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D E C I S I O N
of 28 January 2004

Case Number: T 0349/01 - 3.3.8

Application Number: 88870079.6

Publication Number: 0290419

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
DNA clone of human thrombomodulin

Patentee:
WASHINGTON UNIVERSITY

Opponent:
Novo Nordisk A/S

Headword:
Thrombomodulin fragments/WASHINGTON UNIV.

Relevant legal provisions:
EPC Art. 123(2), 123(3)

Keyword:
"Main request - added subject-matter (yes)"
"Auxiliary request - extension of protection (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0349/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 28 January 2004

Appellant: (Proprietor of the patent)	WASHINGTON UNIVERSITY Campus Box 1137, 1 Brookings Drive St. Louis, Missouri 63130-4899 (US)
Representative:	Hiebl, Inge Elisabeth Kraus & Weisert Patent- und Rechtsanwälte Thomas-Wimmer-Ring 15 D-80539 München (DE)
Respondent: (Opponent)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd (DK)
Representative:	Forstmeyer, Dietmar G. Dr. Patentanwälte Boeters & Lieck Bereiteranger 15 D-81541 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 25 January 2001 revoking European patent No. 0290419 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julia
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent No. 0 290 419, with the title "DNA clone of human thrombomodulin" and based on the European patent application No. 88 870 079.6, was granted with four claims, which read as follows:

"1. Human thrombomodulin protein fragment comprising the amino-terminal ligand-binding domain of 223 amino acids having the sequence from Glu 22 to Asp 244 as shown in FIG. 3 of the drawings.

2. Human thrombomodulin protein fragment of Claim 1 including the EGF-homology region of 236 amino acids having the sequence from Cys 245 to Cys 480 as shown in FIG. 3 of the drawings.

3. Human thrombomodulin fragment of Claim 2 including the serine/threonine rich segment of 34 amino acids having the sequence from Asp 481 to His 514 as shown in FIG. 3 of the drawings.

4. Human thrombomodulin fragment of Claim 3 including the membrane-spanning domain of 23 amino acids having the sequence from Ser 515 to Cys 537 as shown in FIG. 3 of the drawings."

II. The patent was opposed on the grounds mentioned in Article 100(b) EPC (Article 83 EPC) and Article 100(c) EPC (Article 123(2) EPC). The opposition division exercised its discretionary power (Article 114(1) EPC) and admitted Article 100(a) EPC (Article 54 EPC) as a further ground of opposition. The patent was revoked for lack of novelty (Article 54 EPC), lack of

sufficiency of disclosure (Article 83 EPC) and for containing added subject-matter (Article 123(2) EPC).

III. Notice of appeal was filed by the patentee (appellant) and a main request and auxiliary request were filed with the statement of Grounds of Appeal. The opponent (respondent) filed observations in reply thereto. Thereafter, the appellant submitted further observations and filed a new main request and auxiliary request. As an auxiliary measure, the appellant also requested oral proceedings.

IV. The board summoned the parties to oral proceedings on 28 January 2004 and sent, as an annex to the summons, a communication indicating its preliminary opinion. Both the main and auxiliary requests were considered to extend the scope of protection conferred by the claims as granted (Article 123(3) EPC). Further points relevant under Articles 123(2), 84, 54 and 56 EPC were also indicated.

V. The appellant's requests for a postponement of the already scheduled oral proceedings were rejected by the board because of a lack of convincing reasons in accordance with the Notice of the Vice-Presidents Directorates-General 2 and 3, OJ EPO 2000, pages 456 to 458.

VI. On 22 December 2003, a new main request and auxiliary request were filed by the appellant, who withdrew the request for oral proceedings and informed the board of its intention not to attend the oral proceedings in the event that they took place. The respondent filed

further observations in reply thereto and requested, as an auxiliary measure, oral proceedings.

VII. The claims of the **main request** read as follows:

"1. Human thrombomodulin protein sequence consisting of
a) amino acid sequence from Glu 22 to Asp 244 as shown in Fig. 3 of the drawings; and
at least one of the following amino acid sequence fragments:
b) amino acid sequence from Cys 245 to Cys 480 as shown in Fig. 3 of the drawings;
c) amino acid sequence from Asp 481 to His 514 as shown in Fig. 3 of the drawings;
d) amino acid sequence from Ser 515 to Cys 537 as shown in Fig. 3 of the drawings.

2. The human thrombomodulin protein sequence of claim 1 consisting of fragments a) and b).

3. The human thrombomodulin protein sequence of claim 1 consisting of fragments a), b) and c).

4. The human thrombomodulin protein sequence of claim 1 consisting of fragments a) to d)."

VIII. The **auxiliary request** read as follows:

"1. Human thrombomodulin protein fragment consisting of the sequence from Glu 22 to Asp 244 as shown in Fig. 3 of the drawings.

