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Datasheet for the decision of 3 March 2009

Case Number: T 1099/07 - 3.3.08

Application Number: 93923220.3

Publication Number: 0672138

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Chimeric procoagulant proteins

Patentee:
Genetics Institute, LLC

Opponent:
OCTAGEN CORPORATION

Headword:
Chimeric procoagulant proteins/GENETICS INSTITUTE

Relevant legal provisions:
EPC Art. 54(3), 56, 83, 84

Relevant legal provisions (EPC 1973):
-

Keyword:
"Auxiliary request 1: novelty (no)"
"Auxiliary request 2: clarity (no)"
"Auxiliary request 3: novelty (no)"
"Auxiliary request 4: novelty (no)"
"Auxiliary request 5: sufficiency of disclosure (no)"
"New auxiliary request 5: inventive step (yes)"

Decisions cited:
G 0001/03, T 0011/89

Catchword:
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Case Number: T 1099/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 3 March 2009

Appellant: (Patent Proprietor)
Genetics Institute, LLC
87 Cambridge Park Drive
Cambridge, MA 02140 (US)

Representative:
Mannion, Sally Kim
Wyeth Laboratories
Patent & Trademarks Department
Huntercombe Lane South
Taplow, Maidenhead SL6 0PH (GB)

Respondent: (Opponent)
OCTAGEN CORPORATION
105 Bala Avenue
BALA CYNWYD PA 19004 (US)

Representative:
Fisher, Adrian John
CARPMAELS & RANSFORD
43-45 Bloomsbury Square
London WC1A 2RA (GB)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 2 May 2007 revoking European patent No. 0672138 pursuant to Article 102(1) EPC 1973.

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

I. The patentee (appellant) lodged an appeal against the decision of the opposition division dated 2 May 2007, whereby European patent 0 672 138 was revoked. The patent had been granted on European patent application No. 93 923 220.3 entitled "*Chimeric procoagulant proteins*" claiming the priority dates of 13 November 1992 and 14 September 1993, and published under the international publication number WO 94/11503.

II. The patent had been opposed by one opponent. The grounds for opposition relied on were lack of novelty (Article 100(a) EPC), lack of inventive step (Article 100(a) EPC) and insufficiency of disclosure (Article 100(b) EPC).

III. Basis for the revocation were the claims as granted which were refused under the provisions of Article 54(3) and (4) EPC 1973 for reason of lack of novelty over document D6 (see Section XI, infra).

IV. Together with its statement setting out the grounds of appeal dated 11 September 2007, the appellant filed a main request and five auxiliary requests (to be referred to hereafter as "auxiliary requests 1 to 5"). The main request corresponded exactly to the claims as granted.

V. The opponent (respondent) replied to the statement of grounds with a letter dated 22 January 2008.

VI. The board issued on 21 November 2008 a communication pursuant to Article 15(1) of the Rules of Procedure of

the Boards of Appeal in which provisional and non-binding opinions on the issues of novelty and sufficiency of disclosure were expressed.

VII. With a letter dated 27 February 2009, the respondent filed additional submissions regarding the priority date claimed for document D6.

VIII. Oral proceedings took place on 3 March 2009, at which the appellant withdrew its main request (claims as granted) and filed a new auxiliary request, to be referred to hereafter as the "new auxiliary request 5".

IX. Claim 1 of auxiliary requests 1 to 5 read:

Auxiliary request 1 (first auxiliary request filed with the statement of grounds of appeal):

"1. A nucleic acid encoding factor VIII comprising domains A1, A2, B, A3, C1 and C2, wherein said domains are selected from the group consisting of:
(a) human domains A1, B, A3, C1 and C2; and porcine domain A2; and
(b) human domains B, A3, C1 and C2; and porcine domains A1 and A2."

