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D E C I S I O N
of 23 March 2003

Case Number: T 0846/00 - 3.3.4

Application Number: 90909765.1

Publication Number: 0429626

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Language of the proceedings: EN

Title of invention:
Synthetic peptides for use in vivo in thrombus detection

Patentee:
ANTISOMA LIMITED

Opponent:
DuPont Pharmaceuticals Company

Headword:
Thrombus detection/ANTISOMA LIMITED

Relevant legal provisions:
EPC Art. 54(3)

Keyword:
"Main request: novelty (yes)"

Decisions cited:
G 0006/88, T 0007/86

Catchword:
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Case Number: T 0846/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 23 March 2003

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 13 June 2000 revoking European patent No. 0 429 626 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

I. The appeal is against the decision of the opposition division revoking European patent No. 0 429 626 (application No. 90 909 765.1), which had been opposed by the respondent (opponent) on the grounds of lack of novelty and inventive step and insufficiency of disclosure. The patent was granted on the basis of 12 claims for all designated Contracting States, except ES, and 10 claims for the Contracting State ES. Claims 1 and 11 for all designated Contracting States except ES reads as follows:

"1. A radioactively labelled peptide for *in vivo* imaging or detection of a thrombus or a tumour by binding *in vivo* to RGD binding sites on the thrombus or tumour, wherein the peptide comprises the amino acid sequence arginine-glycine-aspartic acid (RGD).

11. A radioactively-labelled peptide wherein the peptide has the sequence RGDSY, RGDFY, RGDSYC or RGDSCRGDSY."

Claims 2 to 10 and 12 were addressed to specific embodiments of the diagnostic use of claim 1 or of the radioactively-labelled peptide of claim 11, respectively. Claims 1 to 10 for the Contracting State ES were drafted as corresponding method claims.

II. The reasons given for the refusal was that the subject-matter of claim 1 of the main and third auxiliary requests lacked novelty (Article 54(3) EPC) over document

(D2): EP-A-0 333 356.

The opposition division further held that claim 1 of the first and second auxiliary requests, comprising a disclaimer to the peptides disclosed in document (D2), infringed Article 123(2) EPC.

III. The following further document is cited in the present decision:

(D21): Mousa S.A. et al., Coronary Artery Disease, Vol. 9, No. 2/9, pages 131-141 (1998).

IV. The claims of the main request for all Contracting States except ES, on which the present decision is based, were filed on 16 August 1997 and represented the main request during the oral proceedings before the opposition division. The patentee foreshadowed (see submission dated 21 July 1997, paragraph bridging pages 1 and 2) that "equivalent amendments will be made to the set of claims for ES when the opposition procedure is terminated". The claims of the first and second auxiliary requests presently on file were submitted on 20 October 2000 to the board. Claims 1 and 10 of the main request read as follows:

"1. Use of a radioactively labelled peptide comprising the amino acid sequence arginine-glycine-aspartic acid (RGD) in the manufacture of a composition for *in vivo* imaging or detection of a thrombus or a tumour by binding *in vivo* to RGD binding sites on the thrombus or tumour.

10. A radioactively-labelled peptide wherein the peptide has the sequence RGDSY, RGDFY, RGDSYC or RGDSCRGDSY."

Claims 2 to 9 and 11 were addressed to specific embodiments of the diagnostic use of claim 1 or of the radioactively-labelled peptide of claim 10, respectively.

V. Oral proceedings were held on 13 March 2003.

VI. The submissions by the appellant in support of the novelty of the claims of the main request can be summarized as follows:

- A thrombus or blood clot was a layered matrix of cross-linked platelets and fibrin. The cross-linking of platelets took place via the GP IIb/IIIa (glycoprotein fibrinogen receptor) present on activated platelets, which bound to cytoadhesive proteins such as fibronectin. As for fibrin, it was produced in the final stages of the well-known blood clotting cascade, wherein the enzyme thrombin converted fibrinogen into fibrin.

- It was true that document (D2) (see page 9, lines 1 to 10) disclosed the use of the hirudin peptides for imaging a thrombus, however, this occurred by binding to thrombin, not to RGD binding sites, since the thrombolytic hirudin-based agents disclosed in document (D2) inhibited or reversed the formation of blood clots by binding very tightly to thrombin and thus preventing the generation of fibrin from fibrinogen.

- It could not be derived from document (D2) that radiolabelled RGD-hirudin peptides were suited for thrombus imaging by binding to the RGD binding

sites on the platelets. Document (D2) also did not exemplify RGD-peptides used for thrombus imaging.

- The affinity of RGD-hirudin peptides for thrombin being 10^6 times than the affinity for the RGD receptor, no incorporation of the RGD-hirudin peptides in the thrombus would have occurred.

