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D E C I S I O N
of 29 January 1999

Case Number: T 0223/96 - 3.3.4

Application Number: 86300823.1

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Title of invention:
Vectors and methods for expression of human protein C activity

Patentee:
Eli Lilly and Company

Opponent:
(01) ZymoGenetics, Inc.
(02) Immuno Aktiengesellschaft

Headword:
Protein C/ELI LILLY

Relevant legal provisions:
EPC Art. 56, 123(3)

Keyword:
"Main Request - inventive step (no)"
"First and second auxiliary requests - extension of protection conferred (yes)"
"Third auxiliary request - inventive step (yes)"

Decisions cited:
G 0002/88, T 0150/82, T 0939/92, T 0219/83, T 0923/92,
T 0296/93, T 0412/93, T 0386/94, T 1046/96, T 0207/94

Catchword:

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Case Number: T 0223/96 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 29 January 1999

Appellant I: (Proprietor of the patent)	Eli Lilly and Company Lilly Corporate Center Indianapolis Indiana 46285 (US)
Representative:	Fisher, Adrian John Carpmaels & Ransford 43 Bloomsbury Square London WC1A 2RA (GB)
Appellant II: (Opponent 02)	Immuno Aktiengesellschaft Industriestraße 67 A-1221 Wien (AT)
Representative:	Kolb, Helga, Dr. Dipl.-Chem. Hoffmann Eitle Patent- und Rechtsanwälte Postfach 81 04 20 D-81904 München (DE)
Respondent: (Opponent 01)	ZymoGenetics, Inc. 2121 North 35th Street Seattle, Washington 98103 (US)
Representative:	Bizley, Richard Edward Hepworth, Lawrence, Bryer & Bizley Merlin House Falconry Court Baker's Lane Epping Essex CM16 5DQ (GB)

Decision under appeal: **Interlocutory decision of the Opposition Division**

of the European Patent Office posted 11 January 1996 concerning maintenance of European patent No. 0 191 606 in amended form.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
W. Moser

Summary of Facts and Submisions

I. The European patent EP-0 191 606 was granted on the basis of claims 1 to 20 for all designated States except Austria (non-AT States) and claims 1 to 31 for Austria.

Claims 1, 4 and 17 (non-AT States) read as follows:

"1. A constructed DNA compound that comprises double-stranded deoxyribonucleic acid that encodes a polypeptide with human protein C activity, wherein the coding strand is:

[specific sequence recited with R_N^1-R_M substitutions at the 5' end]."

"4. A method of producing a polypeptide with human protein C activity in a eukaryotic host cell which comprises:

A. transforming the eukaryotic host cell with a recombinant DNA vector comprising:

i) a DNA sequence that provides for autonomous replication or chromosomal integration of said vector in said host cell;

ii) a promoter and translational activating sequence functional in said host cell; and

iii) a DNA compound of Claim 1 positioned in

transcriptional and translational reading phase with said promoter and translational activating sequence, provided that when N is 1, said translational activating sequence does not encode a translational start codon; and

B. culturing the host cell transformed in step A under conditions suitable for gene expression."

"17. A composition comprising a therapeutically effective amount of a polypeptide with human protein C activity produced by the method of any of Claims 4 to 8 or 10 to 13 in admixture with a pharmaceutically acceptable carrier."

II. The appeals of the appellants I (patentees) and of the appellants II (opponents 02) lie from the interlocutory decision of the opposition division issued on 11 January 1996 whereby the said European patent, which had been opposed under the terms of Article 100(a) and (b) EPC, was maintained in amended form on the basis of the auxiliary request then on file which comprised claims 1 to 6 for non-AT States and claims 1 to 17 for AT and an amended description. Claim 1 (non-AT States) therein corresponded essentially to claim 4 as granted.

III. The opposition division decided that the product claims of the main request then on file did not meet the requirements of Article 56 EPC, but that the auxiliary request, which did not contain said claims, involved an inventive step. The latter finding was essentially based on the consideration that, although the route of finding and identifying a genomic DNA sequence encoding human protein C was obvious in the light of prior art

knowledge, it was not obvious to arrive at the specific DNA sequence referred to in the method claims of the auxiliary request, in view of the huge number of possible DNA sequences.

