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D E C I S I O N
of 19 January 2005

Case Number: T 0699/99 - 3.3.4

Application Number: 89900774.4

Publication Number: 0394326

IPC: C07K 1/00

Language of the proceedings: EN

Title of invention:

Methods for the production of conformationally stabilized cell adhesion peptides

Patentee:

La Jolla Cancer Research Foundation

Opponent:

Merck Patent GmbH

Headword:

Cell adhesion peptides/LA JOLLA CANCER RESEARCH FOUNDATION

Relevant legal provisions:

EPC Art. 123(2), 123(3), 84, 54, 56
RPBA Art. 7

Keyword:

"Main Request - novelty (no)"
"Auxiliary Request I: inventive step (no)"
"New Second Auxiliary Request: added subject-matter (no),
broadening of scope of protection (no), clarity (yes), novelty
(yes), inventive step (yes)"

Decisions cited:

G 0002/88, G 0001/03, T 0124/87, T 0042/02

Catchword:

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Case Number: T 0699/99 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 19 January 2005

Appellant:
(Opponent)

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Respondent:
(Proprietor of the patent)

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Representative:

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Decision under appeal:

Interlocutory decision of the Opposition
Division of the European Patent Office posted
30 April 1999 concerning maintenance of
European patent No. 0394326 in amended form.

Composition of the Board:

Chair: U. Kinkeldey
Members: R. Gramaglia
R. Moufang

Summary of Facts and Submissions

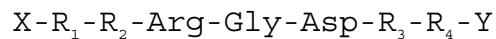
- I. European Patent No. 0 394 326 with the title "Methods for the production of conformationally stabilized cell adhesion peptides" was granted with 24 claims on the basis of European patent application No. 89 900 774.4 (published as WO 89/05150), filed on 8 December 1988 and claiming priority from US 131390 of 10 December 1987.

Granted claim 1 read as follows:

"1. A method of making an Arg-Gly-Asp containing peptide with an altered Arg-Gly-Asp receptor specificity and/or binding affinity, comprising restricting the conformation of the Arg-Gly-Asp sequence in said peptide in comparison to a linear peptide having an analogous sequence."

- II. Notice of opposition was filed by the opponent requesting the revocation of the European patent on the grounds of Article 100(a) EPC. By a decision dated 30 April 1999 the opposition division maintained the patent on the basis of the claims of Auxiliary Request 1 then on file.
- III. The appellant (opponent) lodged an appeal against the decision of the opposition division. The respondent (patentee) identified as **Main Request** to dismiss the appeal. In the set of claims ("first auxiliary request") maintained by the opposition division, claim 13 read as follows:

"13. A peptide containing the sequence



in which R_2 comprises about 0 to 5 amino acids, R_3 comprises about 0 to 5 amino acids, R_1 and R_4 are amino acids connected by a bridge, X is one or more amino acids or H, and Y is one or more amino acids or OH or NH_2 ."

IV. A communication was sent, expressing the board's provisional view. In answer thereto the respondent submitted on 23 December 2002, *inter alia*, a "Second Auxiliary Request" (renumbered as **Auxiliary Request I** in this decision), of which claim 1 read as follows:

"1. A method for altering the Arg-Gly-Asp receptor specificity and/or binding affinity of an Arg-Gly-Asp containing peptide, comprising restricting the conformation of the Arg-Gly-Asp sequence in said peptide in comparison to a linear peptide having an analogous sequence."

V. At the end of the oral proceedings held on 23 January 2003 the board, including Mr V. Di Cerbo as the legal member, announced that the respondent's **Main Request** was rejected and that the proceedings were continued in writing, because claim 13 of Auxiliary Request I comprised a disclaimer and the issue regarding the allowability of disclaimers was pending as case G 1/03 before the Enlarged Board of Appeal.

VI. On 20 September 2004 the appellant filed, *inter alia*, documents (D17) and (D18). A further communication was sent, expressing the board's provisional view and

informing the parties that a new legal member would succeed to Mr V. Di Cerbo, who was about to leave the office. At the end of further oral proceedings held on 20 October 2004 the board, in its new composition, decided that **Auxiliary Request I** was rejected and that the proceedings were continued in writing.

VII. During further oral proceedings held on 19 January 2005 the respondent submitted claims 1 to 13 of a **New Second Auxiliary Request**, of which claims 1 and 5 read as follows:

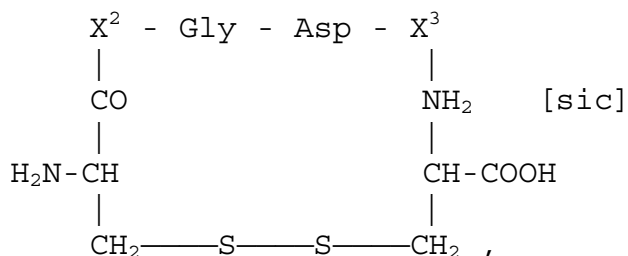
"1. A method of altering the Arg-Gly-Asp receptor specificity and/or binding affinity of an Arg-Gly-Asp containing peptide, comprising restricting the conformation of the Arg-Gly-Asp sequence in said peptide in comparison to a linear peptide having an analogous sequence by cyclizing the Arg-Gly-Asp containing peptide, wherein the cyclic peptide inhibits attachment of rat kidney cells to vitronectin at an at least 10-fold lower molar concentration than the linear peptide, but is ineffective at inhibiting binding of fibronectin to the fibronectin receptor."

