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# D E C I S I O N
# of 23 April 1997

**Case Number:** T 0213/93 - 3.3.4

**Application Number:** 85301959.4

**Publication Number:** 0155852

**IPC:** A61K 37/02

**Language of the proceedings:** EN

**Title of invention:**
Thrombin-binding substance and process for its production

**Patentee:**
KOWA COMPANY, LTD.

**Opponents:**
Boehringer Mannheim GmbH Patentabteilung
Asahi Kasei Kogyo Kabushiki Kaisha

**Headword:**
Thrombin-binding substance / KOWA

**Relevant legal provisions:**
EPC Art. 54, 56

**Keyword:**
"Novelty (yes)"
"Inventive step (yes)"

**Decisions cited:**
T 0268/89

**Catchword:**
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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0213/93 - 3.3.4

# D E C I S I O N
## of the Technical Board of Appeal 3.3.4
## of 23 April 1997

**Appellant:** (Proprietor of the patent)
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**Respondent:** (Opponent 02)
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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 23 December 1992 revoking European patent No. 0 155 852 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey
**Members:** R. E. Gramaglia
J.-C. Saisset

## Summary of Facts and Submissions

I. European patent No. 0 155 852 based on application No. 85 301 959.4 was granted on the basis of claims 1 and 2:

"1. A thrombin-binding substance effective when bonded with thrombin to enhance the activation of protein C, derived from human tissue and having the following characteristics:

(a) molecular weight: 88,000 ± 20,000 in the reduced condition and 71,000 ± 20,000 in the unreduced condition;

(b) isoelectric point: pH 4.2 ± 0.5;

(c) affinity: strong for thrombin;

(d) activities: capable of promoting the thrombin-catalysed activation of protein C and prolonging clotting time; and

(e) stability: stable over a pH range of 2 to 10 and stable to denaturing agents (dodecylsulfate and urea) and to a pepsin treatment.

2. A process for producing a thrombin-binding substance as claimed in Claim 1, which comprises the steps of:

(a) extracting fragments of a human placenta with a buffer containing a non-ionic surfactant; and

(b) isolating said thrombin-binding substance in pure form from the resulting extract by means of diisopropylphosphoro-thrombin affinity chromatography, gel filtration or a combination thereof."

II. Two oppositions were filed on the grounds of Article 100(a) EC., i.e. lack of novelty and lack of inventive step. On 23 December 1992 the Opposition Division issued a reasoned decision whereby the European Patent was revoked pursuant to Article 102(1) EPC. The Opposition Division came to the conclusion that, while the claims satisfied the requirements of Article 54 EPC as regarded novelty, they lacked an inventive step having regard to documents:

(1) Esmon et al., Journal of Biological Chemistry, Vol. 257, pages 859 to 864 (1982)

(2) Esmon et al., Proc. Natl. Acad. Sci. USA, Vol. 78, pages 2249 to 2252 (1981), and

(3) Owen et al., Journal of Biological Chemistry, Vol. 256, pages 5532 to 5535 (1981)

The Opposition Division identified the problem underlying the patent in suit as being the search for an abundant source of human thrombin-binding substance effective when bonded with thrombin to enhance the activation of protein C (human thrombomodulin) to be used in human therapy. This problem had been solved by turning to human placenta. The Opposition Division held the view that it was obvious for a skilled person looking for a rich source of human thrombomodulin to turn to placenta, a highly vascularized tissue already

known to contain a plethora of blood coagulation factors, having regard to documents (1) to (3) teaching that human thrombomodulin was a membrane protein present on vascular endothelium.

III. Further documents cited in the present decision are:

(7) Salem et al., Journal of Biological Chemistry, Vol. 259, pages 12246 to 12251 (1984)

(9) Respondent's Experimental Report received on 25 April 1995

(B) Goodman and Gilman, "The Pharmacological Basis of Therapeutics", Fourth Edition, The Macmillan Company, New York, pages 1446 to 1451 (1970)

(C) Appellant's Experimental Report received on 30 April 1993

(D) Hirahara et al., Thrombosis Research, Vol. 57, pages 117 to 126 (1990)

IV. The Appellant (Patentee) lodged an appeal against this decision and filed a statement of grounds of appeal. The Respondents (Opponents) filed counterarguments.