IV. On 29 October 1998, the board issued a communication with an outline of the issues to be discussed at oral proceedings and a provisional non-binding view on some of these issues.

V. In reply to the board's communication, on 22 December 1998 appellants I withdrew the previous requests and filed a new main request and four auxiliary requests for the non-AT States and a sole claim request for AT. They also submitted further documents and evidence in support of their case, in particular four affidavits.

VI. On 29 December 1998, the respondents (opponents 01) also made further submissions and filed new documents.

VII. Oral proceedings took place on 29 January 1999. The claim requests for the non-AT States filed on 22 December 1998 were amended as follows: in the main request former claims 6 to 10 were substituted by new claims 6 to 8; the first auxiliary request was withdrawn and the second to fourth auxiliary requests were renumbered first to third, respectively. The claim request for AT remained unchanged.

As for the **main request** for the non-AT States, independent method claim 1 therein corresponded essentially to claim 4 as granted, save for the R_N^1-R_M substitutions at the 5' end of the DNA sequence which

were now restricted to one specific sequence combination. Independent product claim 7 therein read as follows:

"A composition comprising a therapeutically effective amount of a polypeptide with human protein C activity produced by the method of any of claims 1 to 5 in admixture with a pharmaceutically acceptable carrier."

As for the **first auxiliary request** for non-AT States, claim 1 thereof read as follows:

"A method of producing a composition comprising a therapeutically effective amount of activated human protein C having a light chain with the amino acid sequence: [amino acid sequence recited]

and a heavy chain with the amino acid sequence: [amino acid sequence recited]

said method comprising

A. transforming a eukaryotic cell with a DNA vector encoding a human protein C precursor,

B. culturing the host cell transformed in step A under conditions suitable for gene expression,

C. activating *in vitro* the polypeptide expressed in step B to obtain activated human protein C, and

D. mixing the activated human protein C obtained in step C with a pharmaceutically acceptable

carrier."

As for the **second auxiliary request** for non-AT States, claim 1 thereof read as follows:

"A method of producing a composition comprising a therapeutically effective amount of activated human protein C, said method comprising

A. transforming a eukaryotic cell with a DNA vector encoding a human protein C precursor having the amino acid sequence: [amino acid sequence recited]

B. culturing the host cell transformed in step A under conditions suitable for gene expression,

C. activating *in vitro* the polypeptide expressed in step B to obtain activated human protein C, and

D. mixing the activated human protein C obtained in step C with a pharmaceutically acceptable carrier."

The **third auxiliary request** for non-AT States consisted of claims 1 to 6 identical to claims 1 to 6 of the main request for non-AT States.

The sole claim request for AT consisted of claims 1 to 17. Claim 1 was identical to claim 1 of the main request for non-AT States, and dependent claims 2 to 17 concerned specific embodiments of the method according to claim 1 of the sole claim request for AT.

VIII. The following documents were in particular discussed:

(1) Foster D. and E. W. Davie, Proc. Natl. Acad. Sci. USA, August 1984, Vol. 81, pages 4766 to 4770;

(2) Long G. L. et al, Proc. Natl. Acad. Sci. USA, September 1984, Vol. 81, pages 5653 to 5656;

(3) Foster D. et al, Proc. Natl. Acad. Sci. USA, July 1985, Vol. 82, pages 4673 to 4677;

(9) Pennica D. et al., Nature, 20 January 1983, Vol. 301, pages 214 to 221;

(12) Kiesel W., J. Clin. Invest., September 1979, Vol. 64, pages 761 to 769;

(18) Esmon C. T and Owen W. G., Proc. Natl. Acad. Sci. USA, April 1981, Vol. 78, pages 2249 to 2252;

(24) Molecular Cloning, A Laboratory Manual, T. Maniatis et al. eds., 1982, Cold Spring Harbour Laboratory, pages 213 to 229 and 310 to 344;

(42) Esmon C. T. and Esmon N. L., Seminars in Thrombosis and Hemostasis, 1984, Vol. 10, No. 2, pages 122 to 130;