2. Human thrombomodulin protein fragment consisting of the sequence from Cys 245 to Cys 480 as shown in Fig. 3 of the drawings.

3. Human thrombomodulin protein fragment consisting of the sequence from Asp 481 to His 514 as shown in Fig. 3 of the drawings.

4. Human thrombomodulin protein fragment consisting of the sequence from Ser 515 to Cys 537 as shown in Fig. 3 of the drawings."

IX. Oral proceedings took place on 28 January 2004, in the absence of the appellant - as announced.

X. The arguments of the appellant in writing insofar as they are relevant to the present decision may be summarised as follows:

Main Request
Article 123(2) EPC

The terms "regions", "domains", "parts", "sections", "sequences" and "segments" used throughout the application as filed implied, directly and unambiguously, fragments of the disclosed human thrombomodulin. The actual separation and isolation of these regions or domains by known conventional methods was a matter of common technology, as exemplified in the application as filed by tryptic cleavage of human thrombomodulin and the isolation of the resulting tryptic peptides. The claimed subject-matter was, directly and unambiguously, derivable from the description of the original application, in particular

from Figures 3 and 7. Page 2, lines 45 to 49 of the published European patent application described and characterized the domains of the human thrombomodulin. The combination of this description with the two figures would have led the skilled person to the claimed human thrombomodulin protein fragments. Moreover, the claimed subject-matter was not concerned with arbitrary combinations. The principle of combining sequences was disclosed on page 9, lines 9 to 11 of the published European patent application, which stated that the invention also included human thrombomodulin from which other sequences that were not required for the human thrombomodulin activity were cleaved, such as the signal sequence or the amino-terminal methionine.

Auxiliary request
Article 123(3) EPC

The claims of the auxiliary request related to four human thrombomodulin protein fragments as such. According to Article 69 EPC, the extent of protection was determined by the terms of the claims. Nevertheless, the description and the drawings had to be used to interpret the claims, which had to be read in the context of the whole description. All granted claims required the presence of the amino-terminal binding-domain having the sequence from Glu 22 to Asp 244 as a part of the claimed human thrombomodulin protein sequence. However, they also referred to human thrombomodulin fragments which as such were indicated *expressis verbis* in the claims and exemplified in Figure 7 of the description too. Thus, the claims as granted implicitly comprised a disclosure of the four thrombomodulin protein fragments as separately claimed

in the auxiliary request. Hence, no extension of scope was seen in these claims compared to the granted claims.

XI. The arguments of the respondent in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarised as follows:

Admissibility of the requests

The requests were filed only shortly before the oral proceedings and long after the summons to the oral proceedings with the board's communication annexed thereto. They did not take account of the outstanding objections. Thus, they had to be held inadmissible.

Main Request
Article 123(2) EPC

The subject-matter of the claims went beyond the disclosure of the application as filed because the specific selection of sequences characterized by particular domains and combinations thereof was not directly and unambiguously derivable from this application. The application as filed only disclosed random tryptic peptides and there was no disclosure to restrict the protein sequences to combinations of particular domains of the complete thrombomodulin protein, such as for instance the combination of fragments (a) and (d). Moreover, the wording "at least one of the following amino acid sequence fragments" in claim 1 was open to interpretation and it did not restrict the number of fragments present in the claimed product nor the possible combinations thereof. Moreover,

if taken to the extreme position, it did not exclude the presence of other fragments.

Auxiliary request
Article 123(3) EPC

All granted claims required the presence of the fragment from Glu 22 to Asp 244. However, claims 2 to 4 of this request related to subject-matter which did not comprise the fragment from Glu 22 to Asp 244.

XII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or the auxiliary request filed on 22 December 2003.

XIII. The respondent (opponent) requested that the appellant's main and auxiliary requests filed on 22 December 2003 be held inadmissible and that the appeal be dismissed.

Reasons for the Decision

Admissibility of the main request and auxiliary request

1. In the communication sent to the parties, the board indicated that "*the final date for receipt of any written submissions in response to this communication is fixed at one month before the oral proceedings*". The oral proceedings were appointed for 28 January 2004, whereas the main request and auxiliary requests were received on 22 December 2003 with a letter of the same date. Thus, the requests were filed within the time

limit set by the board and they cannot be considered late-filed.

2. Furthermore, the board considers that these requests address objections expressed in the board's communication and that they do not introduce subject-matter differing essentially from subject-matter already present in former requests on file. The main request differs from the previous main request, in particular, by requiring the presence of the amino-terminal ligand-binding fragment Glu 22 to Asp 244 in all fragments - introduced as a reply to the board's objection under Article 123(3) EPC, whereas the auxiliary request only differs from the replaced auxiliary request by changing the word "*having*" to the word "*consisting*" - as a reply to an observation made by the board under Article 84 EPC.