Auxiliary request 2 (second auxiliary request filed with the statement of grounds of appeal):

"1. A nucleic acid encoding factor VIII comprising domains A1, A2, B, A3, C1 and C2, wherein said domains are selected from the group consisting of:
(a) human domains A1, B, A3, C1 and C2; and porcine domain A2; and

(b) human domains B, A3, C1 and C2; and porcine domains A1 and A2
provided that the said nucleic acid encoding factor is not as disclosed in WO 93/20093."

Auxiliary request 3 (third auxiliary request filed with the statement of grounds of appeal):

"1. A nucleic acid encoding factor VIII comprising domains A1, A2, B, A3, C1 and C2, wherein said domains are selected from the group consisting of:
(a) human domains A1, B, A3, C1 and C2; and porcine domain A2; and
(b) human domains B, A3, C1 and C2; and porcine domains A1 and A2
provided that the porcine domain A2 is not

TAAGCACCCT AAGACGTGGG TGCACTACAT CTCTGCAGAG GAGGAGGACT
GGGACTACGC CCCCGCGGTC CCCAGCCCCA GTGACAGAAG TTATAAAAGT
CTCTACTTGA ACAGTGGTCC TCAGCGAATT GGTAGGAAAT ACAAAAAAGC
TCGATTCGTC GCTTACACGG ATGTAACATT TAAGACTCGT AAAGCTATTC
CGTATGAATC AGGAATCCTG GGACCTTTAC TTTATGGAGA AGTTGGAGAC
ACACTTTTGA TTATATTTAA GAATAAAGCG AGCCGACCAT ATAACATCTA
CCCTCATGGA ATCACTGATG TCAGCGCTTT GCACCCAGGG AGACTTCTAA
AAGGTTGGAA ACATTTGAAA GACATGCCAA TTCTGCCAGG AGAGACTTTC
AAGTATAAAT GGACAGTGAC TGTGGAAGAT GGGCCAACCA AGTCCGATCC
TCGGTGCCTG ACCCGCTACT ACTCGAGCTC CATTAATCTA GAGAAAGATC
TGGCTTCGGG ACTCATTGGC CCTCTCCTCA TCTGCTACAA AGAATCTGTA
GACCAAAGAG GAAACCAGAT GATGTCAGAC AAGAGAAACG TCATCCTGTT
TTCTGTATTC GATGAGAATC AAAGCTGGTA CCTCGCAGAG AATATTCAGC
GCTTCCTCCC CAATCCGGAT GGATTACAGC CCCAGGATCC AGAGTTCCAA
GCTTCTAACA TCATGCACAG CATCAATGGC TATGTTTTTG ATAGCTTGCA
GCTGTCGGTT TGTTTGCACG AGGTGGCATA CTGGTACATT CTAAGTGTTG
GAGCACAGAC GGACTTCCTC TCCGTCTTCT TCTCTGGCTA CACCTTCAAA
CACAAAATGG TCTATGAAGA CACACTCACC CTGTTCCCCT TCTCAGGAGA

AACGGTCTTC ATGTCAATGG AAAACCCAGG TCTCTGGGTC CTAGGGTGCC
ACAACTCAGA CTTGCGGAAC AGAGGGATGA CAGCCTTACT GAAGGTGTAT
AGTTGTGACA GGGACATTGG TGATTATTAT GACAACACTT ATGAAGATAT
TCCAGGCTTC TTGCTGAGTG GAAAGAATGT CATTGAACCC AGAAGCTTTG
CCCAGAATTC AAGACCCCCT AGTGCGAGCA

Auxiliary request 4 (fourth auxiliary request filed with the statement of grounds of appeal)

Claim 1 read exactly as claim 1 of auxiliary request 2 except that the first nucleotide (T) of the disclaimed sequence was removed.

Auxiliary request 5 (fifth auxiliary request filed with the statement of grounds of appeal)

"1. A nucleic acid encoding factor VIII, comprising human domains B, A3, C1 and C2 and porcine domains A1 and A2."

X. New auxiliary request 5 (as filed during the oral proceedings) consisted of seven claims, of which claims 1 to 5 read:

"1. A nucleic acid encoding factor VIII with amino acids corresponding to:
- human 1-335 and 373-2332; and
- porcine 138-174."