(R1) Bajaj S. P. et al., Throm. Hemostasis, 1983, Vol. 50, page 349, Abstract No. 1094;

(R5) Yan B. S. C. et al, Bio/Technology, July 1990, Vol. 8, pages 655 to 659;

(R9) Gubler U. and Hoffman B. J., Gene, 1983, Vol. 25, pages 263 to 269;

(R10) Comp P. C. and Esmon C. T., J. Clin. Invest., November 1981, Vol. 68, pages 1221 to 1228;

(R11) Broekmans A. W. et al., The New England J. Med., 1983, Vol. 309, No. 6, pages 340 to 344;

(P1) Suzuki Y. et al., 1997, Gene, Vol. 200, pages 149 to 156.

The documents bearing the R or P designations were submitted during the appeal phase by the respondents or by the appellants I, respectively.

IX. Appellants I submitted that the benefit of the sequence referred to in the claims was that it provided, upon expression in a eukaryotic host, a therapeutically useful protein. This was due to the fact that, as it coded for the propeptide, it allowed gamma carboxylation of protein C to occur which was essential for the biological activity. In spite of the fact that cloning a gene was routine in 1985, the circumstances of the present case did not lead to the conclusion that the task of isolating the complete human protein C gene, starting from document (1), was easy and the expectation of success reasonable. As regards the strategies which in the view of appellants II and of the respondents would have led the skilled person in a straightforward manner to the full-length DNA sequence recited in the claims, the following had to be taken

into account:

i) Document (1) did not suggest probing a genomic library with the available cDNA. This was rather suggested with hindsight by the respondents. As a matter of fact, using the genomic route was not a simple matter. None of the prior art documents which concerned other polypeptides indicated how to readily obtain through this route a clone with the missing 5' sequence of the human protein C gene. For example, document (9), which was referred to by the respondents, used a genomic clone to probe a cDNA library which was quite a different procedure. As shown by the later publication by Dr Foster (document (3)), one had to develop his or her own special strategy. In the absence of the full cDNA sequence, the presence of exons and introns did not render the task simple.

ii) As for the route involving a cDNA library, conventional methods for the production of cDNA libraries resulted in partial-length gene fragments containing incomplete gene fragments. The authors of document (1) had screened $2x10^6$ phages and nevertheless had failed to obtain a full-length clone. The probability of finding a full-length DNA encoding human protein C was very low in consequence of the low amounts of mRNA (ie 0.02% which was below the accepted lower limit of 0.05%; cf document (24), passage bridging pages 225 - 226) and of the liability of human liver as a starting material for making a suitable

library. One could not extrapolate from one gene to another as the chances of success were linked to the technical circumstances of the case. Documents such as eg document (9) were of no assistance to the skilled person as they concerned technical situations in which mRNA was available in larger quantities and the in vitro translation of the protein was possible. No general method was available which could guarantee success. Document (R9), which was cited by the respondents as an example of a general applicable method, described the isolation of a full-length cDNA encoding bovine pre-proenkephalin, the corresponding mRNA constituting approximately 0.1% of the total RNA, from a bovine cDNA library which was less problematic. Documents published at a much later date like eg document (P1) pointed to the many difficulties in isolating "full-length" cDNAs, and by explicitly quoting eg document (R9) (cf page 155, left column) stated that cDNA libraries made by the method in question contained many incomplete cDNA copies of mRNAs. There were no obvious ways to make better libraries. Success had been achieved by the present inventors by using inter alia much higher concentrations of deoxynucleoside triphosphates than suggested by common wisdom (cf document (24), page 214).

iii) Other methods such as those based on the use of antibodies or on an incomplete cDNA probe or on a bovine probe were either too complicated or too uncertain. For example, the bovine probe approach

based on the DNA data of document (2) could not guarantee success in view of the many uncertainties about the hybridisability at the level of the 5' region where the highest degree of divergence with the human sequence was found.

Thus, the isolation of a full-length cDNA sequence encoding a polypeptide with human protein C activity could not be reasonably expected to be achieved without difficulties by the skilled person and for this reason the method and, consequently, also the pharmaceutical composition claimed involved an inventive step.

X. In their written submissions, appellants II argued that, as protein C was encoded by a single gene, the skilled person, faced with the problem of isolating a full-length cDNA, would not have expected a huge number of DNA sequences. As a matter of fact, by using the nearly full-length sequence of document (1) as a probe for screening a human gene bank the skilled person would have inevitably isolated the sequence referred to in the claims and would have readily expressed it in eukaryotic cells.

XI. The respondents, apart from formal objections raised under Article 123(2) and (3) EPC against the first and second auxiliary requests for non-AT States, essentially argued against inventive step of the composition claims of the main request for non-AT States and of the method claims of the main request and the third auxiliary request for non-AT States. In particular, as regards the latter, they maintained that the skilled person would have applied known cloning

techniques to human protein C with some considerable confidence in the light of documents (1) and (2) (cf also declarations of Dr T. Harris and Dr D. Foster on file). The skilled person had at least three ways to proceed, namely **i)** using the cDNA of document (1) as a probe for isolating the full-length sequence from a genomic clone, as suggested in document (1) itself; **ii)** using the sequence of document (1) to obtain a 5' clone as disclosed in document (9); **iii)** further screening cDNA libraries using an antibody, as done in document (1), or a human probe based on document (1) or a bovine probe based on document (2). In the prior art there were many examples of full-length cDNAs cloned from liver libraries (see list provided as document (R12)) and many papers referring to general methods for cloning cDNA (cf eg (R9)). As in the technically comparable situation of decision T 386/94 of 11 January 1986, here the expectation was that the cloning and expression of human protein C could be carried out in a fairly straightforward manner, and such indeed proved to be the case (cf late publication by Dr Foster et al., document (3)). The sequence referred to in the claims was just one out of many possible sequences which the skilled person would have isolated without any technical difficulties and nothing had been put forward to show that it was not just an arbitrary choice (cf T 939/92, OJ EPO 1996, 309).

XII. Appellants I requested that the decision under appeal be set aside and that the patent be maintained on the basis of the following documents:

- Claim requests for all designated contracting

States except AT:

a) main request: claims 1 to 5 of the set of claims filed on 22 December 1998 as main request, and claims 6 to 8 submitted during oral proceedings; or

b) first auxiliary request: claims 1 to 8 filed on 22 December 1998 as second auxiliary request; or

c) second auxiliary request: claims 1 to 8 filed on 22 December 1998 as third auxiliary request; or

d) third auxiliary request: claims 1 to 6 filed on 22 December 1998 as fourth auxiliary request; and

- claims 1 to 17 for the designated contracting State AT filed on 22 December 1998.

Appellants II and the respondents requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Late-filed documents

1. Both appellants I and the respondents filed further

documents at a late stage of the appeal procedure, which had not been available to the opposition division. Because of their obvious relevance, the board decided to allow all of them into the proceedings pursuant to Article 114(1) EPC.

The main request (non-AT States)

2. The amendments introduced in the claims at issue in comparison with the corresponding claims as granted result neither in an extension of the protection conferred nor in the creation of subject-matter which was not disclosed in the application as filed, the DNA sequence recited in claim 1 being now restricted to one of the possible embodiments originally disclosed and referred to in the claims as granted. Thus, there are no objections under Article 123(2) and (3) EPC.

3. Novelty of the claimed subject-matter is acknowledged as none of the documents on file discloses a method of producing a polypeptide with human protein C activity comprising the same operational steps as the method of claim 1, or a pharmaceutical composition comprising a polypeptide with human protein C activity.

4. The set of claims at issue comprises two independent claims, namely method claim 1 and product claim 7. The **inventive step of claim 7** is hereinafter examined.

5. Appellants I submitted that, when considering the issue of whether the subject-matter of claim 7 involves an inventive step, the closest prior art was represented by document (1) and that, as this document did not

render obvious a method of preparation of a therapeutically useful polypeptide with human protein C activity, the pharmaceutical composition of claim 7 derived its non-obviousness from the non-obviousness of the method by which its active ingredient was made. They further submitted that nothing in the prior art relative to human protein C would have suggested to the skilled person a composition comprising a therapeutically effective amount of a polypeptide expressed in eukaryotic cells, which had a different glycosylation pattern than natural human protein C (cf the later document (R5)).