3. Thus, both the main request and the auxiliary request are admitted into the proceedings.

Main request
Article 123(2) EPC (Added subject-matter)

4. Article 123(2) EPC requires that a European patent application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. In accordance with the established case law of the Boards of Appeal, the content of an application comprises the whole disclosure that is directly and unambiguously derivable from the application including information which a person skilled in the art reading the application would consider implicitly present (cf

"Case Law of the Boards of Appeal of the EPO", 4th edition 2001, III.A.3.3, pages 218 to 221).

5. The subject-matter of claim 1 of the main request is directed to human thrombomodulin protein sequences consisting of (a) the fragment having the amino acid sequence from Glu 22 to Asp 244 and at least one of three other possible amino acid sequence fragments, namely (b) Cys 245 to Cys 480, (c) Asp 481 to His 514, (d) Ser 515 to Cys 537. Thus, the claim embraces all possible combinations of human thrombomodulin protein sequences as long as fragment Glu 22 to Asp 244 is present therein.

6. It follows from the foregoing that claim 1 embraces combinations of **non-contiguous** fragments or domains, such as a human thrombomodulin protein sequence consisting of domains (a) Glu 22 to Asp 244 and (d) Ser 515 to Cys 537, or a combination of domains (a) Glu 22 to Asp 244, (c) Asp 481 to His 514 and (d) Ser 515 to Cys 537, but without domain (b) Cys 245 to Cys 480, etc.

7. Claim 1 also embraces combinations of fragments or domains having an **altered amino- and carboxyl-termini** in comparison with the sequence of human thrombomodulin shown in Figures 3 and 7 of the application as filed. In other words, the domains can be combined without taking into account their relative position within the disclosed sequence of the human thrombomodulin sequence. Thus, a human thrombomodulin protein sequence consisting of a combination of fragments (b) Cys 245 to Cys 480 and (a) Glu 22 to Asp 244, wherein the amino-terminus is Cys 245 and the carboxyl-terminus is Asp

244, ie the sequence N-Cys245-Cys480-Glu22-Asp244-COOH, falls within the scope of claim 1 of this request. In a similar manner, the presence of several copies of one or more domains are embraced by claim 1 too, such as a combination of fragment (a) with two copies of fragment (b), ie the sequence N-Glu22-Asp244-Cys245-Cys480-Cys245-Cys480-COOH.

8. The application as filed identifies different domains within the sequence of the human thrombomodulin. In particular, page 2, lines 45 to 48 and page 8, lines 25 to 37 (of the published application) in combination with Figure 7 refer - in a contiguous sequence from the amino-terminus to the carboxyl-terminus - to a thrombin-binding domain (Glu 22 to Asp 244), the EGF-homology domain (Cys 245 to Cys 480), a serine/threonine-rich domain (Asp 481 to His 514), a membrane-spanning domain (Ser 515 to Cys 537) and a cytoplasmic domain (His 538 to Leu 575), wherein the numeration and composition follows those indicated in Figure 3.

9. Partial cDNA clones of the human thrombomodulin are also disclosed in the application as filed, in particular λHTm10 and λHTm12, which are said to have the nucleotide sequences, respectively, 1208 to 2403 and 671 to 2142 as shown in Figure 3 (cf Figure 2, page 7, lines 41 to 44 and claims 7 and 9 of the application as published). Thus, these cDNA encode human thrombomodulin peptides - in a contiguous sequence from the amino-terminus to the carboxyl-terminus - from Asn 354 to Leu 575 and from Cys 175 to Leu 575.

10. The application as filed refers to several tryptic fragments obtained by enzymatic cleavage or digestion of the human thrombomodulin with the enzyme trypsin (cf page 3, lines 11 to 13, page 5, line 50 to page 6, line 14, page 7, lines 16 to 24). In particular, the following peptides are disclosed: T-R1 (Ala 372 to Pro 396), T-M1-R1 (Glu 238 to Glu 248), T-M1-R2 (Cys 323 to Pro 333), T-M1-R3 (Leu 125 to Leu 127), wherein the composition and numeration is shown - in a contiguous sequence from the amino-terminus to the carboxyl-terminus - in Figure 3A.

11. It is noted that all references concern peptides or fragments having contiguous sequences within the corresponding human thrombomodulin sequence shown in Figure 3 of the published application. There is no suggestion of possible peptides corresponding to this human thrombomodulin sequence with internal deletions, ie peptides with **non-contiguous** domains. Moreover, all references concern peptides or fragments having the amino- and carboxyl-termini in accordance with their position within the human thrombomodulin sequence shown in Figure 3. There is no suggestion whatsoever to modify or alter their amino- and/or carboxyl-terminus and to have combinations with **altered amino- and carboxyl-termini**, let alone of a human thrombomodulin protein sequence with several copies of a certain domain(s).