"2. The nucleic acid encoding factor VIII with amino acids corresponding to:
- human 1-335 and 741-2332; and
- porcine 138-541."

"3. A nucleic acid encoding factor VIII with amino acids corresponding to:
- human 1-699 and 741-2332; and
- porcine 501-541."

"4. A nucleic acid encoding factor VIII with amino acids corresponding to:
- human 1-335, 373-699 and 741-2332; and
- porcine 138-174 and 501-541."

"5. A viral or circular nucleic acid plasmid comprising a nucleic acid of any one of claims 1 to 4."

Claim 6 was dependent on claim 5 and directed to a particular embodiment thereof.

Claim 7 was directed to a host cell transformed or transfected with a nucleic acid of any one of claims 1 to 4 or with a plasmid of claim 5 or 6.

XI. The following documents are referred to in the present decision:

(D5) John J. Toole et al., Proc. Natl. Acad. Sci. USA, Vol. 83, August 1986, pages 5939 to 5942

(D6) WO 93/20093 (with a priority date of 7 April 1992; published on 14 October 1993)

(D8) John F. Healey et al., Blood, Vol. 88, No. 11, 1 December 1996, pages 4209 to 4214

(D9) Pete Lollar et al., J. Biol. Chem., Vol. 267, No. 33, 25 November 1992, pages 23652 to 23657

XII. The submissions made by the appellant (patentee), insofar as they are relevant to the present decision, may be summarised as follows:

Auxiliary request 1 (as filed with the statement of grounds of appeal)

Document D6 did not provide a full and unmistakable disclosure of the claimed nucleic acids. The hybrid factor obtained by substituting a porcine domain for the corresponding human domain as referred to on page 7, lines 10 and 12, was not a clear and unambiguous disclosure of the hybrid factor encoded by a nucleic acid according to claim 1. Claim 27 of document D6 referred to nucleic acids encoding for hybrid factors VIII in which a given porcine domain could be substituted for one or more human domains. In document D6 there were differing amino acid sequences for the porcine A2 domain and none of them exactly matched the full nucleic acid sequence provided as SEQ ID NO:1.

Auxiliary request 2 (as filed with the statement of grounds of appeal)

The disclaimer of claim 1 which referred to document D6 as a whole was introduced in claim 1 as a means to avoid any possible novelty objection based on that document.

Auxiliary request 3 (as filed with the statement of grounds of appeal)

Document D6 disclosed only one particular nucleic acid sequence encoding the complete A2 domain of the porcine factor VIII (see the sequence SEQ ID NO: 2). Disclaiming that particular sequence was sufficient to restore novelty of claim 1 vis-à-vis document D6.

Auxiliary request 4 (as filed with the statement of grounds of appeal)

The remark made with respect to auxiliary request 3 applied similarly as the disclaimed sequence was the same except for the first unwanted nucleotide (T) which had been removed.

Auxiliary request 5 (as filed with the statement of grounds of appeal)

Relying on the teaching of the patent and on general knowledge the skilled person could have cloned and sequenced the complete A1 domain of the porcine factor VIII without undue burden. This was obvious from the statement found in the patent reading "*Having discovered the sequence of porcine factor VIII A1/A2 domains as described above, it was now possible to construct a highly specific probe to specifically isolate the remaining sequence isolate the remaining sequence of the porcine factor VIII cDNA*" (see page 14, lines 17 to 21 in WO 94/11503). The disclosure of the porcine A1 domain and of the corresponding coding nucleic acid sequence was therefore sufficient to enable the skilled person to prepare a nucleic acid according to claim 1.

New auxiliary request 5 (as filed during the oral proceedings)

No substantial comments were made.