Moreover, the appellants I submitted that in the case of decision T 412/93 of 21 November 1994 the then competent board had allowed a claim directed to a pharmaceutical composition comprising a polypeptide produced by a recombinant DNA method based on the fact that the said method was considered to involve an inventive step (cf point 148 of the decision). In their view, the same conclusion had to be reached in the present case which was similar.

6. The composition of claim 7 is essentially characterised in terms of the process of preparation of its active ingredient. It is well established jurisprudence that "product-by-process" claims have to be examined like conventional product claims, ie independently of the process in question. In fact, whilst a process may well be novel and inventive, the same may not be true for the product(s) thereby prepared if it (they) is (are) known or obvious in the light of the state of the art (cf eg T 150/82, OJ EPO 1984, 309 and T 219/83 OJ EPO,

1986, 211). In the present case, it is not necessarily true that, as submitted by appellants I, product claim 7 has automatically to be found non-obvious if the method of production of its effective ingredient is found to be non-obvious. The conclusion reached in case T 412/93 (supra) was based on different technical circumstances (different product(s), different prior art etc.) then in the present case. As said above, the patentability of the subject-matter of claim 7 at issue has to be assessed separately from that of the method of preparation on the basis of a comparison of its properties and structural features with those of known products of the prior art which are structurally close.

7. The prior art products which are structurally close to the claimed pharmaceutical composition are the known compositions containing active human protein C. Document (12), for example, describes such a composition, which contains protein C isolated from human plasma, and shows its anticoagulant activity in an in vitro assay. This knowledge about activated human protein C and its biological role in the control of coagulation is considered to represent the closest prior art.

8. Starting from this knowledge, the problem to be solved can be defined as the provision of a composition suitable for therapeutic use. As a solution thereto, claim 7 proposes a composition comprising a therapeutically effective amount of a polypeptide with human protein C activity produced by the method of any of claims 1 to 5 in admixture with a pharmaceutically acceptable carrier.

9. In the board's view, no contribution to inventive step can be seen per se in posing the problem of the therapeutic use of a polypeptide with human protein C activity in view of the many indications in the prior art of the known important role of protein C in controlling the coagulation pathway and of the clinical consequences of its deficiencies (cf documents (18), (42), (R1) and (R11)). Prior art document (R10) had also shown that **bovine**-activated protein C, administered intravenously to dogs, had fibrinolytic activity.

   Furthermore, no contribution to inventive step is seen in the features "a therapeutically effective amount" and "in admixture with a pharmaceutically acceptable carrier", as they are measures that a skilled person would routinely adopt when making a pharmaceutical composition.

10. It remains to be established whether the method of preparation of the effective ingredient contributes to inventive step.

   The skilled person had a priori no reasons to believe that a polypeptide with human protein C activity produced by a method other than the isolation from natural sources would not be suitable for use in a pharmaceutical composition. If a molecule displays the required biological activity, it is normally considered to be a suitable candidate for such a use, regardless of how it has been prepared, unless other reasons prevail such as eg the presence of contaminants. In 1985, in view of the developments in recombinant DNA

technology and also in view of the disclosure of document (1), the skilled person had no basis to believe that, if prepared as a product of expression of a eukaryotic cell by recombinant DNA techniques, a polypeptide with human protein C activity would not have been a suitable candidate for such a use. As a matter of fact, one of the important purposes of recombinant DNA techniques was generally considered to be producing in large amount authentic molecules which could as closely as possible mimic the effect of the natural molecules (cf eg document (9), page 214, right column, last paragraph).

11. The appellants I strongly emphasized that, being produced by recombinant DNA techniques in a eukaryotic host, the polypeptide with human protein C activity of the claimed composition had or was expected to have a different glycosylation pattern compared with the natural product (cf Table 2 in document (R5)) and thus that it was not obvious for the skilled person to use it in a pharmaceutical composition.

