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Datasheet for the decision of 28 April 2008

Case Number: T 1408/06 - 3.3.08

Application Number: 96931450.9

Publication Number: 0848755

IPC: C12N 15/19

Language of the proceedings: EN

Title of invention:
VEGF-related protein

Patentee:
GENENTECH, INC.

Opponent:
The Ludwig Institute for Cancer Research
Human Genome Sciences, Inc.

Headword:
VEGF-related protein/GENENTECH

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

Relevant legal provisions (EPC 1973):
EPC Art. 54(3)

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

Decisions cited:
G 0002/93

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1408/06 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 28 April 2008

Appellant I: (Patent Proprietor)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 14 July 2006 concerning maintenance of European patent No. 0848755 in amended form.

Composition of the Board:

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

Summary of Facts and Submissions

I. The patentee (appellant I) and the two opponents (opponent 01/appellant II and opponent 02/appellant III) each lodged an appeal against the interlocutory decision of the opposition division dated 14 July 2006, whereby European patent No. 0 848 755, which had been granted on European application No. 96 931 450.9 published under the international publication number WO 97/09427 with priority from US 3491 filed on 8 September 1995, was maintained in an amended form on the basis of auxiliary request 2 filed at the oral proceedings of 25 April 2006. The main request (claims 1 to 35 filed on 23 February 2006) and auxiliary request 1 (filed during oral proceedings on 25 April 2006) had been refused for non-compliance with Rule 57a EPC 1973 and with Articles 84 and 123(2) EPC, respectively.

II. The patent had been opposed on the grounds as set forth in Articles 100(a), (b) and (c) EPC that (i) the invention was neither new (Article 54 EPC) nor inventive (Article 56 EPC), (ii) the invention was not sufficiently disclosed (Article 83 EPC) and (iii) the patent contained subject-matter which extended beyond the content of the application as filed (Article 123(2) EPC).

III. Together with its statement of grounds of appeal, appellant I filed a main request and auxiliary requests 1 to 3, all dated 24 November 2006.

IV. In its statement of grounds, appellant I complained that the opposition division committed a substantial

procedural violation at the oral proceedings held before it in contravention of Article 113(1) EPC and requested refund of the appeal fee under Rule 67 EPC 1973.

V. Both appellants II and III filed their statements of grounds.

VI. In reply to the statements of grounds of appellants II and III, appellant I filed additional submissions which were accompanied by three further auxiliary requests numbered 4 to 6, all dated 16 April 2007.

VII. Each of appellants II and III replied to appellant I's statement of grounds and filed additional written submissions.

VIII. The board issued a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal in which provisional and non-binding opinions were expressed.

IX. In reply to that communication, appellants I and II filed additional submissions. Appellant I also filed a main request and auxiliary requests 1 to 6, all dated 28 March 2008, to replace all of its previous requests.

X. Oral proceedings took place on 28 April 2008, at which appellant I also filed a new main request (claims 1 to 8) and withdrew its request for reimbursement of the appeal fee.

Claim 1 of the main request read:

"1. An isolated biologically active human vascular endothelial growth factor-related protein (VRP) which comprises residues 1 through 399, inclusive, of Figure 1 or residues -20 through 399, inclusive, of Figure 1, and which binds to and stimulates the phosphorylation of receptor tyrosine kinase Flt4."

Claims 2 and 3 were each directed to a pharmaceutical composition comprising the protein of claim 1.

Claim 4 was directed to a pharmaceutical composition comprising an isolated biologically active human VRP protein which contained at least 265 amino acids of Figure 1 and which bound to and stimulated phosphorylation of receptor tyrosine kinase Flt4, and a pharmaceutically acceptable carrier, which composition comprised a further cell growth factor other than said VRP protein.

Claim 5 was directed to an isolated nucleic acid molecule encoding the protein of claim 1 further comprising a heterologous inducible promoter operably linked to the nucleic acid molecule.

Claim 6 was directed a vector comprising the nucleic acid molecule of claim 5.

Claim 7 was directed a host cell comprising the nucleic acid molecule of claim 5.