12. It has been argued that the reference on page 9, lines 9 to 11 of the application as published, reading "*It should be understood that the invention includes human thrombomodulin from which sequences that are not required for the human thrombomodulin activity have*

been cleaved, for example, the signal sequences or the N-terminal methionyl", discloses the principle of combining peptides. The simple cleavage of sequences or domains - as implied by this reference - cannot be equated, however, to cleaving at two different internal sites (such as at Cys 245 and Cys 480), deleting the resulting intermediate or internal fragment (N-Cys245-Cys480-COOH) and additionally linking the remaining two fragments (N-Glu22-Asp244-COOH and N-Asp481-Cys537-COOH) so as to obtain the claimed non-contiguous protein sequence. There is no suggestion to link non-contiguous domains in this reference, which thus cannot formally support - either explicitly or implicitly - any possible sequence comprising **non-contiguous** domains with respect to the sequence of the human thrombomodulin shown in Figure 3. Similarly, this reference cannot be seen as a formal support - either explicit or implicit - for combinations of domains or sequences with an **altered amino- and carboxyl-termini**, let alone for the presence of several copies of one or more domains. There is no suggestion of such combinations, which would not only require a cleavage and additional linkage of the resulting domains but a change in their number, order and position of their amino- and carboxyl-termini with respect to the original position within the sequence disclosed in Figure 3 of the application as filed.

13. It follows from the foregoing that the subject-matter of claim 1 does not fulfil the requirements of Article 123(2) EPC and consequently, the main request, which comprises it, is not found to satisfy the requirements of the EPC.

Auxiliary request
Article 123(3) EPC (Extension of the scope of protection)

14. The subject-matter of claim 1 as granted relates to human thrombomodulin fragments **comprising** - as a characterizing feature - the amino-terminal ligand-binding domain from Glu 22 to Asp 244 shown in Figure 3. Claims 2 to 4 as granted define other fragments of the human thrombomodulin, in particular the EGF-homology region (claim 2), the serine/threonine rich segment (claim 3) and the membrane-spanning domain (claim 4). However, all these claims are directly (claim 2) or indirectly (claims 3 and 4, which are dependent on claim 2 and 3, respectively) dependent on claim 1 and thus, they all require the presence of the amino-terminal ligand-binding domain from Glu 22 to Asp 244. There is no granted claim directed to a fragment of human thrombomodulin as such - ie isolated from any other fragment - other than the fragment from Glu 22 to Asp 244. The scope of protection of the granted patent is limited to subject-matter - fragments of human thrombomodulin - always comprising at least the fragment from Glu 22 to Asp 244.

15. The claims of the present request are all independent claims and directed to specific fragments of the human thrombomodulin. The subject-matter of claim 1 **consists** of the amino-terminal ligand-binding domain from Glu 22 to Asp 244 and the subject-matter of independent claims 2 to 4 of this request consists of other fragments of human thrombomodulin which, however, do not comprise this amino-terminal ligand-binding domain. In fact, the fragments of claims 2 to 4 correspond,

respectively, to the fragments defined in granted claims 2 to 4 - the EGF-homology region (claim 2), the serine/threonine rich segment (claim 3) and the membrane-spanning domain (claim 4). However, whereas in granted claims 2 to 4 - by their dependency on claim 1 as granted - these fragments required the presence of the amino-terminal ligand-binding domain, in claims 2 to 4 of the present request - being independent claims - this amino-terminal ligand-binding domain is not required anymore. Thus, there is an extension of the protection conferred, in the sense that the claims of the present request extend the protection to fragments of human thrombomodulin without having the limitation present in the granted claims, namely the presence of the amino-terminal ligand-binding domain from Glu 22 to Asp 244.

16. In the present case, the subject-matter of all granted claims - the specific products falling within the terms of the claims - requires the presence of the amino-terminal ligand-binding domain from Glu 22 to Asp 244. There is no need for a further interpretation of this requirement under Article 69(1) EPC by reference to the description. Even if each and every domain is disclosed as such (isolated from other fragments) in the description - which is, in any event, an issue under Article 123(2) EPC - and the granted claims mention *expressis verbis* these other domains, they are not claimed as such - ie alone or isolated as compounds *per se* without any further limitation - but always in combination with the amino-terminal ligand-binding domain from Glu 22 to Asp 244. The description may certainly be used to define - interpret - these domains by reference to their complete amino acid sequence but

it cannot be used to add other requirements or limitations which are not present in the wording of the claims.

17. In conclusion, claims 2 to 4 of this request - which do not comprise the domain from Glu 22 to Asp 244 - are directed to completely different subject-matter with respect to the former granted claims. The subject-matter of these claims is an "aliud" which extends the protection conferred by the claims as granted. Thus, the request does not satisfy the conditions of Article 123(3) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani