is refused for lack of novelty.

Auxiliary request 1

Article 123(2)(3) EPC; claim 1

19. Claim 1 is now addressed to a polynucleotide which is not defined by its own sequence but by the sequence of the TFP which it encodes ("a biologically active tissue factor protein whose sequence is given in Figure 2"). The expression "whose sequence is given in Figure 2" refers to the sequence of the protein ie to the amino acid sequence reported in Figure 2. The application as filed (Figure 2) discloses a polynucleotide which encodes a protein with identical amino acid sequence. The claim is allowable under Article 123(2) EPC.

20. The question arises whether the amendment introduced in claim 1 results in an offence against Article 123(3) EPC, ie. in an extension of the protection conferred by the granted patent. Solving this question requires that the scope of present claim 1 be compared not only with that of granted claim 1 but with the scope of protection conferred by the granted claims taken as a whole. In this context, it is noted that while granted claim 1 was directed to the polynucleotide specifically defined in Figure 2, granted claim 20 related, in particular, to a nucleotide sequence encoding a TFP as defined in, *inter alia*, granted claim 11, this latter claim relating to a TFP **capable** of being encoded by a polynucleotide as defined in claim 1, ie a polynucleotide as defined in Figure 2, which lacks glycosylation or has non-mammalian glycosylation. Regardless of the glycosylation which might depend upon the host or upon the conditions of culture, "a TFP capable of being encoded by a polynucleotide as defined in claim 1" is "a TFP whose sequence is given in Figure 2". Thus, granted claim 20 broadly covers any nucleotide sequence encoding a TFP with that amino acid sequence. Consequently, the scope of claim 1 at issue is no larger than that of claim 20 as granted.

21. The requirements of Article 123(2)(3) EPC are fulfilled.

Article 83 EPC

22. The amendment introduced in claim 1 is not of such a nature that the conclusion previously reached by the Board (point 14, supra) that sufficiency of disclosure is achieved in relation to the subject-matter of claim 1 of the main request would not apply in relation

to the subject-matter of claim 1 of this request. The requirements of Article 83 EPC are fulfilled.

Article 87 and 88 EPC; priority rights

23. Priority document I discloses a polynucleotide encoding a polypeptide having the same amino acid sequence as the polypeptide depicted in Figure 2 of the patent in suit. This polypeptide is shown to induce coagulation *in vivo* (example 5). RFP variants or fragments with coagulating activity are also disclosed on page 10 onwards as well as how to obtain them by altering the corresponding encoding polynucleotides, which polynucleotides are therefore disclosed as such and not only as forming part of the overall nucleotide sequence. Thus, claim 1 and all of the remaining claims of this request relate to the **same subject-matter** as disclosed in the first priority application and enjoy its filing date as priority date.

Article 54 EPC; novelty: claims 9 and 11

24. Documents (N15),(N16),(N2) and (N38) have been argued to be detrimental to the novelty of the subject-matter of claims 9 and 11. Documents (N15) and (N16) disclose the purification from brain tissue or placenta, of proteins defined as TFP. Because of their origin, both these proteins carry mammalian glycosylation. In contrast, the TFP of claims 9 and 11 lacks glycosylation or has non-mammalian glycosylation. Thus, the teachings of documents (N15) and (N16) do not affect novelty.

25. Document (N2) discloses the 100.000 fold purification of TFP from human placenta and brain "employing several techniques including Factor VII-affinity chromatography" as well as the removal of the N-linked carbohydrates. No further instructions than those just mentioned are given as regards the steps to be taken to achieve purification. The Appellants argued that those steps would be known to the skilled person from documents (N15) and (N16). Neither of these two documents is mentioned in document (N2). Taking them into account would mean combining their teachings with that of document (N2) which is not permissible when assessing novelty. For this reason, and in absence of detailed information in document (N2) as to the protocol to be followed to purify TFP, the Board considers that said document is not enabling ie. that it is not relevant to novelty.

26. The disclosure in document (N38) (prior art under Article 54(3)(4) EPC) of a recombinant TFP is restricted to page 5, lines 31 and 32: " Included within the scope of tissue factor protein is tissue factor from recombinant ...sources." Human tissue is mentioned as one possible source of TFP on page 5, line 24, the rest of the document being concerned with the cloning of bovine TFP cDNA. In the Board's judgement, this disclosure is not enabling with regard to obtaining recombinant human TFP.