Claim 8 was directed to a method of producing VRP protein comprising culturing the host cell of claim 7 and recovering the protein from the host cell culture.

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

(D1) WO 97/05250 (published on 13 February 1997 with four priority dates, the earliest being 1 August 1995)

(D2) USSN 08/510,133 with a filing date of 1 August 1995 (earliest priority document of D1)

(D5) WO 96/39515 (published on 12 December 1996 with an international filing date of 6 June 1996 and claiming a priority of 6 June 1995)

(D6) USSN 08/465,968 with filing date 6 June 1995 (priority document of D5)

(D10) J.-P. Borg et al., Oncogene, Vol. 10, 2 March 1995, Pages 973 to 984

(D11) K. Pajusola et al., Oncogene, Vol. 9, December 1994, Pages 3545 to 3555

(D12) A. Kaipainen et al., Proc. Natl. Acad. Sci. USA, Vol. 92, April 1995, Pages 3566 to 3570

(D14) Receipt dated 9 August 1995 issued by the American Type Culture Collection for the deposit of plasmid FLT4-L

(D15) K. Pajusola et al., Cancer Research, Vol. 52, 15 October 1992, Pages 5738 to 5743

(D16) V. Joukov et al., The EMBO Journal, Vol. 15, No. 2, 15 January 1996, Pages 290 to 298

(D27) Declaration by Dr. Mihaela Skobe dated 22 November 2006

(D28) Declaration by Dr. Stuart A. Aaronson dated 22 November 2006

(D29) Declaration by Dr. John J. Chicca dated 22 November 2006

(D40) Witness statement by Dr. Vincenzo Cerundolo dated 24 November 2006

XII. The submissions made by appellant I with respect to the main request, insofar as they are relevant to the present decision, may be summarised as follows:

Article 123(2) EPC

The passage bridging pages 13 and 14 of the description in the application as filed taught beyond any doubt that heterologous inducible promoters were appropriate to control the transcription and translation of a nucleic acid sequence encoding a VRP protein such as a protein according to claim 1. Therefore, support existed in the application as filed for claims 5 to 8.

The amendment during the examination proceedings of Figure 1 and SEQ ID NO:3 in the application by the

substitution of a reference to tyrosine (Y) for the previous references to threonine (T) at position 114 of SEQ ID NO:3 and position 94 in Figure 1 did not introduce subject-matter extending beyond the content of the application in file. It was unquestionable that an obvious error had been made as the experimentally determined codon TAT did not code for threonine (T) but for tyrosine (Y).

Article 83 EPC

There was no requirement in the EPC that each and every embodiment of a claimed invention should be exemplified. Appellant II had not presented any realistic difficulties which would have been encountered by a skilled person when preparing a nucleic acid molecule according to claim 5.

Article 54(3) EPC 1973

The inconsistency between the reference used in document D2 to designate the plasmid encoding the protein, namely pFLT-4, and that indicated in document D1, pFLT4-L a plasmid deposited with the ATCC under the accession number 97231, meant that document D2 failed to meet the requirement set out in decision G 2/93 (OJ EPO 1995, 275) that it should be possible to link the accession number of the deposited biological material unambiguously to the reference in the application as filed.

It could not be unambiguously derived from the passage on page 26, lines 5 to 12 of document D2 which plasmid had been actually deposited with the ATCC with the

designation pFLT4, as the said passage referred to a "Flt4-L plasmid vector clone" and to a "Flt4-L expression vector clone".

There was no disclosure in document D1, implicit or explicit, of a pharmaceutical composition comprising a protein according to claim 1 and another cell growth factor.

Furthermore, carrying out the process disclosed in document D5 would not inevitably provide a VEGF2 protein with the exact sequence of Figure 1 of the patent. Document D5 did not describe any procedure in sufficient detail for it to be carried out with certainty or predictability. Even if the correct hybridisation and wash conditions had been given, the hybridisation might have identified a splice variant, or a genomic or cDNA fragment. It might even have identified an allelic variant. The mere fact that no allelic variations of the protein had been identified did not in any way mean that none existed.