"5. A peptide containing the sequence



in which R_2 comprises about 0 to 5 amino acids, R_3 comprises about 0 to 5 amino acids, R_1 and R_4 are amino acids connected by a bridge, X is one or more amino acids or H, and Y is one or more amino acids or OH or NH_2 , wherein the peptide inhibits attachment of rat kidney cells to vitronectin at an at least 10-fold lower molar concentration than the linear peptide, but

is ineffective at inhibiting binding of fibronectin to the fibronectin receptor, with the proviso that the peptide is not



where

X² represents a residue of L-Arg or D-Arg,
X³ represents a residue of L-Trp, N-Trp [sic], L-Leu, D-Leu, L-Ile, D-Ile, L-Phe, D-Phe or a chain containing 2 or 3 of these residues."

Claims 2 to 4 covered specific embodiments of the method of claim 1. Claims 6 and 7 were directed to specific embodiments of the peptide of claim 5. Claims 8 and 9 were to uses of the peptide of claims 5 to 7. Claim 10 was addressed to a composition containing the peptide of claims 5 to 7, whereas claims 11 to 13 were to a medical device coated with such a peptide.

VIII. The following documents are cited in the present decision:

(D1) EP-A-0 275 748;

(D3) Kessler H., Angew. Chem. Int. Ed. Engl., Vol. 21, pages 512-523 (1982);

- (D6) Dedhar S. et al., J. Cell. Biol., Vol. 104,
No. 3, pages 585-593 (1987);
- (D8) Huang Tur-Fu et al., J. Biol. Chem., Vol. 262,
No. 33, pages 16157-16163 (1987);
- (D9) Ruoslahti E. et al., Cell, Vol. 44, pages 517-518
(1986);
- (D10) Hruby V.J., Life Sciences, Vol. 31, pages 189-199
(1982);
- (D12) Aumailley M. et al., FEBS Letters , Vol. 291,
No. 1, pages 50-54 (October 1991);
- (D13) Müller G. et al., Angew. Chem. Int. Ed.
Engl., Vol. 31, No. 3, pages 326-328 (1992);
- (D16) Pfaff M. et al., J. Biol. Chem., Vol. 269,
No. 82, pages 20283-20288 (1994);
- (D17) Ruoslahti E. and Pierschbacher M.D., Science,
Vol. 238, pages 491-497 (23 October 1987);
- (D18) Pierschbacher M.D. and Ruoslahti E., J. Biol.
Chem., Vol. 262, No. 36, pages 17294-17298
(25 December 1987);
- (D20) Test report by Prof. H. Kessler dated 19 December
2004 (appellant).

IX. The submissions by the appellant (opponent), insofar as they are relevant to the present decision, can be summarised as follows:

Admissibility of documents (D17) and (D18) into the proceedings

- Publication (D17) (ref. (3) in document (D12)), co-authored by the inventors of the patent in suit, was highly relevant to the issue of the inventive step. Document (D18) served to emphasize an argument already on file.

Main Request

Article 54 EPC

Claim 13

- The claim lacked novelty, as the general formula in claim 13 of this request covered the cyclic peptides described on page 3, lines 9-19 of document (D1).

Auxiliary Request I

Article 56 EPC

Claim 1

- Document (D9) page 517, 1-h column, and page 518, 1-h column, taught that the Arg-Gly-Asp motif bound to many receptors such as the fibronectin or vitronectin receptor and suggested the role of the conformation of this sequence for receptor recognition.
- Document (D17) suggested two hypotheses for explaining the specificity of Arg-Gly-Asp-containing peptides to their receptors and stated that recent experimental data pointed towards the conformation-specificity theory.

- Document (D3) taught that cyclizing a peptide in proximity of the active site achieved a restriction of the conformation and was effective in altering the affinity/specificity of the peptide for a specific receptor. The skilled person would thus arrive at the claimed subject-matter when applying this technical teaching to the Arg-Gly-Asp-containing peptides disclosed by documents (D9) or (D17).

- Document (D6) already suggested the relationship between the conformation of an Arg-Gly-Asp-containing peptide and the binding properties, since it taught that collagen-binding polypeptides including Arg-Gly-Asp bound to triple-helical collagen but failed to recognize the collagen if the triple helical conformation was unfolded by heating.

New Second Auxiliary Request

Article 123(2) EPC

- The feature in claims 1 and 5 "at an at least 10-fold lower molar concentration" represented an unallowable generalization, while "at least" had no basis in the application as filed.

Article 123(3) EPC

- Granted claim 1 comprised two steps (synthesis of the linear peptide and the change of its conformation), whereas the method according to present claim 1 no longer required the step of

synthesis of the linear peptide. This represented a broadening of the scope of granted claim 1.