12. Claim 7 does not refer to a given glycosylation pattern nor is it likely that the method claimed inevitably leads always to the same specific pattern. The molecules resulting from said method will be variably glycosylated depending on the cell lines used and other technical circumstances. Whether these variable glycosylation patterns can overlap with the variable glycosylation patterns of the natural product is not known. The submission by the appellants I that they **never** overlap is unsubstantiated. Although Table 2 of document (R11) - used as an expert opinion - shows that

in three specific instances (three specific cell lines) differences in glycosylation were observed between the recombinant human protein C and the plasma-derived human protein C, there is no evidence to show that such differences are **always** found. In any case, the same table shows that these differences did not affect the anticoagulant activity, which was present at a comparable level in all samples, this being the biological activity relevant for a pharmaceutical use. For the skilled person the **primary** concern, when deciding to make a pharmaceutical preparation is the presence of biological activity, not whether a particular glycosylation pattern is present or not. As already stated (cf point 10 supra), in view of the prior art and in the absence of dissuasive information, the skilled person would have readily taken into consideration any polypeptide displaying human protein C activity, regardless of the method of production, in making a composition for pharmaceutical use.

13. For these reasons, the board considers that the subject-matter of claim 7 lacks an inventive step and, consequently, the main request of which it is part, is not allowable under Article 56 EPC.

The first and second auxiliary requests (non-AT States)

14. Claim 1 in both these requests involves a change of category from product (a composition) to method of producing a composition, which being of a restrictive character raises no issues under Article 123(3) EPC (cf eg decision G 2/88 OJ EPO 1990, 93), and a change in

how the polypeptide with human protein C activity is defined, which raises inter alia a critical issue under Article 123(3) EPC. Since - as seen below - the concerns in this respect are the same, the two requests can be treated together.

15. As regards the definition of the polypeptide with human protein C activity,

- **claim 1 of the first auxiliary request** refers to the amino acid sequence of the light and heavy chains of the protein and to a method for its preparation involving the use of a DNA vector encoding a precursor thereof (cf item A);

- **claim 1 of the second auxiliary request** refers to a DNA vector encoding a human protein C precursor having a given amino acid sequence (cf item A).

Thus, in claim 1 of both requests the method for preparing the active ingredient of the composition is no longer restricted to the use of a given, specific DNA sequence, as in the granted claims (cf claims 4 and 17), but it covers the use of **any** DNA sequence as long as the respective amino acid sequences recited in the claim are encoded.

16. The rationale given by the appellants I for such a change in wording is as follows. While it was true that claim 17 as granted conferred protection for a composition comprising a polypeptide with human protein C activity as obtained inter alia by the method of claims 4 to 8 which involved the use of a specific

DNA sequence, it was also a fact that a polypeptide with the same amino acid sequence could be made by using other DNA sequences. This was now rendered explicit by the new wording of the claims and thus there was no problem under Article 123(3) EPC because the extent of protection was the same as before.

17. The board does not agree with appellants' I view for the following reasons:

It is true that a "product-by-process" claim confers absolute protection to the product as such, ie to any product - however made - the features of which are **identical** with those of the product resulting from the process to which reference is made. The difficulty in such a situation, especially when dealing with complex molecules such as proteins, lies in defining the precise contribution of the process to the structure and properties of the product and thus in establishing the identity of **all** the features which characterise it. This is especially true when, as in the present case, both method and products thereof are defined in general functional terms. It is not appropriate to limit a biologically active protein resulting from a complex process of expression in a eukaryotic host only to its primary structure, ie to the sequence of its amino acids, and to assert that for producing it in a recombinant system the choice of the DNA sequence to be expressed makes no difference. Codon usage and codon context may, for example, influence any of the series of biological processes occurring between gene expression via mRNA to protein expression (eg susceptibility of the encoded mRNA to degradation) and thus may ultimately have an influence on one or more of the many features of the final product.