- Moreover, a radiolabelled agent had to be quickly incorporated into the rapidly growing thrombus, followed by a rapid clearance of the agent from the vasculature, in order to allow radioimaging of the thrombus (see document (D21), cited as expert opinion, page 132, left hand column, third paragraph and page 140, right hand column, last paragraph). The peptides disclosed in document (D2) were not capable of fulfilling these requirements.

- Document (D2) did not make available to the public in the sense of decision G 6/88 (OJ EPO 1990, 114, point 8.1) the technical effect stated in claim 1 at issue, namely that imaging of the thrombus was achieved as a result of binding of the radiolabelled peptide to the RGD receptor.

VII. The submissions by the respondent against the novelty of the claims of the main request can be summarized as follows:

- Document (D2) did disclose the use of RGD-containing peptides for thrombus imaging by binding to the RGD binding sites on platelets. This technical teaching could be derived from the following passages of document (D2):

(a) On page 9, lines 31 to 34 it was stated:

"This invention also relates to hirudin peptides which are identical to the above-described peptides, except they are characterized by the replacement of Asp_{53} or Asn_{53} with an arginine residue. These peptides contain an Arg_{53}-Gly_{54}-Asp_{55} sequence which binds to and inhibits the platelet surface glycoprotein IIb/IIIa."

(b) It was further stated (see page 9, lines 1 to 2): "Furthermore, the peptides of the present invention may be used for ex vivo thrombus imaging in humans and other mammals."

(c) On page 9, lines 35 to 36 it was further stated: "...the presence of the Arg-Gly-Asp sequence serves to target these peptides to the site of a platelet-rich clot."

- Finally, the use of RGD-containing peptides for thrombus imaging by binding to the RGD binding sites on platelets could also be derived from claims 11, 31 and 32 of document (D2) read together.

- The appellant's argument relating to the affinity of RGD-hirudin peptides for thrombin being 10^6 times that for the RGD receptor, had to be balanced with the number of binding sites on the platelets vs the number of binding sites on thrombin (5×10^4 to 9×10^4 :1). Moreover, document (D21), cited as expert opinion,

contradicted the alleged binding preference of the RGD-hirudin peptides for thrombin.

VIII. The appellant (patentee) requested that the decision under appeal be set aside and that the case be remitted to the opposition division for further prosecution on the basis of the main request filed on 16 August 1997 or the first or second auxiliary request as filed on 20 October 2000.

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

Reasons for the Decision

1. The appeal is admissible.

Main request
Novelty (Article 54(3) EPC)
Tumour imaging/detection

2. Insofar as claim 1 of this request relates to the second/further diagnostic use of radioactively labelled RGD-peptides for in vivo imaging/detecting of a tumour by binding in vivo to RGD binding sites on the tumour (see Section IV supra), no objections of lack of novelty were raised by either the respondent or the opposition division. Nor does the board have any such objections, as no prior art document disclosing said diagnostic use is before the board.

Thrombus imaging/detection

3. The only point at issue is therefore to decide the

novelty of the second/further diagnostic use according to claim 1, in the case of the in vivo imaging/detection of a thrombus by binding in vivo to RGD binding sites on the thrombus.

4. Expressed in simple words, a thrombus or blood clot is a layered matrix of cross-linked platelets. The cross-linking of platelets takes place via the GP IIb/IIIa (glycoprotein fibrinogen receptor) present on activated platelets, which binds to cytoadhesive soluble proteins (fibrinogen, fibronectin and von Willebrand factor). As for fibrin, produced in the final stage of the well-known blood clotting cascade upon conversion from fibrinogen by means of the enzyme thrombin, it serves to further strengthen and cross-link the thrombus matrix.

5. Document (D2) relates to hirudin peptides derived from the C-terminal region of hirudin, which exhibit the thrombolytic properties of native hirudin. On page 9, lines 31 to 34 of this document it is stated: "This invention also relates to hirudin peptides which are identical to the above-described peptides, except they are characterized by the replacement of Asp_{53} or Asn_{53} with an arginine residue. These peptides contain an Arg_{53}-Gly_{54}-Asp_{55} sequence which binds to and inhibits the platelet surface glycoprotein IIb/IIIa.". Therefore, a sub-class of the peptides disclosed by document (D2) exhibits the RGD motif referred to in claim 1 at issue. There appears to be no doubt that these RGD-hirudin peptides, be they radiolabelled or not, are able to bind to the RGD receptor of a thrombus. This is shown by Example 24 on page 23, lines 34 to 38 of document (D2)("We also examined the inhibition of platelet activation by N-acetyl-Arg_{53}hirudin$_{53-64}$ ... Figure 17

demonstrates that N-acetyl-$Arg_{53}$$hirudin_{53-64}$ inhibited platelet aggregation...") illustrating the binding of an unlabelled RGD-hirudin peptide to a thrombus via the RGD receptor on the platelets.