V. On 18 and 22 April 1997, further documents were filed by the Appellant and one Respondent, respectively.

VI. Oral Proceedings were held on 23 April 1997.

VII. In support of their request the Appellant submitted substantially the following arguments:

*Novelty*

- According to document (1), the separation of a thrombin-binding substance from cultured human umbilical cord cells was impossible. Therefore the document was not enabling for the preparation of the claimed cofactor.

*Inventive step*

- The Appellant maintained that human and rabbit thrombomodulins were completely different molecules in the sense that human thrombomodulin was better than rabbit thrombomodulin. Rabbit thrombomodulin was not suited as thrombolytic and anticoagulant substance because it could induce bleeding, i.e. it had the same adverse side effect of heparin. Human thrombomodulin exhibited an unexpected advantageous effect over rabbit thrombomodulin having a heparin-like action (see the post published document (D)). Exhibit (C) indeed showed that rabbit thrombomodulin was even worse than heparin when used as anticoagulant. In view of this, the skilled person had no incentive to turn to document (1) and to human thrombomodulin.

  Based on an unexpected superiority of human thrombomodulin, the Appellant reformulated the problem to be solved by the patent in suit, when applying the "problem-solution approach" for assessing the inventive step. Instead of document (1), document (B) describing anticoagulants for human use, such as heparin, was viewed as the closest prior art. The problem which the invention wished to solve in comparison with this closest prior art was, according to the Appellant, to

provide a thrombolytic or anticoagulant substance which was useful as medicament for human medicine for prolonging the blood clotting time and which avoided the risk of bleeding, an adverse side effect of heparin.

- It was not obvious to turn to human placenta as a source of human thrombomodulin.

VI. The Respondents essentially submitted the following arguments:

*Novelty*

- The claimed human thrombomodulin was already known from documents (2) and (3). No difference could be seen between the "endothelial cell cofactor for thrombin-catalyzed activation of protein C" referred to in documents (2) and (3) and the claimed human thrombomodulin.

- The claimed cofactor was not novel since document (1) disclosed both the process for isolating the cofactor and the starting material which were human endothelial cells from umbilical cord. For the purpose of the novelty issue, it was not important that the authors of document (1) had not actually carried out the isolation of the claimed human cofactor for the reason of the insufficient amount of starting material. However, had the skilled person departed from a higher amount of starting material and applied the purification technique of document (1), he or she would have obtained a product matching the claimed one. Experimental Report (9) showed this.

*Inventive step*

- Document (1) was the closest prior art since it disclosed the isolation and the characterization of an endothelial cofactor for thrombin-catalyzed activation of protein C from rabbit lung. Document (2) disclosed the thrombin-catalyzed activation of protein C by a cofactor occurring in human endothelial cell, and in particular in human umbilical cord endothelial cells. The problem to be solved by the patent in suit compared with this state of the art could not be seen in the search for a novel factor, but was rather the isolation of the known factor having the biological effect shown in documents (1) and (2).

- The alleged advantageous effect of the claimed human thrombomodulin over rabbit thrombomodulin was doubtful since the experimental test (C) had not been carried out under physiological conditions but under arbitrary conditions (in which, inter alia, the AT III concentration was 1/50 relative to the normal AT III concentration in blood) so as to make the difference between human and rabbit thrombomodulin unreasonably large.

- In view of this, the problem underlying the patent in suit was to find an abundant source of human thrombomodulin. The selection of human placenta to solve this problem was obvious, since placenta was a vascular tissue and document (1) taught to use vascular tissues. Further, placenta has always been a known source of several molecules biologically active in the field of thrombosis and haemostasis, e.g. the fibrinolytic agents mentioned in the introductory part of the patent in suit.

VII. The Appellant (Patentee) requested that the decision under appeal be set aside and the patent be maintained as granted.

The Respondents (Opponents) requested that the appeal be dismissed.

## Reasons for the Decision

*Lately filed documents*

1. Because the documents (see section V supra) were filed on 18 and 22 April 1997, i.e. between one and three days before oral proceedings were held, and since they were not more relevant than the other documents on file, the Board decided to disregard them according to Article 114(2) EPC.