Article 84 EPC

- The disclaimer in claim 5 was not allowable because the necessary limitation over document (D1) could have been expressed in simpler positive features (see decision G 1/03, OJ EPO 2004, 413).
- The terms "ineffective", "at least 10-fold" and "inhibits attachment" referred to in claim 1 lacked clarity. It was also not clear to the skilled person which biological test had to be used for measuring these parameters or which kind of cyclization should be used.

Article 56 EPC

- The claimed technical effect had not been demonstrated because (i) the patent in suit failed to compare a cyclized peptide with a linear peptide having the same amino acid sequence as required by claim 1, (ii) test report (D20) showed that cyclization of the decapeptide Gly-Pen-Gly-Arg-Gly-Asp-Ser-Pro-Cys-Ala and the des-Ala analog did not achieve any change in specificity/binding affinity, nor any restriction of the conformation and (iii) the claimed technical effect had not been demonstrated in the whole area covered by claim 1, e.g. for large peptides of 500 amino acids.
- Post-published document (D18) taken as expert opinion confirmed the view that the cell adhesion

assay illustrated by Figure 2 of the patent in suit had been performed in the presence of a cyclic and a linear peptide not having the same amino acid sequence, since it was stated in the legend to Figure 5 (identical to Figure 2 of the patent) that the cyclic peptide had been compared with the "prototype" peptide GRGDSPC, not with Gly-Pen-Gly-Arg-Gly-Asp-Ser-Pro-Cys-Ala.

- Document (D9) (page 518) in combination with document (D10) (see page 197, last paragraph) rendered the claimed method obvious.
 - The "10-fold" figure could be derived from page 493, 1-h column, line 9 of document (D17).
- X. The submissions by the respondent (patentee), insofar as they are relevant to the present decision, can be summarised as follows:

Admissibility of documents (D17) and (D18) into the proceedings

- The filing of new documents at that late stage represented an abuse of the proceedings.

Main request

Novelty

Claim 13

- Document (D1) disclosed linear peptides with no requirement of conformational restraint. Therefore, the peptides covered by claim 13 were novel over document (D1).

Auxiliary Request I

Article 56 EPC

Claim 1

- No document of the prior art was concerned with the problem of altering the Arg-Gly-Asp receptor specificity and/or binding affinity of an Arg-Gly-Asp containing peptide. No document either suggested the claimed solution to this problem. The prior art documents rather suggested that the Arg-Gly-Asp receptor specificity and/or binding affinity depended on additional binding sites.

- Restricting the conformation of the Arg-Gly-Asp motif in a peptide was not to be confused with the 3-D structure or "natural" folding of a protein. Post-published document (D13) taken as expert opinion showed that the Arg-Gly-Asp sequence could be located in a highly flexible region of an overall rigid (folded) protein.

- Many prior art documents pleaded for the "second binding site" theory.

- Documents (D17), (D12) and (D18) emphasized the importance of the residues adjacent to the Arg-Gly-Asp sequence for binding to the receptor.

New Second Auxiliary request

Article 123(3) EPC

- The wording now claimed represented a limitation of the scope of granted claim 1. It was implicit that

the claimed technical effect could only be achieved if the linear peptide existed.

Article 84 EPC

- The biological assay referred to in claim 1 was the cell adhesion assay disclosed in detail in Example V of the patent in suit. This assay was also known from the prior art cited on page 7, lines 39-40 of the patent and in document (D6). Therefore, the skilled person was well acquainted with the cell adhesion assay and the terms "ineffective", "at least 10-fold" and "inhibits attachment" referred to in claim 1.

Claim 5

Article 84 EPC

- The disclaimer in claim 5 was allowable under Article 84 EPC.

Novelty

Claim 1

- None of the prior art documents taught the skilled person any correlation between cyclizing an Arg-Gly-Asp containing peptide and some change in biological activity, let alone the "switch" in receptor specificity/binding activity stated in claim 1.

Claim 5

- In order to render the claim novel, the complete teaching of document (D1) overlapping with claim 5

had been removed by way of disclaimer. The disclaimer excluded structures known from document (D1).

Inventive step

- The claimed technical effect had been demonstrated.
- No document of the prior art was concerned with the problem of "switching" the Arg-Gly-Asp receptor specificity and/or binding affinity of an Arg-Gly-Asp containing peptide so that the peptide inhibited attachment of kidney cells to vitronectin at an at least 10-fold lower molar concentration than the linear peptide, while being ineffective at inhibiting binding of fibronectin to the fibronectin receptor, let alone with its solution.
- The peptide of claim 5 also did not follow from the prior art in an obvious manner, document (D1) being a document according to Article 54(3) EPC.

XI. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 394 326 be revoked.

The respondent (patentee) requested that the appeal be dismissed (main request) or that the patent be maintained on the basis of Auxiliary Request I (former Second Auxiliary Request) submitted on 23 December 2002, or on the basis of claims 1 to 13 of the New Second Auxiliary Request filed in the oral proceedings of 19 January 2005.

He further requested an apportionment of costs.