For a product to be considered as the inevitable result of a disclosed process, the process should be described at a level of detail far beyond the vague statements of document D5.

Article 56 EPC

The inventive step issue was argued with reference to submissions made in writing during the opposition proceedings and to the decision under appeal.

In its letter of 10 December 2004, re-submitted with its letter of 16 April 2007, appellant I had argued that the identification of the ligand to a known receptor was not routine and straightforward. At the priority date of the invention, the Flt4 tyrosine kinase receptor had been known for three years. As it was identified by the group of Alitalo and Joukov, the inventors of WO 97/05250 (document D1), it was presumably known to them for longer. Three years was a long time in the fast-moving area of molecular biology, and the lengthy wait between the identification of the receptor and the identification of its ligand suggested that finding the ligand was not obvious.

XIII. The submissions made by appellant II with respect to the request in issue, insofar as they are relevant to the present decision, may be summarised as follows:

Article 123(2) EPC

The recital of "*a heterologous inducible promoter*" in claim 5 was added subject-matter. There was no specific disclosure in the application as filed of an isolated nucleic acid encoding the protein of claim 1 operably linked to a heterologous inducible promoter. The paragraph bridging pages 13 and 14 included only a discussion of certain promoter characteristics but it did not disclose a nucleic acid sequence that encoded a protein of the nature defined in claim 1 operably linked to a promoter that was both heterologous and inducible. The objection extended to claims 6 to 8, the subject-matter of which was defined with a back-reference to claim 5.

The amendment during the examination proceedings of Figure 1 and SEQ ID NO:3 in the application by the substitution of a reference to tyrosine (Y) for the previous references to threonine (T) at position 114 of SEQ ID NO:3 and position 94 in Figure 1 had also introduced subject-matter which extended beyond the content of the application as filed.

Article 83 EPC

A nucleic acid molecule according to claim 5 was not exemplified in the patent. This failure resulted in an undue burden for a skilled person willing to construct such a molecule. The objection extended also to claims 6 to 8.

Article 54(3) EPC 1973

Document D1, for which document D2 provided priority, formed part of the state of the art under Article 54(3) EPC 1973.

Document D2 disclosed a human protein that was capable of binding to and stimulating the phosphorylation of Flt4. The 350 amino acid sequence of that protein was shown in SEQ ID NO:33. A clone was also disclosed which was said to contain a cDNA sequence including an open reading frame encoding the 350 amino acid sequence. That clone was shown in SEQ ID NO:32 and its preparation was described in Example 11. That example also described experiments showing that the protein produced by cells transfected with this clone was capable of binding to and stimulating the phosphorylation of Flt4. Immediately after the

description of these experiments, it was stated that a plasmid "*pFLT4 [had] been deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852 as accession number -----.*" (see page 26, lines 10 to 12).

The amino acid sequence set out in SEQ ID NO:33 of document D1 included 69 N-terminal amino acids that were not shown in SEQ ID NO:33 of document D2. Otherwise, these two amino acid sequences were identical.

A plasmid vector clone "Plasmid pFLT4-L" which was deposited under the Budapest Treaty on 24 July 1995 with the American Type Culture Collection (ATCC) under accession number 97231 (see document D14), was described in document D1 as containing the human cDNA sequence which encoded the 419 amino acid sequence set out in SEQ ID NO:33 of document D1. The cDNA sequence was set out in SEQ ID NO:32 of the same document.

On behalf of appellant II LGC Promochem was requested to supply a sample of the plasmid "pFLT4" identified in document D2 (see the witness statement By Dr. Cerundolo; document D40). The only information provided to LGC Promochem was (i) the reference given to this plasmid in document D2, namely "pFLT4", (ii) the fact that document D2 stated that this plasmid had been deposited with the ATCC, and (iii) the identities of the inventors/applicants named in document D2, Kari Alitalo and Vladimir Joukov. In response, LGG Promochem advised that they could supply the requested plasmid and that its ATCC accession number was 97231 which was the

accession number given in document D1 for the "plasmid pFLT4-L".