*Novelty*

2. The Respondents argue lack of novelty because they see no difference between the claimed human thrombomodulin and the "endothelial cell cofactor for thrombin-catalyzed activation of protein C" referred to in documents (2) and (3). In the Board's view, however, document (2) (see page 2251, right hand column, lines 6 to 7 from the bottom) and document (3)(see page 5533, left hand column, lines 3 to 4 and page 5534, end of right hand column) are concerned with preliminary investigations involving whole organs or endothelium cells that demonstrate the existence on the endothelial cell surface of a cofactor for thrombin-catalyzed activation of protein C. These experiments are carried out by incubating thrombin and protein C in the supernatant of these cells and measuring protein C concentration (see eg document (3), page 5533, left

hand column, lines 1 to 4 and Figure 2). Thus, thrombomodulin is **not** released in the supernatant but still remains embedded in the cell membrane (see document (1), page 859, right hand column, lines 7 to 10 from the bottom). Documents (2) and (3), moreover, do not teach how this membrane protein should be isolated and obtained in a pure form. Therefore, these documents do not make the molecule available to the public, as required by Article 54(2) EPC, in the form as defined in claim 1 of the patent in suit.

3. Unlike documents (2) and (3), document (1) does report a general method for isolating thrombomodulins based on the solubilization of these membrane proteins with a non ionic detergent followed by affinity chromatography on diisopropylphosphorothrombin-agarose. The authors thereof succeeded in isolating and characterizing rabbit thrombomodulin. However, before doing this, they tried to isolate and to characterize human thrombomodulin present in cultures of human umbilical cord endothelium cells. They had to give up after they realized that the concentration of the protein looked for on these cells' surface was too low (see paragraph bridging pages 860 and 861: "The low concentration of the receptor on cultured endothelium excluded cultured cells as a source for the isolation.").

4. The Respondents' Experimental Report (9) purports to show that it was possible for a skilled person to scale up the process of document (1), i.e. had the skilled person departed from **a higher amount** of human umbilical cord endothelium cells as starting material, the isolation of a product matching the claimed one would have been successful. In Experimental Report (9), 2.40 x $10^9$ endothelial cell have been gathered and used as starting material: human thrombomodulin has been indeed isolated and characterized.

5. The Board, though, observes that the unsuccessful attempt to isolate thrombomodulin referred to in document (1) was, in the authors' view, already a "large scale isolation of the cofactor" (see page 860, right hand column, lines 7 to 8). Thus, they had taken all the measures available at that time for gathering the highest amount of starting endothelial cells from human umbilical cord. The statement made in document (1) (loc. cit.) by a team of highly skilled persons that if human umbilical cord endothelium cells are used as a source for the protein, **no** human thrombomodulin can be isolated, convinces the Board. In conclusion, document (1) does not provide an enabling disclosure for the claimed human thrombomodulin.

6. As to Experimental Report (9), it would be of crucial importance to know whether means have possibly been used or not by the authors thereof for enriching the endothelial cell cultures, which means might not have been available to the authors of document (1) and to the skilled person before the priority date of the patent in suit. In other words, this test report would deserve the Board's attention only if it shows in detail which measures have actually been taken by the authors thereof in order to gather more human umbilical cord endothelium cells ($2.40 \times 10^9$). Yet, while Experimental Report (9) give a great many details on the extraction and successive characterization steps, only three lines (see page 1):

"Human umbilical cord endothelium cells were cultured using M-199 medium containing FCS, thereby obtaining $2.40 \times 10^9$ of human umbilical cord endothelium cells."

of the six pages constituting the test report are dedicated to this aspect the Board holds as vital. This is not sufficient to alter the Board's view that document (1) is a non enabling disclosure and that the subject-matter of claims 1 and 2 fulfil the requirements of Article 54 EPC.

*Inventive step*

7. In applying the "problem-solution approach", the Appellant has reformulated the problem to be solved (see paragraph VI supra). However, this reformulation cannot be accepted by the Board on the following grounds.

Firstly, in identifying the problem, it is not permissible to draw on knowledge acquired only after the priority date (see decision T 268/89, OJ EPO 1994, 50). In the present case, the Appellant has relied on post facto evidence which turned up later when more thorough investigations on human thrombomodulin were carried out (see document (D), published 1990 and document (C) received on 30 April 1993). This is not permissible since before the priority date of the patent in suit, the skilled person could not know in advance that human thrombomodulin exhibited an unexpected advantageous effect over rabbit thrombomodulin in view of the fact that human thrombomodulin still awaited to be isolated.