18. In the granted claims the appellants I had relied on a method using a specific DNA sequence for defining the polypeptide with human protein C activity to be included in the claimed composition. This means that they attached importance to specific codon selections and thus to specific codon contexts. Although the exact influence of such a selection upon the structure and

properties (these not being limited to the mere primary sequence of the polypeptide) cannot be defined in qualitative terms, their choice was not without significance, as it served the purpose of defining by way of implication a number of features (not only the primary amino acid sequence of the polypeptide) **which could not be otherwise defined**. Therefore, by broadening the spectrum of possible DNA sequences and, consequently, covering eg other codon choices and contexts, the appellants I have now possibly extended the scope of protection to embodiments which were not covered by the claims as granted. Whenever the granted claims are amended, it is the responsibility of the different instances of the EPO vis-à-vis third parties to ensure beyond all doubt that the extent of the protection conferred is not extended as a result of the amendments. As there are such doubts here, the board has to conclude that claim 1 of both the first and second auxiliary requests offend against Article 123(3) EPC and, consequently, these requests cannot be allowed.

Third auxiliary request (non-AT States)

19. This request consists of claims 1 to 6 identical to claims 1 to 6 of the main request for which there were no objections as to their formal admissibility and their novelty (cf points 2 and 3 supra). The issue to be discussed is now whether the claimed method involves an inventive step (Article 56 EPC).

20. The closest prior art is represented by document (1) which describes the isolation and characterisation of a

cDNA-fragment encoding human protein C. The isolated cDNA clones were not complete as they lacked the 5' end, which was expected to encode 63 amino acid in the light chain and a leader sequence (ibidem, page 4768, right-hand column). These clones permitted the prediction of the amino acid sequence starting from residue 64 in the light chain (cf Figure 2). Alignment with the corresponding bovine sequence showed about 75% conservation of amino acids, with the highest degree of divergence being found in the amino-terminal end, the gap or insertion region, and the carboxy-terminal end (ibidem, page 4767, right-hand column). Expression of the cloned sequence in a eukaryotic host was not described.

21. Having regard to this prior art, the technical problem to be solved is defined as being the isolation of a full-length sequence encoding a polypeptide with human protein C activity to be used for producing such a polypeptide in a eukaryotic host. As a solution thereto, claims 1 to 6 propose a method centred on the use of a specific DNA sequence which, as shown in the description of the patent in suit, results in the expression of measurable levels of the desired polypeptide.

22. The key question is whether the skilled person, starting from the disclosure of document (1) and other prior knowledge about protein C, would have reasonably expected to be able to complete the work described in document (1) and so achieve by applying routine experimentation the isolation of a full-length cDNA, in particular the sequence referred to in claim 1, which

could be used for expressing a polypeptide with human protein C activity in a eukaryotic host.

23. A number of decisions of the boards of appeal in this area of technology have pointed out that, in evaluating the attitude of the skilled person, one should not confuse the "hope to succeed", which is linked to his or her wish that a result be achieved (here: the isolation and expression of a full-length sequence), with the "reasonable expectation of success", which is linked to his or her ability to reasonably predict, based on the particular technical circumstances, a successful conclusion of the project within acceptable time limits (cf T 296/93 OJ EPO 1995, 627; T 923/92 OJ EPO 1996, 564). In this respect, each case has to be assessed on its own merits. In the case of decision T 386/94 (supra), which dealt with cloning and expression of chymosin DNA and its precursors, the technical situation was **to some extent** similar to that of the case at issue as a cDNA encoding 80% of the prochymosin molecule was known from the prior art and the task for the skilled person was to complete the work. The board there decided that the technical circumstances were such that the skilled person could be expected to perform the work in a fairly straightforward manner as the cloning, although requiring much work, did not pose problems as to prove that the expectation of success was ill-founded.

24. As in the case of decision T 386/94 (supra), also in the case at issue, it is evident that the skilled person, departing from the disclosure of document (1), would have readily undertaken to isolate a full-length

DNA encoding human protein C **in the hope to succeed**. He or she knew that, if such a DNA could be isolated, it could be expressed in a eukaryotic cell by conventional techniques. The question remains whether, when evaluating realistically the chances of success, he or she would have had a reasonable expectation of achieving the desired result.

25. In seeking an answer to this question, the board found the arguments put forward by the appellants I more convincing than those put forward by the the appellants II and the respondents for the reasons given hereinafter:

26. The skilled person, faced with the stated technical problem, had first to decide the strategy to follow. He or she knew that working according to the experimental plans of a particular piece of prior art relating to another gene (cf eg document (9) relating to human tissue-type plasminogen activator) could only be of limited value, because of the unique characteristics of each and every gene which make extrapolations highly speculative (cf in this respect also the conclusions reached in the case of decision T 412/93 (supra), in particular point 142 iv) of the reasons), especially when the technical circumstances (eg availability of a mRNA source, abundance of mRNA etc.) were different.

27. In the board's judgement, essentially two options were open to the skilled person: **i)** to repeat the work of document (1) in the hope to find a full-length cDNA clone; and **ii)** to use the cDNA described in document (1) for probing either a genomic or cDNA

library. In the board's view, other options such as the bovine probe approach would not have been readily taken into consideration by the skilled person as they were more complicated and less likely to succeed than those two.

28. When realistically examining the said two options, the following considerations would have undermined the expectation of success by the skilled person.

Since - differently from the case of decision T 386/94 - no particular source of mRNA for human protein C was available other than human liver where it was low in abundance, the isolation of a full-length DNA depended on it being present in the cDNA library and thus on the quality of the human liver cDNA library used in the screening step. The skilled person was aware of the difficulties in finding full-length cDNA clones. In 1985, although in a number of cases success had been achieved, these matters were largely empirical and very much linked to the more or less favourable circumstances of the case, no generally applicable method being available which could guarantee success in each and every technical situation. Indeed, the fact that the authors of document (1) had failed to obtain a full-length clone from the library they used confirmed that the chances of success were very much linked to statistically have a chance of preparing a library containing it. He or she knew that even the availability of the cDNA described in document (1) for probing such a library would not have helped if a full-length DNA was not present. As regards the quality of a human liver cDNA library, the skilled person knew that

it could not be better than the mRNA from which it was derived, and it was conditioned by the liability of human liver as a starting material, this being an element of uncertainty on which little control could be exerted.

29. As regards the genomic approach, the skilled person was aware of the fact that the non-availability of the complete cDNA sequence would have rendered the task of isolating a genomic clone and distinguishing therein between exons and introns more difficult. Here again the reference to documents concerned with different genes (eg document (9)) would not have been of help for the skilled person in view of the differences among genes. Nor can the reading of the later publication (document (3)), which reported the successful completion of the work described in document (1), be used as a demonstration that after all the introns would not have represented an insurmountable obstacle for the skilled person because this would be based on hindsight. Not having access to the complete cDNA, the skilled person knew that he or she could not readily identify introns or exons in a genomic clone.

30. In the board's judgement, the above considerations would have negatively influenced the degree of confidence of the skilled person in the possibility of successfully achieving the desired result within acceptable time limits merely by way of routine experimentation. For these reasons, the board concludes that the isolation and characterisation of the specific sequence could not be reasonably expected and, consequently, that its use in a method for expressing a

polypeptide with human protein C activity in a eukaryotic host cell involved an inventive step.

31. This finding is not at variance with the finding in case T 386/94 (supra) because, in spite of the partial similarity (cf point 23 supra), a closer examination of the technical circumstances in the present case by applying the rationale of the said decision has revealed that the skilled person would not have reasonably expected to be successful in arriving at the claimed subject-matter. Nor is the present decision at variance with the finding in case T 207/94 of 8 April 1997 where, having examined the technical situation of the case, the board denied inventive step because the skilled person would have had a reasonable expectation of achieving expression of the known ß-interferon cDNA in a host.

Claim request for AT

32. Claim 1 of this request is identical to claim 1 of the request just discussed. Claims 2 to 17 are concerned with specific embodiments of the method of claim 1. For the same reasons outlined in points 20 to 30 above inventive step is acknowledged.

Conclusions

33. Thus, the third auxiliary request for all designated contracting States except AT and the sole request for AT are allowable.

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 on the basis of the third auxiliary request for all designated contracting States except AT, and claims 1 to 17 for AT, and the description to be adapted accordingly.

The Registrar: The Chairperson:

U. Bultmann U. M. Kinkeldey