Therefore, the information provided in document D2 was sufficient to identify the plasmid unambiguously as the plasmid deposited with the ATCC under accession number 97231. Following the reasoning set out in decision G 2/93 (see *supra*), this latter deposited plasmid, therefore, formed part of the disclosure in document D2. Moreover, since it was precisely this plasmid that was referred to in document D1, it also followed that the reference to this plasmid in document D1 was entitled to the priority of document D2.

Although it was suggested in document D2 that the cDNA contained within this plasmid encoded a protein with the shorter sequence shown in SEQ ID NO:33 of document D2, that cDNA did in fact encode the entire 419 amino acid sequence shown in SEQ ID NO:33 of document D1, including the 69 N-terminal amino acid residues that were not shown in the document D2 sequence.

Therefore, the invention disclosed in document D2 was the same as the invention described in document D1. Thus, document D1 was therefore entitled to its priority date and as such was part of the state of the art under Article 54(3) EPC 1973.

Article 56 EPC

Documents D10, D11, D12 and D15 all disclosed the Flt4 receptor and included a great deal of information about its properties, including the fact that none of the VEGF ligands that were known when these documents were

published had the capacity to bind to and activate this receptor. At the time these documents were published, the person skilled in the art knew that a tyrosine kinase receptor, such as Flt4, would have at least one associated ligand which was capable of binding to or activating it.

Therefore, it would have been entirely obvious for a person skilled in the art, who had read any one of documents D10, D11, D12 and D15 soon after they had been published and before the priority date claimed for the patent, to try to find a ligand or ligands for the Flt4 receptor. This indeed was precisely what several teams of investigators did. What was more, as witnessed by the publication of documents such as D1, D5 and D16, and the patent itself, all of them succeeded in their endeavours by identifying the very same ligand, that now known as VEGF-C (the human VRP protein of the patent), within a short period of time.

Accordingly, not only was it obvious to search for the Flt4 ligand in the light of the information disclosed in documents D10, D11, D12 and D15, but it was also obvious, on the basis of this information and the application of conventional techniques, to arrive at that protein, i.e. the 419 amino acid protein (consisting of residues -20 through 399 of Figure 1 in the patent). Once the skilled person had found human VRP/VEGF-C, he/she would have quickly realised that its first 20 N-terminal amino acids constituted a signal sequence. In so doing, he/she would have identified a polypeptide consisting of residues 1 through 399 of Figure 1 in the patent that was also claimed in claim 1.

In the light of the knowledge set out in documents D10, D11, D12 and D15, it would have been entirely obvious to employ the Flt4 ligand for pharmaceutical purposes.

Nucleic acid molecules, vectors, host cells and methods of the nature as recited in claims 6 to 8 would have been developed, as a matter of course, by a person skilled in the art working from documents D10, D11, d12 and D15.

XIV. The submissions made by appellant III with respect to the request in issue, insofar as they are relevant to the present decision, may be summarised as follows:

Article 54(3) EPC 1973

Document D5 which was part of the state of the art under Article 54(3) EPC 1973 and the patent had contributed to the art in a very similar way in disclosing the same protein which was a ligand for the Flt4 tyrosine kinase receptor.

The declaration by Dr. John J. Chicca (document D29) indicated that it was reasonable to assume that the two amino acid differences in the sequences of the Flt4 ligands as represented in Figure 1 of document D5 (see positions 3 and 414) (with a leucine and a lysine at positions 3 and 414, respectively) and in Figure 1 of the patent (see positions -18 and 394), with a serine and a glutamine in document D5 instead of a leucine and a lysine in the patent, were due to sequencing errors.

As it was established that no validated naturally-occurring allelic variants had been reported

that would cause a change in the amino acid sequence of the Flt4 ligand (see the declarations by Dr. Mihaela Skobe and by Dr. Stuart A. Aaronson; documents D27 and D28, respectively), there could be no doubt that a skilled person using the cDNA clone referred to in document D5 would have been in a position to reobtain the Flt4 tyrosine kinase receptor ligand as represented in Figure 1 of the patent in issue, which ligand was implicitly disclosed in document D5. Thus, the main request as a whole was not new over document D5.