XIII. The submissions made by the respondent (opponent), insofar as they are relevant to the present decision, may be summarised as follows:

Auxiliary request 1 (as filed with the statement of grounds of appeal)

Claim 27 of document D6 disclosed a nucleic acid encoding a hybrid human/porcine factor VIII in which any porcine factor VIII domain, including A, A2, B, A3, C1 or C2 was substituted for the homologous factor VIII domain. Furthermore, page 7, lines 10 to 12 of the same document, and page 30, lines 27 to 35, specifically disclosed substituting a porcine domain for the corresponding human domain. From the wording of claim 27 and from that passage, the skilled person would primarily contemplate the substitution of a single domain. Furthermore, on page 30 of document D6, the advantages of such a hybrid were discussed. Therefore, not only did document D6 disclose hybrids that fell within the scope of claim 1 but it also specifically pointed to the advantages of a hybrid containing the porcine A2 domain. Thus, document D6 provided a full and unmistakable disclosure of a recombinantly produced human/porcine factor VIII molecule where the human A2 domain had been replaced by the porcine one. Claim 1 lacked novelty over this disclosure.

Auxiliary request 2 (as filed with the statement of grounds of appeal)

The disclaimer of claim 1 aiming at excluding all nucleic acid sequences encoding factor VIII that were disclosed in document D6 was too broad and unclear.

Auxiliary request 3 (as filed with the statement of grounds of appeal)

Claim 1 disclaimed sequence SEQ ID NO:1 of document D6 which encoded the porcine A2 domain as represented in the sequence SEQ ID NO:2 (except the four first N-terminal amino acids). Nevertheless, as document D6 disclosed more generally the concept of nucleic acid sequences encoding hybrid porcine/human factor VIII molecules in which the porcine A2 domain had been substituted for the human A2 domain, it embraced more than just sequence SEQ ID NO:1. Therefore, the disclaimer could not restore novelty over document D6.

Auxiliary request 4 (as filed with the statement of grounds of appeal)

The remark made with respect to auxiliary request 3 applied similarly as the disclaimed sequence differed only in that the first unwanted nucleotide (T) had been removed.

Auxiliary request 5 (as filed with the statement of grounds of appeal)

Claim 1 referred to the sequence encoding the porcine A1 domain. However, the patent disclosed neither the

entire sequence of that domain nor a nucleic acid sequence encoding the same. The sequences of the patent were only partial. The cloning and sequencing of the porcine A1 domain cDNA was reported only later in document D8 which was published in 1996. Moreover, the difficulties encountered when performing those cloning and sequencing as mentioned in the chapter bridging pages 4209 and 4210 of the document showed that the skilled person would not have been able to carry them out without undue burden at the relevant filing date of the patent.

New auxiliary request 5 (as filed during the oral proceedings)

In this request, only claim 3 was objectionable. It did not involve an inventive step in view of document D9, which was prior art in view of the fact that the first priority was invalid for the claimed subject-matter, taken in combination with document D5. The respondent argued that document D9 disclosed the concept of the preparation of recombinant hybrid human/porcine factor VIII molecules in which only a part of the porcine A2 domain had been substituted for the corresponding part of the human A2 domain, the resulting hybrid being useful for the treatment of patients in need of factor VIII. As the porcine A2 domain "501-541" (of SEQ ID NO:3 in the patent) amino acid subsequence referred to in claim 3 was disclosed in Figure 1 (see page 5940) of document D5, the skilled person aware of document D9 would have found an incentive to prepare the nucleic acid of claim 3. Preparing that nucleic acid could not anyway be inventive as the encoded hybrid human/porcine factor VIII of claim 3 had been

proved in the patent to have a weaker coagulant activity than human factor VIII (see in Table IV, on page 23 in WO 94/11503, the line for the construct $pHVIIIP_{700-740}$).

XIV. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of one of auxiliary requests 1 to 5 filed with the statement of grounds of appeal or of new auxiliary request 5 filed during the oral proceedings.

XV. The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

Auxiliary request 1 (as filed with the statement of grounds of appeal)

1. According to the embodiment (a), claim 1 of this request, which is identical to claim 1 as granted, covers a nucleic acid sequence encoding a human factor VIII with a complete domanial structure in which the porcine A2 domain has been substituted for the human A2 domain, the sequence of the nucleic acid not being limited to any particular sequence.