27. For these reasons, novelty is acknowledged.

Article 56 EPC; inventive step: claim 1

28. At oral proceedings, the Respondents argued that it could not be clearly derived from document (N1) what teachings were actually presented to the audience during the oral presentation made by Dr Bach at the 59th Scientific Sessions of the American Heart Association on 19 November 1986. Indeed, no conclusive evidence is on file as to the exact extent of what was disclosed and in which way this was done. Yet, both parties agree that Dr Bach gave a presentation entitled "Tissue Factor Protein Structure and Function", where partial amino acid sequences of the N- and C-terminal ends as well as of tryptic peptides from human and bovine TFPs as disclosed in document (N1) were shown. The Board has no reason to doubt that this information was provided since it is mentioned on page 11 of the patent: "*Two oligonucleotide probes...were designed and synthesized based on the following amino acid sequences presented at the American Heart Association meeting*", whereas on page 3, it is stated*: "Amino terminal sequences of tissue factor (Bach et al., Am. Heart Assoc. (Nov.1986)...and a CNBr peptide fragment (Bach et al. supra) have been determined."* The specific amino acid sequences disclosed on pages 11 and 12 correspond to the sequences described in document (N1). In the absence of any evidence as to what else may also have been disclosed, the reasoning on inventive step will solely take into account the amino acid sequences.

29. In September 1985 and January 1986, two documents (N15) and (N16) purportedly reported the purification of TFP from human brain tissue or placenta as well as the characterisation of the N-terminal amino acid sequences.

The TFP partial amino acid sequences of document (N1) were presented in November 1986. In accordance with the case law (T 379/93 of 11 January 1996), if more than one document relate to the same technical subject-matter, one should choose as closest prior art the one which represents the latest development in the art. For this reason, the Board considers that document (N1) is the closest prior art. As already mentioned above, it is entitled "Tissue Factor Protein Structure and Biological Activity". It provides a comparison of the amino-acid sequences of the N- and C- terminal ends as well as of tryptic peptides originating from human and bovine TFPs.

30. Starting from document (N1), the objective technical problem to be solved can be defined as the provision of high quantities of human TFP.

31. The solution given in the patent in suit is to clone the TFP cDNA and express it in transformed hosts, the cloning being achieved with the help of DNA probes derived from the amino-acid sequences shown by Bach at his oral presentation.

32. At the priority date, TFP was undoubtedly a protein of great interest to the scientific community (document (N16), page 299, passage bridging the left- and right-hand columns); obtaining it in pure form was considered a difficult task (document (N15), page 10917, left-hand column); it had also long been known that recombinant means were a very convenient way to produce a protein in great quantity. Thus, attempting to clone the TFP cDNA in order to obtain TFP was not inventive in itself.

33. The question which is to be answered is whether the skilled person would have had a reasonable expectation of success to isolate the cDNA. Devising a screening probe on the basis of the teachings of document (N1) may have been an obvious task. Yet, other steps in the cloning procedure may have required inventive skills.

34. The patent in suit (page 12) reveals that placenta tissue, although being one of the tissues commonly used as starting material for the purification of TFP (document (N16)), was not a suitable source of mRNA from which to prepare a cDNA library because of faulty splicing. The Respondents, thus, had to choose a different tissue to prepare a successful cDNA library. This tissue, adipose tissue, had been described as containing TFP some ten years before the priority date (document (N29)). It is not disputed by the Appellants that the TFP mRNA was in very low abundancy. Its size turned to be very large, which, of course, implied that the recombinant clones may not contain the full length cDNA. To take this fact into account, the Respondents took the initiative of using a probe which hybridized to the internal part of the cDNA, thus going against the common practice of using a probe which hybridizes to the 5' end of the cDNA as a mean to ensure that the cloned cDNA corresponds to full length transcripts. For these reasons, the Board concludes that there were difficulties to the cloning which necessitated inventive skill to be solved.

35. The Appellants argued that at the priority date one could have used any tissues as source of TFP mRNA since all tissues produced the protein, that the scarcity of mRNA could have been compensated by probing more clones, that cDNA libraries existed comprising cDNAs of 2000 to 3000 base pairs in length and that one could "walk over the cDNA", were only partial cDNAs obtained in the first place.

36. The Board agrees that the techniques just mentioned were available but the question is not whether one had at its disposal the means to achieve the cloning but whether taking the specific case at hand, these means could reasonably be expected to succeed (cf eg T 60/89, OJ EPO 1992, 268; T 207/94, OJ EPO 1999, 273; T 816/90 of 7 September 1993). The present case is similar to that dealt with favorably in decision T 223/96 (*supra*): there, the claimed invention was the cloning of a cDNA starting from a specific tissue, the mRNA was of low abundancy and a previously cloned cDNA fragment could be used as a probe, with the additional difficulty arising in the present case from the length of the mRNA.

37. In view of the above, inventive step is acknowledged to the subject-matter of claim 1. Claims 2 to 26 which are directly or indirectly dependent on claim 1 also fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Opposition Division with the order to maintain the patent with the claims of auxiliary request 5 filed on 3 June 2003, description and Figures as maintained by the Opposition Division.

The Registrar: The Chairman:

A. Wolinski L. Galligani