No further objections were raised against the patentability of the main request.

XV. Appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed during the oral proceedings.

XVI. Appellants II and III (opponents 01 and 02) requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Main request

Article 123(2) EPC

1. Appellant II has objected to claims 5 to 8 for the presence of added matter, the objection being associated with the reference to a heterologous and inducible promoter in claim 5.

2. Promoters are discussed in a dedicated subsection of the description, namely subsection (iv) (see pages 13 and 14 of WO 97/09427 which represents the published counterpart of the application as filed), which is part of Section B (see pages 11 to 16), explaining, in general and not within the context of a particular example, how to choose the various components of the replicable vectors into which the nucleic acid encoding native or variant VRP protein is to be inserted into a replicable vector for further cloning or for expression (see page 11, lines 21 to 22). This is a clear indication that any information relating to the promoters contained in subsection (iv) is intended to be taken into account for the preparation of any isolated nucleic acid molecule encoding the protein VRP according to claim 1. As indicated in the passage bridging pages 13 and 14 inducible promoters which are heterologous, as opposed to the native VRP promoter (as found in human cells), are appropriate.

3. Thus, support exists in the application as filed for the feature relating to the promoter contained in claim 5. This leads to the conclusion that claim 5 as well as claims 6 to 8, the subject-matter of which is defined with a direct or indirect back-reference to claim 5, do not contain subject-matter which extends beyond the content of the application as filed.

4. Appellant II has also objected to the correction made under Rule 88 EPC 1973 during the examination proceedings by which Figure 1 and SEQ ID NO:3 were amended by the substitution of a reference to tyrosine (Y) for the previous references to threonine (T) at

position 114 of SEQ ID NO:3 and position 94 in Figure 1, respectively.

5. A careful reading of the description indicates that not the amino acid sequence of the VRP protein but the acid nucleic sequence encoding it was experimentally determined. That acid nucleic sequence is represented in Figure 1. The amino acid sequence was determined by a mental operation consisting in deducing it from the nucleic acid sequence using the genetic code and attributing to each 3-nucleotide codon the corresponding amino acid residue. Whereas the sequence analysis of the cDNA tested and represented in Figure 1 had revealed the presence of a codon TAT from position 711 to position 713 (see Figure 1B), which codon corresponds to tyrosine, in the application as filed in the corresponding position of the amino acid sequence the presence of a threonine is indicated (see position 94 in Figure 1B and position 114 in SEQ ID NO:3).

6. A skilled person presented with the nucleic acid sequence of Figure 1 would have realised that, as TAT can only code for tyrosine, a mistake had been made and would have immediately found it evident that nothing else would have been intended than what was offered as the correction by replacing the threonine (noted "T" in Figure 1B and "Thr" in SEQ ID NO:3) by a tyrosine (noted "Y" in Figure 1B and "Tyr" in SEQ ID NO:3). Such a correction which was allowable under Rule 88 EPC 1973 does not offend against Article 123(2) EPC.

7. The board is satisfied that amendments contained in the main request other than those objected to by appellant II are allowable under Article 123(2) EPC.

Article 83 EPC

8. It has been argued by appellant II that the preparation of a nucleic acid molecule according to claim 5 has not been exemplified in the description and, therefore, an undue burden was placed on the skilled person when carrying out the invention.

9. The objection has not been substantiated by any verifiable facts. Moreover, notwithstanding the fact that there is no obligation in the EPC to describe each and every embodiment using one or more examples, in the board's view choosing a promoter, whether inducible or not, heterologous or not, and operably linking it to a nucleic acid molecule encoding a protein was at the relevant filing date a pure matter of routine for the skilled person.

10. Therefore, the invention to which claim 5 is directed is considered to be disclosed in the application as filed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The same conclusion applies to the inventions to which claims 6 to 8 are directed as their subject-matter is defined with a direct or indirect back-reference to claim 5.

Article 54(3) EPC 1973

11. Lack of novelty has been objected to by appellant II with respect to claims 1 to 4 in view of document D1 and by appellant III with respect to the whole set of claims in view of document D5.

Novelty over document D1

12. Document D1 is an International application published on 13 February 1997 under the PCT with the international publication number WO 97/05250. It claims the priority of four previous patent applications, the earliest of which, US 08/510,133 (referred to as document D2 in the present proceedings) was filed on 1 August 1995. It has entered the regional phase before the EPO. The same Contracting States, i.e. AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT and SE have been designated in both the resulting European application (EP 96925768.2) and the patent in issue. Therefore, WO 97/05250 (document D1) is a Euro-PCT application which is to be considered as comprised in the state of the art under Article 54(3) EPC 1973, when assessing whether the subject-matter of claims 1 to 4 of the main request is novel, provided that it actually enjoys the priority of US 08/510,133 (document D2).

Claims 1 to 3

13. Document D1 indeed describes a vascular endothelial growth factor-related protein according to claim 1 of the request in issue as well as a pharmaceutical composition comprising the same according to claim 2 (see respectively (i) claim 16 when dependent on claim 7 - account being taken of the fact that SEQ ID NO:33 of document D1 is a 419 amino acid protein exactly corresponding to the protein of Figure 1 in the patent and (ii) claim 31 when dependent on claim 16).

14. The question to be answered is whether the same protein and pharmaceutical composition as described in document D1 are also described in its first priority document D2.

14.1 Document D2 does not explicitly describe the 419 amino acid protein of document D1 but only a 350 amino acid protein which corresponds to a portion thereof starting at amino acid residue 70 (Met) and ending at amino acid residue 419 (Ser) as represented in SEQ ID NO:33 of document D1.

14.2 However, appellant II argues that document D2 implicitly describes the 419 amino acid protein of document D1, for the reason that, upon expression of the cDNA contained in the plasmid with the trivial designation pFLT4 as referred to in Example 11 (see page 26) of document D2, the 419 amino acid residue protein would have been obtained.

14.3 This latter argumentation is not supported by any experimental evidence. In reality, the plasmid which LGC Promochem, the exclusive European distributor for ATCC cultures, offered to appellant II, is a plasmid having a different trivial designation, namely **pFLT4-L** (see the witness statement by Dr. Vincenzo Cerundolo, document D40). The only indication in document D2 (see page 26, lines 10 to 12) that plasmid **pFLT4** had been deposited with the American Type Culture Collection (ATCC) with no accession number being given, was insufficient to permit it to be ordered by LGC Promochem from that international deposit authority. Moreover, appellant II has not submitted any official document issued from the USPTO indicating which accession number the deposited pFLT4 biological

material as referred to in document D2 had been allocated by the ATCC. Thus, there is no evidence on file that the accession number was ATCC 97231 (notwithstanding the fact that, according to the receipt issued by the deposit authority (see document D14), that accession number has been allocated to a plasmid having a different designation, namely **FLT4-L**) and that the terms **pFLT4** and **pFLT4-L** were intended by the applicants and inventors of documents D1 and D2 to be used interchangeably to designate the very same plasmid.

14.4 In its statement of grounds of appeal, appellant II has relied on the passage in point 11 of the Reasons of decision G 2/93 (see *supra*) which reads "*If the file number (accession number) of the culture deposit given by the depositary institution is not already indicated in the application as filed, the microorganism must be identified in such a way that the later submitted file number (accession number) can be linked back without ambiguity. This can normally be done by indicating the identification reference given by the depositor to the micro-organism within the meaning of Rule 6.1(iv) of the Budapest Treaty or of Point 12(a)(iv) of the 'Model Agreement' (published in OJ EPO 1982, 454, 457) as well as the name of the depositary institution*". It is clear that the situation referred to in that passage is not the situation of WO 97/05250 (document D1) and its priority document (document D2), as the failure to indicate the accession number occurred not in the European application (see document D1, page 49, lines 21 to 24) but in its priority document (see document D2, page 26, lines 10 to 12). Therefore, appellant II's position is not tenable.

14.5 In view of the remarks made at points 14.1 to 14.4 (see *supra*), it has to be concluded that document D1 does not enjoy its priority date as regards the disclosure of the 419 amino acid protein. Thus, document D1 is not part of the state of the art for the novelty assessment of claim 1 and also of claims 2 and 3 which are each directed to a pharmaceutical composition comprising the protein of claim 1.

Claim 4

15. A pharmaceutical composition according to claim 4, i.e. comprising a vascular endothelial growth factor-related protein which contains at least 265 amino acids of SEQ ID NO:33 of document D1, a pharmaceutically acceptable carrier **and** a further cell growth factor is not referred to in document D1. Indeed, the only pharmaceutical composition of document D1 is a composition comprising a polypeptide which is capable of binding to the Flt4 receptor tyrosine kinase (see claim 31 and page 15, lines 20 to 24). Therefore, claim 4 cannot be objected to for lack of novelty over document D1.

Novelty over document D5

16. Document D5 is an International application published under the PCT under the international publication number WO 96/39515 on 12 December 1996. It claims the priority of a previous patent application, namely US 08/465,968 (referred to as document D6 in the present proceedings) filed on 6 June 1995. It has entered the regional phase before the EPO. The same

Contracting States, i.e. AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT and SE, have been designated in both the resulting European application (EP 96918130.4) and the patent in issue. Therefore, WO 96/39515 is a Euro-PCT application which is to be considered as comprised in the state of the art under Article 54(3) EPC 1973 when assessing whether the subject-matter of claims 1 to 8 of the main request is new, provided that it actually enjoys the priority of US 08/465,868 (document D6). In the circumstances, the board is satisfied that the validity of the priority right has not been challenged by appellant I.

Claims 1 to 3 and 5 to 8

17. A protein according to claim 1 as such is not disclosed in document D5 as the latter describes a 419 amino acid protein (referred to therein as VEGF2) which differs from the 419 amino acid protein of the patent at positions -18 and 394 (according to the numbering used in Figure 1 of document D5), where, respectively, a serine residue replaces a leucine residue and a glutamine residue replaces a lysine residue.

18. Appellant III argues that in reality the two deviations in the amino acid sequence of the protein of document D5 compared to that of the patent had resulted from sequencing errors (see the Declaration by Dr. John J. Chicca; document D29) and that upon expression of the cDNA contained in the clone as referred to in document D5, the skilled person would inevitably have arrived at the 419 amino acid protein of the patent. In an attempt to reinforce its position, appellant III has submitted a Declaration by Dr. Mihaela Skobe (see document D27)

and a Declaration by Dr. Stuart A. Aaronson (see document D28) in each of which the belief was expressed that there were no reports of validated, naturally-occurring allelic variants that would result in an amino acid sequence alteration of the VEGF-C/VRP protein.

19. It is accepted jurisprudence that novelty assessment cannot be based just on assumptions as made by appellant III (see documents D27 to D29). Firstly, in the present case, the skilled person should have been provided at the priority date as claimed for document D5 with a sample of the described clone. However, appellant III has acknowledged in its statement of grounds (see Section 2.2.1 on page 6) that document D5 discloses the wrong ATCC accession number for the deposited clone, stating that it should have actually referred to ATCC deposit No. 97149 of 12 May 1995 instead of ATCC deposit number 97161 of 24 May 1995 (as referred to on page 7, fourth full paragraph in document D5). As appellant III has not provided any evidence that the skilled person would have known at the priority date of WO 96/39515 (document D5) that the clone to be tested was the one with the ATCC accession number 97149 (in this respect, it is noted that in the priority document (US 08/465,968 which is document D6), the ATCC deposit accession number has been omitted (see page 7, fourth paragraph)), appellant III's argument is not tenable.

20. Therefore, the board concludes that a protein according to claim 1 is not disclosed in document D5. Thus, the subject-matter of claim 1 is novel over that document. The same conclusion also applies to the subject-matter

of claims 2, 3 and 5 to 8 as it is defined with a direct or indirect back-reference to claim 1.