2. This embodiment was considered to lack novelty vis-à-vis document D6 by the opposition division. The respondent also argues that document D6 discloses the very same concept which is the basis for claim 1.

3. Document D6 is an international application from which the European patent application 93912141.4 was derived. It claims a priority date of 7 April 1992, which precedes the earliest priority date of the patent in suit. Thus, since the content of document D6 is substantially the same as that of its priority document, it belongs to the state of the art to be taken into account for the assessment of novelty of claim 1 under the provisions of Article 54(3) EPC.

4. The concept of hybrid human/porcine factor VIII molecules produced recombinantly in which a porcine domain has been substituted for the corresponding human domain is indeed disclosed in document D6 (see the last paragraph on page 30 and claim 27), the emphasis being put in the disclosure on a molecule in which the porcine A2 domain is the substituted domain (see page 47, lines 10 to 15), the substitution allowing for a better stability of the hybrid molecule compared to the human factor VIII (see the second paragraph on page 30).

5. Thus, as claim 1 in its embodiment (a) is not limited to any particular nucleic acid sequence which encodes a human factor VIII with a complete domanial structure in which the porcine A2 domain has been substituted for the human A2 domain, its novelty is affected by document D6, which discloses the same scheme of substitution.

6. There are indeed differences between the particular nucleic acid coding sequence of document D6 and that of the patent as is apparent when comparing the stretch from nucleotide 5 to nucleotide 16 of the sequence

SEQ ID NO:1 in document D6 with the stretch from nucleotide 535 to nucleotide 546 in the sequence SEQ ID NO:3 of the patent, which are different but code for the same peptide His_5-Pro_6-Lys_7-Thr_8 of the porcine A2 domain (with the numbering of sequence SEQ ID NO:2 of document D6). However, as porcine A2 domain of claim 1 is not identified by that particular sequence, the existence of a difference is immaterial and cannot contribute to render novel the nucleic acid of claim 1 over document D6.

7. The appellant argues that the porcine A2 domain as referred to in the patent differs to some extent from the polypeptide referred to as the porcine A2 domain in document D6 (see the sequence SEQ ID NO:2), with the result that the corresponding encoding nucleic acid sequences, because they code for different amino acid sequences, will necessarily differ. Again, it has to be observed here that claim 1 does not contain any form of limitation to any particular amino acid sequence which is encoded and, thus, the discussion on this point is merely academic.

8. Therefore, claim 1 lacks novelty under Article 54(3) EPC and consequently auxiliary request 1 cannot form a basis for the maintenance of the patent.

Auxiliary request 2 (as filed with the statement of grounds of appeal)

9. Claim 1 differs from claim 1 of auxiliary request 1 in that a disclaimer reading "*providing that the said nucleic acid encoding factor is not as disclosed in WO 93/20093*" (see Section IX *supra*) has been added.

10. This undisclosed disclaimer was introduced in an attempt to restore novelty by delimiting claim 1 vis-à-vis document D6 which is prior art under Article 54(3) EPC. As stated in decision G 1/03 (OJ EPO 2004, 413; see point 2.4 of the order and the third paragraph of point 3 of the Reasons), the clarity requirement of Article 84 EPC is applicable to claims containing disclaimers. As indicated e.g. in T 11/89 of 6 December 1990, claims containing a disclaimer should clearly show the technical features by which the claimed subject-matter is distinguished from the excluded matter. The publication number of the conflicting document cannot *per se* convey such technical information as it creates an unclear situation leaving the skilled person in doubt as to the actual subject-matter which is to be disclaimed.

11. Therefore, claim 1 lacks clarity under Article 84 EPC and, consequently, auxiliary request 2 cannot form a basis for the maintenance of the patent.

Auxiliary requests 3 and 4 (as filed with the statement of grounds of appeal)

12. Claim 1 of each of these requests differs from claim 1 of the main request in that a disclaimer aiming to exclude the particular nucleic acid sequence SEQ ID NO:1 of document D6 has been introduced. In auxiliary request 3 the disclaimer sequence is that of SEQ ID NO:1. In auxiliary request 4 the disclaimed sequence is that of SEQ ID NO:1 minus the thymine nucleotide (T) at position 1 which, according to the

description in document D6 (see page 48, last sentence) is "unwanted".

13. As document D6 discloses not only the particular nucleic sequence SEQ ID NO:1 which encodes amino acids 4 to 367 of the A2 domain as represented in the sequence SEQ ID NO:2 with or without the thymin nucleotide, but also the more general teaching of creating human/porcine hybrid molecules wherein, irrespective of a particular sequence, a porcine A2 domain is substituted for the corresponding human domain, the present disclaimer does not sufficiently delimit claim 1 against document D6 and, therefore, is insufficient to restore novelty.

14. Therefore, claim 1 lacks novelty Article 54(3) EPC, and, consequently, neither of auxiliary requests 3 and 4 can form a basis for the maintenance of the patent.

Auxiliary request 5 (as filed with the statement of grounds of appeal)

15. Claim 1 is directed to a nucleic acid encoding a hybrid human/porcine factor VIII, wherein domains A1 and A2 are porcine. This corresponds to embodiment (b) of claim 1 as granted.

16. The respondent objects that there is no disclosure in the patent of a complete nucleic acid sequence which encodes the porcine A1 domain and that this puts undue burden on the skilled person.

17. The only nucleic acid sequence represented in the patent in relation with the porcine A1 domain is the

sequence SEQ ID NO:3 (see pages 43 to 45 of WO 94/11503), wherein, according to the description (see page 8, lines 5 to 15 of WO 94/11503), the N-terminal moiety, encodes only part of the A1 domain, the rest of the sequence encoding the A2 domain.

18. Admittedly, the cloning and sequencing of the complete porcine A1 domain cDNA have not been reported until document D8, cited as an expert opinion, was published on 1 December 1996. This latter document shows that the porcine A1 domain referred to in the sequence SEQ ID NO:3 of the patent lacks its first 199 amino acids (starting from the N-terminal one). The corresponding nucleic acid sequence is lacking too. The deficiency in the patent is such that the board is of the view that a skilled person would have been left with the burden to find a nucleic acid sequence encoding the complete porcine A1 domain. This burden is in the view of the respondent "undue". The appellant is, of course, of the opposite view.

19. The mere statement found in the patent (see page 14, lines 17 to 21 in WO 94/11503) that "*Having discovered the sequence of porcine factor VIII A1/A2 domains as described above, it was now possible to construct a highly specific probe to specifically isolate the remaining sequence isolate the remaining sequence of the porcine factor VIII cDNA*" is only speculative and does not provide the necessary guidance to achieve such cloning and subsequent sequencing. This is confirmed by the unexpected difficulties reported by the authors of document D8 when trying to clone and sequence the complete cDNA porcine A1 domain (see the passage entitled "*Isolation of porcine fVIII cDNA clones*

containing 5' UTR sequence, signal peptide and A1 domain codons" bridging pages 4209 and 4210).

20. In the board's judgment, the subject-matter of claim 1 is not sufficiently disclosed within the meaning of Article 83 EPC because the description of one of its essential component parts is incomplete and an undue burden is placed on the skilled person wishing to reproduce it. Thus, auxiliary request 5 cannot form a basis for the maintenance of the patent.

New auxiliary request 5 (as filed during the oral proceedings)

21. The wording of the claims (1 to 7) corresponds exactly to that of claims 3, 4 and 6 to 10 as granted except that the back-reference to claim 1 in claim 4 as granted has been removed and the preamble of the claim has been amended accordingly (see present claim 2). Furthermore, the back-references in present claims 5 to 7 have been adapted. The respondent had no formal objections to this request. Also, in the board's view all amendments are formally allowable.