Secondly, contrary to the Appellant's view, there was in fact an incentive to isolate human thrombomodulin. This is demonstrated by document (1) referring to an unsuccessful attempt to isolate and to characterize human thrombomodulin present in cultures of human

umbilical cord endothelium cells. There was also an incentive to look for human thrombomodulin having regard to the possible adverse reaction of the human immune system to rabbit thrombomodulin.

8. Thus, the closest prior art is represented by document (1) disclosing a general method for isolating thrombomodulins based on the solubilization of these membrane proteins with a non ionic detergent followed by affinity chromatography on diisopropylphosphoro-thrombin-agarose. As to human thrombomodulin, there was a blockage preventing the skilled person from isolating the molecule because of the too low concentration of the protein looked for on human umbilical cord endothelium cells (see point 2 supra).

The problem to be solved in the light of document (1) is, in the Board's opinion, the one correctly identified by the opposition division, namely to find an endothelial tissue as a sufficiently rich source of human thrombomodulin. The solution to this problem is the choice of placenta. In view of the Example of the patent in suit, the Board is satisfied that the problem has been solved.

9. It has to be decided whether the proposed solution is obvious or not, i.e. whether the prior art documents, possibly completed by the skilled person's general knowledge, pointed or not towards placenta as source of human thrombomodulin sufficiently rich for enabling human thrombomodulin to be isolated.

Documents (2) and (3) taught that the protein looked for was present on the endothelial cell's surface (see eg document (2), page 2249, left hand column, end of second paragraph). Document (1) showed that the

presence of thrombomodulin on endothelial cells was no guarantee that one could isolate the protein, because the protein had also to be present **in a sufficient amount** and this additional condition was not fulfilled for human umbilical cord endothelial cells.

10. The Respondents maintain that the selection of human placenta was obvious, since placenta was a vascular tissue and document (1) taught to use vascular tissues. The Board is however of the opinion that "vascularity" alone is not a critical feature for ensuring a high concentration of human thrombomodulin on the endothelial cells' surface. The skilled person had no valid reason to consider umbilical cord less "vascular" than placenta, of which it is an appendix. Thus, document (1) would prima facie discourage the skilled person from replacing umbilical cord with human placenta as a source of human thrombomodulin. The skilled person would rather turn to human lungs in view of the disclosure by document (1) of a successful isolation of rabbit thrombomodulin from rabbit lungs.

This is what the authors of the post published document (7), disclosing the first successful isolation of human thrombomodulin, actually did. Although human placentae are easily available, they first departed from human lungs. However, they had to give up when they realized that the cofactor activity in the Triton® (detergent) extract was only 100 units/lung (see page 12247, right hand column, under the heading "Results"). They then turned to human placenta only after having checked the cofactor activity in the Triton® extract of placenta and found that this activity was "much greater" (loc. cit.).

11. Document (7) also shows that no theoretical forecast based on the degree of vascularization could be made about the suitability of a given tissue to the isolation of human thrombomodulin, but this was left to the empirical determination. In other words, there was no pointer to human placenta. Rather, any tissue comprising veins, arteries, capillaries such as lung, heart, brain and a great many other organs could not a priori be excluded as possible successful candidates.

12. The fact that, before turning to human placenta, there have been two prior failures with highly vascularized organs, namely with umbilical cord endothelial cells and with human lungs, suggests that finding a rich source for human thrombomodulin was not that straightforward task the Respondents maintain. Also the unexpected finding by the authors of document (7) that rabbit lungs were good for isolating rabbit thrombomodulin, while human lungs were not for obtaining human thrombomodulin suggests that this field was of great complexity, which induced, before the priority date of the patent in suit, uncertainty as to which tissue was suitable and which was not.

13. Also the Respondents' proposition that placenta had always been a known source of several molecules biologically active in the field of thrombosis and haemostasis and that, in view of this, the skilled person looking for a rich source of human thrombomodulin would have turned to human placenta, is not convincing. This is because, as stated in point 8 supra, the assumed presence of thrombomodulin in human placenta was no guarantee that one could isolate the protein, because the protein had also to be present **in a sufficient amount.** This could not be established in advance by the skilled person.

14. For these reasons, the Board must conclude that the selection of human placenta source sufficiently rich for enabling human thrombomodulin to be isolated, do not follow from the prior art in an obvious manner. Therefore, the subject-matter of claims 1 and 2 as granted fulfils the requirements of Article 56 EPC.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent as granted.

The Registrar: The Chairwoman:

D. Spigarelli U. Kinkeldey