6. The technical effect stated in claim 1 requires that imaging of the thrombus has to be achieved as a result of binding of the radiolabelled peptide to the RGD receptor. Therefore, in the board's judgement, in contrast to the opposition division's conclusion (see paragraph bridging pages 9 and 10 of the decision under appeal), it is not sufficient that document (D2) teaches (and exemplifies) the binding of an unlabelled (and "inherently" also of radiolabelled) RGD-hirudin peptide to a thrombus via the RGD receptor on the platelets. The document should also make available to the public the teaching that such binding is made for the purpose stated in claim 1, namely that of "in vivo imaging or detection of a thrombus by binding in vivo to RGD binding sites on the thrombus". Thus, the question to be decided is what has been made available to the public and is not what might have been "inherent" in putting into practice the teaching of document (D2) (see decision G 6/88 (ibidem, point 8.1)).

7. In answering this question, the board observes that according to document (D2), the purpose of introducing a RGD motif "...serves to target these peptides to the site of a platelet-rich clot. Once the peptides reach this target, they inhibit both additional platelet aggregation and the generation of fibrin. This action prevents the expansion of a blood clot, effectively resulting in increased clot dissolution." (see page 9, lines 36 to 38; see also page 23, lines 34 to 38) or

"... may serve to target this peptide to a thrombus and thus increase the local concentration of a thrombin inhibitor at that site." (see page 23, lines 43 to 44). All these technical effects are thus **not** related to "in vivo imaging or detection of a thrombus".

8. Rather, in the board's view, the sought technical effect of increasing clot dissolution by introduction of a RGD motif precludes interpreting the disclosure of document (D2) as a teaching (inherent or not) of "in vivo imaging or detection of a thrombus by binding in vivo to RGD binding sites on the thrombus". This is because in order to radioimage a thrombus, the radiolabeled agent has to be incorporated in the "rapidly growing venous thrombus" (see document (D21), cited as expert opinion, page 132, end of left hand column). But "growing" is the opposite of "dissolving".

9. In view of the foregoing, the board concludes that document (D2) does not make available to the public the technical effect stated in claim 1, namely the achieving imaging of the thrombus by binding of the radiolabelled peptide to the RGD receptor.

10. It is argued by the respondent that the use of RGD-containing peptides for thrombus imaging by binding to the RGD binding sites on platelets can also be derived from claims 11, 31 and 32 of document (D2) read together. Claim 11 indeed relates to, inter alia, the peptide **RGD**FEEIPEEY (RGD sequence emphasised by the board). Claim 31 relates to, inter alia, a peptide according to claim 7 radiolabelled with ^{125}I, ^{123}I or ^{111}In, while claim 32 reads: "A composition for ex vivo imaging of a fibrin or platelet thrombus in a patient comprising a peptide according to claim 31".

11. The board notes that the feature "by binding *in vivo* to RGD binding sites on the thrombus" is absent from these claims. Thus, no correlation between imaging of the thrombus and binding of the radiolabelled peptide to the RGD receptor can be derived from these claims.

12. Even interpreting these claims in the light of the description, no different result is arrived at. The description teaches that, for the purpose of radioimaging, the binding of the peptide to either platelet clots or to fibrin clots occurs **always** via thrombin, not via the RGD receptor (see page 9, line 7: "...bind to thrombin in a fibrin clot..." and page 9, lines 9 to 10: "This technique also yields images of platelet-bound thrombin and meizothrombin."). While it may be true (see point 5 supra) that the RGD-hirudin peptide also binds via the RGD receptor, this is described as inhibiting additional platelet aggregation, and there is no suggestion that it assists in radioimaging. Finally, interpreting the description as suggesting "in vivo imaging or detection of a thrombus by binding in vivo to RGD binding sites on the thrombus", as the claim requires, would also be in contradiction with the "dissolving" effect looked for (see point 8 supra).

13. In conclusion, the subject-matter of claim 1 and dependent claims 2 to 9 fulfils the requirements of novelty insofar as they relate to both tumour and thrombus imaging.

As for the radioactively labelled peptides of claims 10 and 11, although they conceptually fall under the general formula of claim 11 (via claim 31) of document (D2), the latter fails to disclose any of these

peptides (RGDSY, RGDFY, RGDSYC or RGDSCRGDSY) explicitly. Therefore, the subject-matter of claims 10 and 11 is also considered novel (see eg decision T 7/86, OJ EPO 1988, 381).

14. No need arises to consider the first and second auxiliary requests.

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 for further prosecution on the basis of the main request filed on 16 August 1997.

The Registrar: The Chairwoman:

G. Rauh U. M. Kinkeldey