22. The respondent objects to claim 3 only, for reasons of lack of inventive step in view of the combination of document D9 with document D5. Referring to the last paragraph on page 23657 of document D9, the respondent argues that the document disclosed the concept of the provision of recombinant hybrid human/porcine factor VIII molecules useful for the treatment of patients in need of factor VIII, in which a part of the porcine A2 domain has been substituted for the corresponding part of the human A2 domain. Contending further that the porcine "501-541" (of SEQ ID NO:3 in

the patent) amino acid subsequence referred to in claim 3 is disclosed in Figure 1 of document D5 (see page 5940), the respondent concludes that the skilled person would have found in document D9 an incentive to prepare the nucleic acid of claim 3. The respondent is of the additional view that preparing that nucleic acid cannot be inventive anyway as the encoded hybrid human/porcine factor VIII molecule (which is $pHVIIIP_{700-740}$ on page 21 of WO 94/11503) has been proved in the patent to have a weaker coagulant activity than human factor VIII (see in Table IV, on page 23 in WO 94/11503, the line for the construct $pHVIIIP_{700-740}$).

23. Analysis of documents D5 and D9 leads to the following remarks:

23.1 Document D9 was published on 25 November 1992, i.e. at a date comprised between the two priority dates of the patent. As the earliest priority date, namely 13 November 1992, is indeed regarded as not valid in view of the fact that the claimed nucleic acid is not disclosed in the earliest priority document, document D9 becomes relevant for the assessment of inventive step.

23.2 Document D9 reports *in vitro* experiments in which the complete A2 domain of the porcine factor VIII was added to the human A1/A3-C1-C2 dimer, the reconstituted factor VIII showing an increased coagulant activity compared to human factor VIII. Only coagulant activity was measured. Treatment of patients, let alone patients with inhibitory antibodies to human factor VIII, was not included in the reported investigation. Therefore, the last paragraph of page 23657 of document D9 is to

be regarded as essentially speculative. The skilled person would not have found in document D9 any guidance which would have suggested to him/her that only a portion of the porcine A2 domain could be advantageously (in terms of coagulant activity or neutralisation by inhibitory antibodies) substituted for the corresponding portion of the human A2 domain.

23.3 Document D5 does not point to any particular portion of the porcine A2 domain. Moreover, the subsequence in the sequence of Figure 1 which corresponds to the sequence 501 to 541 of the porcine domain as referred to in claim 3 is identified as belonging to both the A2 and the B domains (see from the arginine (R) at position 15 to the arginine (R) at position 55). Therefore, the skilled person, even if looking for a portion of the porcine A2 domain, would have paid no attention at all to Figure 1 of document D5. Thus, the combination of the two documents is considered to be improbable.

24. If, for the sake of argument, document D9 is considered to represent the closest state of the art, the technical problem to be solved may be regarded as the provision of a nucleic acid sequence useful for the preparation of a recombinant hybrid human/porcine factor VIII molecule which, when activated, is an alternative to the hybrid factor VIII comprising the complete porcine A2 domain of document D9.

25. The solution proposed in claim 3 is a nucleic acid of the particular structure. As the skilled person would have found no incitation in the available relevant state of the art to prepare a nucleic acid encoding a hybrid human/porcine factor VIII molecule in which the

only sequence of porcine origin is the sequence from amino acid 501 to amino acid 541 of the sequence SEQ ID NO:3 of the patent, claim 3 is to be regarded as inventive. The results presented in Table IV of the patent (see page 23 in WO 94/11503) only confirm that such a hybrid has a significant coagulant activity, even if inferior to that of the human factor VIII. This *per se* cannot be seen as detrimental to inventive step.

26. Therefore, new auxiliary request 5 complies with the requirements of Article 56 EPC. As it also complies with the other requirements of the EPC, this request can form a basis for the maintenance of the patent.

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 auxiliary request 5 filed during the oral proceedings and a description to be adapted thereto.

The Registrar The Chairman

K. Götz L. Galligani