Claim 4

21. Although claim 4 is directed to a pharmaceutical composition which comprises a protein having at least 265 amino acids of the 419 amino acid protein of Figure 1 of the patent, i.e. possibly a protein disclosed in document D5, that composition also contains both a pharmaceutically acceptable carrier **and** a further cell growth factor other than that protein. Such a pharmaceutical composition is not disclosed in document D5 which refers to pharmaceutical compositions comprising the VEGF2 polypeptide and a pharmaceutically acceptable carrier or excipient, it being furthermore specified without any detail that such pharmaceutical compositions may be employed in conjunction with other therapeutic compounds (see page 26, third and fourth full paragraphs).

22. Therefore, the board concludes that a pharmaceutical composition according to claim 4 is not disclosed in document D5. Thus, the subject-matter of claim 4 is novel over that document.

23. In view of the conclusions reached at points 14.5, 15, 20 and 22 (see *supra*), account being taken of appellant II's and appellant III's arguments, the main request is considered to comply with the novelty requirements of Article 54(3) EPC 1973.

Article 56 EPC

24. Document D10, which was published on 2 March 1995, i.e. only a few months before the priority date validly claimed for the patent, is considered to represent the closest state of the art. It reports on a biochemical characterisation of Flt4, identified as a VEGF receptor-related tyrosine kinase. In the "Discussion" on page 979, the remark is made that the FLT4 specific ligand had not been characterised on the date on which the paper was written (see the sentence reading "*neither the FLT4 specific ligand nor cytoplasmic substrates of these RTKs of have yet been characterized*").

25. In view of document D10, the technical problem solved by the invention may be seen as the identification and provision of the Flt4 specific ligand, the solution thereto being a protein according to claim 1. The question to be answered is whether any of the other prior art documents on file available at the priority date for the assessment of inventive step would have suggested to the skilled person that the expected ligand was that particular receptor disclosed in the patent.

26. In the board's view, none of the prior art documents referred to in Section 3.3 on pages 12 to 13 of appellant II's statement of grounds, which deal with either the expression of the gene encoding the Flt4 receptor (see document D12) or the further characterisation of the same (determination of its amino acid sequence and of its expression pattern in different tissues and cell lines in document D15 and

determination of its signalling properties in document D11) would have provided the skilled person with all the necessary guidance to arrive at the protein according to claim 1, which, while retaining all eight cysteine residues typical for growth factors of the VEGF/PDGF family as well as several other conserved residues, is nevertheless significantly different from the other members of the family already known at the priority date (see in the post-published document D16, taken as an expert opinion, the Section entitled "*Flt4 ligand is a novel member of the PDGF family, VEGF-C*" in the hand-right column on page 291 in combination with Figure 3 on page 293).

27. Appellant II alleged in its statement of grounds (see section 3.3 on page 12) that in view of documents D10, D11, D12 and D15, the skilled person would have known that a tyrosine kinase receptor, such as the Flt4 receptor, would have had at least one associated ligand which is capable of binding and activating it and, thus, it would have been entirely obvious for him/her to attempt "*to find **a** ligand or ligand**s** for Flt4*" (emphasis added). This however is itself a clear admission that there was no reasonable certainty that he/she would have arrived at the precise protein according to claim 1.

28. It is therefore concluded that, starting from document D10, the skilled person would not have arrived at the protein of claim 1 without the exercise of inventive skill, which means that the subject-matter of claim 1 involves an inventive step. Furthermore, the same conclusion applies to the subject-matter of claims 2 to 3 and 5 to 8, as it is defined with a direct or

indirect back-reference to claim 1, as well as to the subject-matter of claim 4, as it is directed to a pharmaceutical composition comprising at least a major portion of the protein according to claim 1. Thus, the request in issue complies as a whole with the inventive step requirement 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 first instance with the order to maintain the patent on the basis of claims 1 to 8 of the main request filed during the oral proceedings and a description and figures to be adapted thereto.

The Registrar The Chairman

A. Wolinski L. Galligani