Reasons for the Decision

1. The appeal is admissible.

Procedural matters

Change of composition of board

2. The first oral proceedings of 23 January 2003 took place before the board in a composition which included Mr V. Di Cerbo as legal member (above, section V). At the end of these oral proceedings the board deliberated and announced that the respondent's Main Request was rejected and that the proceedings were continued in writing. Thus, when the previous legal member Mr V. Di Cerbo was replaced by the present legal member in September 2004, an interim decision with respect to the Main Request of the respondent had already been taken.
3. It follows from Article 7(2) Rules of Procedure of the Boards of Appeal that the new member is bound to the same extent as the other members by this interim decision. However, if, as in the present case, the reasons for the interim decision have not yet been provided in written form to the parties, but were intended to be integrated into the final written decision, the new member is not allowed to deliberate on or otherwise contribute to those parts of the final written decision which give or reflect the reasons for the interim decision. This is in line with the principle that any decision announced orally must only

be written on behalf of and represent the views of the members responsible for that oral decision. Its written reasons shall not be influenced by the views of the new member which were neither formed on the occasion of the respective oral proceedings, nor communicated to the parties on this occasion (see decision T 42/02 of 28 February 2003, point 8).

4. Thus, the new legal member has refrained from deliberating on or contributing to points 7 to 9 of the Reasons below. The same applies to those passages in the above sections III-V, IX and X of the Summary of Facts and Submissions which relate to the Main Request of the respondent. These parts of the decisions only represent the views of the board in its composition at the first oral proceedings. In this respect, the previous legal member, who is unable to act since his service for the Boards of Appeal ended in 2004, is not replaced by an alternate (application of Article 7(3), first sentence, Rules of Procedure of the Boards of Appeal by analogy).

Admissibility of documents (D17) and (D18) into the proceedings

5. It has to be considered whether, notwithstanding the lateness of their filing, documents (D17) and (D18) should be admitted into the proceedings. The board considers that the content of document (D17) is *prima facie* relevant to the question of inventive step, while document (D18) is taken as expert opinion to emphasise arguments already on file (see points 21 and 42 *infra*). The respondent, while quite understandably objecting to the admissibility of the new evidence on procedural

grounds, could not satisfy the board during the oral proceedings that the new documents were not relevant. Accordingly, on the criterion of relevance, which has been the prime criterion hitherto used by the boards of appeal for admitting new documents into the proceedings, these new documents should be allowed into the proceedings. Moreover, the content of documents (D17) and (D18) is deemed to be well known to the respondent since these publications are both co-authored by the inventors of the patent in suit. Therefore, the board does not consider that the filing of these documents might have taken the respondent by surprise.

Substantive issues

General remark

6. For the sake of expediency, the discussion in respect of the requests considered to be unallowable will be confined to the first issue that arises on the claims of that request considered in numerical order, in respect of which the board considers that the requirements of the EPC are not met. Reasons for any remaining claim being regarded as allowable, despite the arguments of the appellant to the contrary, will be confined to the New Second Auxiliary Request.

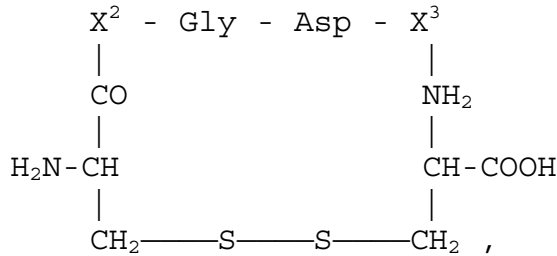
Main Request

Novelty

Claim 13

7. Document (D1) discloses linear peptides of formula $X^1-X^2\text{-Gly-Asp-}X^3\text{-}X^4$ wherein X^2 may be Arg (see page 2, lines 43-50), and hence containing an Arg-Gly-Asp motif. It is further stated on page 3, lines 9 to 19 that if X^1

= X² = Cys, these linear peptides may be cyclized via the two cysteines to yield cyclic peptides of formula:



wherein X² represents a residue of L-Arg or D-Arg and X³ represents a residue of L-Trp, D-Trp, L-Leu, D-Leu, L-Ile, D-Ile, L-Phe or D-Phe or a chain containing 2 or 3 of these residues.

8. The above class of cyclic compounds known from document (D1) thus falls under the general formula in claim 13 of the main request. In the case of a generic formula vs. another generic formula, the same principles apply for the assessment of novelty as in other cases, e.g. it has to be decided which subject-matter has been made available to the public by a prior art disclosure and thus forms part of the state of the art. In the present case, it is true that the specifically described examples in document (D1) do not disclose the preparation of particular cyclic compounds within the class defined by general formula disclosed on page 3, lines 10-19 of that document. However, the skilled person would inevitably arrive at such compounds by following the suggestion in document (D1) to cyclize the corresponding linear peptide via the two cysteines, using his/her common general knowledge that this can be done e.g. by oxidation, so that the disclosure of document (D1) is not confined to the exemplified compounds, but extends to the general formula on page 3

of this document falling under claim 13 at issue, which thus lack novelty (see e.g. decision T 124/87, OJ EPO 1989, 491 and "Case Law of the Boards of Appeal of the European Patent Office", 4th Edition 2001, pages 77-78).

9. The main request is therefore refused.

Auxiliary Request I

Article 56 EPC

Claim 1

Closest prior art

10. In accordance with the problem and solution approach, the closest prior art which provides the best starting point for assessing inventive step should be prior art relating to subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (cf. "Case Law", 4th edition 2001, Chapter I.D.3).

11. The invention according to claim 1 aims at obtaining a biological effect, namely the alteration of the Arg-Gly-Asp receptor specificity and/or binding affinity of an Arg-Gly-Asp containing peptide. In the board's view, the closest prior art is represented by documents (D9) and (D17) which both address the question of the specificity of the interaction between the various Arg-Gly-Asp proteins and the corresponding receptors and teach (see document (D9), page 517, 1-h column and document (D17), page 492, end of 1-h column) that Arg-Gly-Asp proteins such as fibronectin or vitronectin

bind to the corresponding receptors via the Arg-Gly-Asp motif.

Problem to be solved

12. The relevant question is whether or not the solution proposed in the claim for altering the Arg-Gly-Asp receptor specificity and/or binding affinity, namely restricting the conformation of the Arg-Gly-Asp sequence in said peptide in comparison to a linear peptide having an analogous sequence, follows in an obvious manner from the prior art.

13. On page 518, l-h column, penultimate paragraph of document (D9), two hypotheses are formulated for explaining the specificity of the interaction between the various Arg-Gly-Asp proteins and the corresponding receptors: (i) the specificity is generated by a second binding site in the protein or (ii) the Arg-Gly-Asp motif contains all the information needed and the role of the surrounding sequences would be to force the Arg-Gly-Asp determinant into an appropriate conformation for the receptor to recognize. According to document (D9) (see page 518, r-h column, lines 3-8) this second hypothesis of the conformation-dependent recognition finds support in the work of Wilson et al., PNAS, 82, 5255-5259 (1985), showing that peptides with identical sequences can assume totally unrelated conformations in different proteins and these conformations are recognized by unique antibodies.

14. Document (D17) (see page 495, l-h column, last full paragraph), published a few months before the earliest priority date of the patent in suit, refers again to

- hypotheses (i) and (ii) above. However, it also states that "recent data support the latter possibility", i.e. the conformation-dependent recognition hypothesis (ii) above. Moreover, according to document (D17), hypothesis (ii) is in agreement with the observation that Arg-Gly-Asp sequences assume different conformations in different proteins as illustrated in Figure 5, which shows three molecular models of the Arg-Gly-Asp sequences derived from the crystalline structures from three Arg-Gly-Asp proteins having different conformations.
15. The respondent argues that many prior art documents pleaded for the "second binding site" theory (i) above (document (D9), page 518, 1-h, last full paragraph: "...the specificity is generated by a second binding site specific for each protein."; document (D6), page 591, 1-h column, lines 5-6: "...the contribution of other non-Arg-Gly-Asp-dependent collagen-binding proteins..."; document (D8), page 16162, 1-h column, lines 9-10: "...another sequence..."); document (D17), page 495, 1-h column, last paragraph, first two lines).
16. However, in the board's judgement, a skilled person wishing to achieve the biological effect stated in claim 1 and coming across documents (D9) and (D17), would consider that the "conformation-activity" hypothesis (ii), a theory buttressed by substantial experimental evidence, is more plausible than the unproven "second binding site" hypothesis (i).
17. Hence, the solution proposed in claim 1, namely restricting the conformation of the Arg-Gly-Asp sequence in said peptide in comparison to a linear

- peptide having an analogous sequence, *prima facie* follows in an obvious manner from the stronger hypothesis (ii) above, according to which the claimed biological effect can be achieved by "**forcing** the Arg-Gly-Asp determinant into an appropriate conformation" (emphasis by the board).
18. Much emphasis has been placed by the respondent on the fact that one cannot equate conformation restriction with the 3-D structure (natural folding) of a protein, e.g. the "conformation of the molecule" (see document (D8), page 16162, line 9) does not necessarily imply any restriction of the conformation of the Arg-Gly-Asp sequence in said protein.
19. However, the board is not convinced by this line of argument. According to document (D6) (see page 590, r-h column, under "Discussion"), recognition of collagen by receptors requires the presence of Arg-Gly-Asp sequences within a triple helix conformation, as denatured collagen does not bind. This shows that the whole protein molecule serves as a 3-D scaffolding which holds the active site (Arg-Gly-Asp) in a "constrained" conformation. This view is supported by the patent in suit, according to which the formation of a triple helical structure (see Example III) or of an alpha helical structure (see Example IV) are expedients for obtaining conformationally constrained Arg-Gly-Asp sequences.
20. To support his case further, the respondent relies on post-published document (D13) as expert opinion, according to which the Arg-Gly-Asp sequence may be located in a highly flexible region of an overall rigid

(folded) protein (see page 328, last paragraph). In the board's view, however, the fact that an Arg-Gly-Asp sequence is present in a highly flexible loop does not mean that it is not "constrained" within the loop according to the broad definition of this term given in the patent in suit (see page 5, lines 3-7) that an Arg-Gly-Asp binding site is "constrained" if the chemical structures surrounding it limit the possible structural conformations thereof to less than those assumable by the tripeptide sequence alone.

21. A further respondent's argument is that document (D17) (see page 495, l-h column, lines 10-12 of the last full paragraph) emphasizes the importance of the contribution to the receptor binding strength made by residues adjacent to the Arg-Gly-Asp sequence, this view finding further support in documents (D12) and (D18). However, in the sentence following the passage cited by the respondent, the authors of document (D17) state that "... the conformation would be the **main** factor in determining the ligand binding..." (emphasis by the board). As for post-published documents (D12) and (D18), they do not reflect the skilled person's knowledge before the priority date of the patent at issue.

22. For these reasons claim 1 of Auxiliary Request I does not satisfy the requirements of Article 56 EPC. This request is thus rejected.

New Second Auxiliary Request
Article 123(2) EPC

23. The appellant questions the feature in claims 1 and 5 "at an at least 10-fold lower molar concentration" as

being an unallowable generalization, while "at least" has no basis in the application as filed.

It is true that the above "10-fold" language is cited in connection with a defined peptide (see page 14, second full paragraph of the published application WO 89/05150). However, the skilled person taking the application as a whole would understand that it is a general feature not confined to an exemplified compound. This is because it is expressly stated on page 9, last paragraph of the published application WO 89/05150 as filed that the binding behaviour of this specific peptide is an illustration "by way of example" of the advantageous technical effect of the invention.

As regards "at least", this feature can be derived from Figure 2 of the patent application, showing that the first and second curves from the left are shifted by a factor 10 or more, as measured on the logarithmic abscissa (see point 28 *infra*).

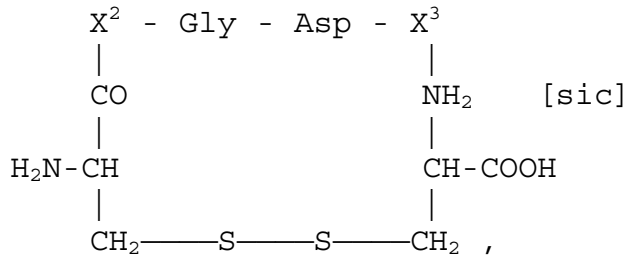
In conclusion, the feature "at an at least 10-fold lower molar concentration" does not infringe Article 123(2) EPC.

Claim 5

Allowability of the disclaimer under Article 123(2) EPC

24. In claim 5 of this request, a delimitation of the claimed subject matter from the teachings of document (D1) is made by introducing into the claim the disclaimer:

"...with the proviso that the peptide is not



where

- X² represents a residue of L-Arg or D-Arg,
- X³ represents a residue of L-Trp, N-Trp [sic], L-Leu, D-Leu, L-Ile, D-Ile, L-Phe, D-Phe or a chain containing 2 or 3 of these residues."

In accordance with the Enlarged Board of Appeal decision G 1/03 (*supra*), a disclaimer which has not been disclosed in the application as filed may be used to restore novelty by delimiting a claim against state of the art under Article 54(3) EPC. The present disclaimer [wherein "N-Trp" (X³) and "NH₂" (right part of the cyclic formula) appear to be typing errors for "D-Trp" and "NH", respectively (see document (D1), page 2, line 52 and page 3)] excludes cyclic structures known from conflicting application (D1), which inherently possess the claimed specificity. The scope of the disclaimer is no wider than that necessary to restore novelty over document (D1). For instance, some D-amino acids are also disclaimed in view of the possibility that the claimed peptides comprise enantiomeric forms of the naturally occurring amino acids such as D-Arg (see page 9, first full-paragraph of the published application WO 89/05150). Accordingly, the disclaimer fulfils the criteria stated in points 2.6.5 and 3 of the Enlarged Board of Appeal

decision G 1/03 (*supra*). It is, thus, concluded that this disclaimer is allowable under Article 123(2) EPC.

Article 123(3) EPC

Claim 1

25. Granted claim 1 was to a "method of making an Arg-Gly-Asp containing peptide with an altered Arg-Gly-Asp receptor specificity and/or binding affinity". Claim 1 of this request is now directed to a "method of altering the Arg-Gly-Asp receptor specificity and/or binding affinity of an Arg-Gly-Asp containing peptide". In the appellant's view, the method as granted comprised two steps, namely the synthesis of a linear peptide and the change of its conformation (see Examples I (cf. "synthesis"), II (cf. "cyclizing") and IV of the patent), whereas the method now claimed no longer requires the step of synthesis of the linear peptide, so that anybody cyclizing an already synthesized linear peptide would infringe claim 1 of this request.
26. However, the board does not interpret granted claim 1 as being restricted to a two-step method consisting of synthesizing the peptide and then changing its conformation. Rather, it also covered the possibility of directly starting from a natural or previously synthesized Arg-Gly-Asp containing peptide and changing its conformation. Thus, claim 1 of this request does not extend the protection conferred by the granted patent and is allowable under Article 123(3) EPC.

Article 84 EPC

27. The appellant maintains that the terms "ineffective", "at least 10-fold", "inhibits attachment" referred to in claims 1 and 5 lack clarity and that it is not clear to the skilled person which biological test should be used for measuring these parameters or which kind of cyclization should be used.
28. The biological assay referred to in claims 1 and 5 is the cell adhesion assay disclosed in detail in Example V of the patent in suit. This assay is also known from the prior art cited on page 7, lines 38-39 of the patent (Ruoslahti et al., Meth. Enz. Vol. 82, pages 803-ff (1982)) and in document (D6), page 586, r-h column, under "Cell attachment assay". The purpose of the cell adhesion assay is to measure the ability of the cyclic vs. the linear peptide (of the same length) to inhibit adhesion of normal rat kidney cells to the fibronectin and vitronectin substrates. The results are plotted in a graph as shown in Figure 2 of the patent. Four sigmoidal curves are obtained, relating to the percent maximum cell attachment to the vitronectin (first and second curves from the left) and to the fibronectin (third and fourth curves from the left) receptor vs. the concentration of the added cyclic or linear peptides. The first and second curves from the left turn out to be shifted and the distance corresponds to a factor 10 or more (see "0.1" and "1.0" on the logarithmic abscissa): this is what is meant by the expression in claim 1: "... wherein the cyclic peptide inhibits attachment of kidney cells to vitronectin at an at least 10-fold lower molar concentration than the linear peptide...". It can also

be derived from Figure 2 that the cyclic peptide fails to inhibit the attachment of kidney cells to the fibronectin receptor at these concentrations ("0.1" and "1.0"), although some inhibition takes place at very high cyclic peptide concentrations (cf. "...but is ineffective at inhibiting binding of fibronectin to the fibronectin receptor" in claims 1 and 5).

29. Therefore, the skilled person being well acquainted with the cell adhesion assay and the terms "ineffective", "at least 10-fold", "inhibits attachment" referred to in claims 1 and 5, is able to measure these parameters and to establish whether a given cyclic peptide behaves as required by claims 1 and 5.

30. As for which kind of cyclization should be used, the skilled person may turn to document (D10) disclosing on page 194 cyclization via an amide bond (see "15"), via an ϵ -amino of Lys and a C-terminal (see "16") or via a disulfide (see "19").

Claim 5

Allowability of the disclaimer under Article 84 EPC

31. Relying on decision G 1/03 (*supra*) the appellant maintains that the disclaimer in claim 5 is not allowable under Article 84 EPC because the necessary limitation over document (D1) could have been expressed in simpler positive features. However, the appellant has not shown that a simpler way for excluding the cyclic structures known from conflicting application (D1) exists, and the board also sees none. Rather to

the contrary, it seems that a "positive" delimitation would lead to an undesirable complex claim construction.

32. The board concludes that no case has been made out that the claims lack clarity.

Novelty

Claim 1

33. The relevant question is whether or not any prior art document discloses the correlation between cyclizing an Arg-Gly-Asp containing peptide and the change in biological activity stated in claim 1.

34. Regardless of whether this correlation might have been "inherent" somewhere upon carrying out some prior art methods, the question to be decided under Article 54(2) EPC is what has been "made available" to the public, not what may have been "inherent" in what was made available to the public (see e.g. decision G 2/88, OJ EPO 1990, 93, point 10.1).

35. It is the board's view that none of the documents published before the first claimed priority date of the patent in suit teaches the skilled person any correlation between cyclizing an Arg-Gly-Asp containing peptide and the change in biological activity stated in claim 1. Thus claim 1 is novel.

Claim 5

36. In order to re-establish novelty, the complete teaching of document (D1), a document under Article 54(3) EPC, which would overlap with the subject matter of claim 5 without a disclaimer has been removed by way of

disclaimer. The latter excludes structures known from document (D1) (see point 24 *supra*) which the respondent does not dispute to inherently possess the claimed specificity.

37. In view of the foregoing the board concludes that claims 1 and 5 of the New Second Auxiliary Request satisfy the requirement of Article 54 EPC. This conclusion also extends to claims 2 to 4 and 6 to 13, relying on the novel method of claim 1 or novel peptide of claim 5.

Inventive step

Closest prior art

38. The invention according to claim 1 of this request aims at obtaining a biological effect, namely the alteration of the Arg-Gly-Asp receptor specificity and/or binding affinity of an Arg-Gly-Asp containing peptide so that the peptide inhibits attachment of rat kidney cells to vitronectin at an at least 10-fold lower molar concentration than the linear peptide, while being ineffective at inhibiting binding of fibronectin to the fibronectin receptor.

Unlike the situation dealt with under point 10 *supra*, no document of the prior art serves the purpose or objective of "switching" the Arg-Gly-Asp receptor specificity and/or binding affinity of an Arg-Gly-Asp containing peptide in the above way.

39. *A fortiori*, none of the prior art documents can suggest to the skilled person any correlation between cyclizing an Arg-Gly-Asp containing peptide and the "switch" in

receptor specificity/binding activity stated in claim 1. Therefore, the subject matter of claim 1 appears *prima facie* to involve an inventive step.

40. The appellant argues that the claimed technical effect has not been demonstrated because (i) the patent in suit fails to compare a cyclized peptide with a linear peptide having the same amino acid sequence as required by claim 1, (ii) test report (D20) shows that cyclization of the decapeptide Gly-Pen-Gly-Arg-Gly-Asp-Ser-Pro-Cys-Ala and the des-Ala analog does not achieve any change in specificity/binding affinity, nor any restriction of the conformation and (iii) the claimed technical effect has not been demonstrated in the whole area covered by claim 1, e.g. for large peptides of 500 amino acids.
41. As for (i) above, there is indeed a discrepancy between the cyclic and the linear peptide used in the cell adhesion assay disclosed in the patent in suit. The cyclic peptide is Gly-Pen-Gly-Arg-Gly-Asp-Ser-Pro-Cys-Ala prepared according to Example II, whereas the linear peptide is Gly-Pen-Gly-Arg-Gly-Asp-Ser-Pro-Cys (see page 8, line 5) lacking the C-terminal Ala residue. It is also stated (*ibidem*) that the results of this cell adhesion assay are illustrated in Figure 2.

However, the discrepancy noted by the appellant has to be balanced with the passage under the heading "Brief Description of the Drawing" on page 4 of the patent in suit, from which it can be derived that the cell adhesion assay illustrated by Figure 2 has been performed in the presence of a cyclic and a linear

peptide having the same amino acid sequence (see line 48).

It is also unlikely that the C-terminal Ala of the decapeptide Gly-Pen-Gly-Arg-Gly-Asp-Ser-Pro-Cys-Ala (see Example I) went lost upon a mild oxidation of the sulfhydryls with $K_3[Fe(CN)_6]$ (see Example II, line 44 and page 5, line 55 to page 6, line 1).

42. The appellant relies on post-published document (D18) as expert opinion. If anything, this document would rather support the view the board has come to that the cell adhesion assay illustrated by Figure 2 has been performed in the presence of a cyclic and a linear peptide having the same amino acid sequence (see page 17297, 1-h column, line 2: "...than did the **same** peptide before cyclization..."; emphasis by the board).
43. As regards (ii) above, the negative results of test report (D20) by Prof. H. Kessler seem to contradict the positive results illustrated in Table I on page 20235 of document (D16) and in Table I on page 61 of document (D12), both co-authored by Prof. H. Kessler.
44. As for (iii) above, the compounds referred to in claim 1 are no 500 amino acid-long proteins but rather peptides of between 3 and 100 amino acids (see page 3, line 57 of the patent in suit). But a 72 amino acid-long peptide such as trigramin (see document (D8), page 16162, 1-h column, end-note) is able to inhibit fibrinogen binding to its receptor owing to its "constrained" (presence of disulfide bridges) Arg-Gly-Asp-containing structure: this shows that also large peptides may exhibit the required specificity. In any

- case the skilled person is able to establish whether a given cyclic peptide, regardless of its size, behaves as required by claim 1 (see point 29 *supra*).
45. In conclusion the board is satisfied that performing the method of claim 1 achieves the claimed technical effect shown in Example V and Figure 2 of the patent in suit.
46. The appellant argues that the passage bridging the l-h and the r-h columns on page 518 of document (D9) taken in the light of document (D10) (see page 197, last paragraph: cyclization achieves an increase in specificity for a particular receptor) renders the claimed method obvious.
47. However, the passage cited by the appellant merely deals with explaining why a synthetic peptide derived from fibronectin or an 108-amino acid fragment of fibronectin reacts better with the vitronectin receptor than with the fibronectin receptor. It is postulated that a switch in the conformation of these Arg-Gly-Asp containing peptides takes place. Even assuming that this would suggest to a skilled person (knowing from document (D10) (*ibidem*) that cyclization achieves an increase in specificity for a particular receptor) a correlation between cyclizing an Arg-Gly-Asp containing peptide and the "switch" in receptor specificity/binding activity, there is no suggestion in these documents that this "switch" would go into the direction of the specificity defined in claim 1.
48. The appellant also relies on the "10-fold" figure on page 493, l-h column, line 9 of document (D17). However,

this "10-fold" figure turns up in the context of "...the decrease in binding affinity...for the vitronectin receptor..."(see lines 5 to 8). Therefore it goes in the opposite direction to the increase in vitronectin affinity defined in claim 1.

49. In view of the foregoing, the subject matter of claim 1 satisfies the requirements of Article 56 EPC.

50. The board's conclusions arrived at under points 38 to 39 *supra* also apply *mutatis mutandis* to the cyclized peptide of claim 5, exhibiting the biological activity recited in claim 1. The subject matter of claim 5 thus also does not follow from the prior art in an obvious manner, document (D1) being a document according to Article 54(3) EPC. This conclusion also extends to the subject matter of claims 2 to 4 and 6 to 13, relying on the inventive method of claim 1 or peptide of claim 5.

Apportionment of costs (Article 104(1) EPC)

51. Having regard to the board's considerations indicated above (see point 5 *supra*) concluding that in applying the criteria developed by the boards of appeal for deciding on the admissibility of late-filed documents, the introduction of documents (D17) and (D18) into the proceedings did not point towards circumstances that would amount to an abuse of the proceedings, to an excessive delay in the proceedings, or to the respondent being taken by surprise, there is no reason of equity as required by Article 104(1) EPC, which would justify an apportionment of costs in the respondent's favour.

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 in amended form on the basis of claims 1 to 13 of the New Second Auxiliary Request filed in the oral proceedings of 19 January 2005 and a description to be adapted thereto.
3. The request of the respondent for apportionment of costs is refused.

Registrar:

Chair:

P. Cremona

U. M. Kinkeldey