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D E C I S I O N
of 8 May 2006

Case Number: T 1074/03 - 3.3.08

Application Number: 94902224.8

Publication Number: 0675953

IPC: C12N 15/10

Language of the proceedings: EN

Title of invention:
Soluble peptides having constrained, secondary conformation in solution and method of making same

Applicant:
Ixsys, Inc.

Opponent:
-

Headword:
Soluble peptides/IXSYS

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - (yes)"

Decisions cited:
T 0195/84

Catchword:
-

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Case Number: T 1074/03 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 8 May 2006

Appellant: (Applicant)
IXSYS
3550 General Atomics Court
Suite L-103
San Diego, CA 92121 (US)

Representative:
Ingham, Stephen
European Patent Operations
Eli Lilly and Company Limited
Lilly Research Centre
Erl Wood Manor
Sunninghill Road Windlesham GU20 6PH (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 29 April 2003 refusing European application No. 94902224.8 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent application No. 94 902224.8 published under the International Publication No. WO 94/11496 with the title: "Soluble peptides having constrained, secondary conformation in solution and method of making same" was refused by the examining division.

II. The reason given for this refusal was that the claimed subject-matter lacked inventive step over the combination of the general teaching that the introduction of constraints within peptides generally increases affinity to a given binding partner (as exemplified in document (2) or (5)) with the notion of randomized peptide libraries as in document (1).

III. The appellant (applicant) filed a notice of appeal against this decision, paid the appeal fee and submitted a statement of grounds of appeal with the request that the same claims as refused by the examining division be considered.

IV. The appealed decision was not rectified by the examining division and the case was remitted to the board of appeal (Art. 109(2) EPC).

V. The board sent a communication pursuant to Article 110(2) EPC raising a number of objections under Articles 123(2) and 84 EPC against the claim request on file.

VI. On 27 February 2006, the appellant filed a further submission in answer to this communication together with a new claim request to replace the previous one.

VII. In a telephone conversation which took place on 14 March 2006, the rapporteur informed the appellant's representative that further amendments were needed for the new claim request to be considered to comply with the requirements of Articles 123(2) and 84 EPC.

VIII. In reply thereto, the appellant filed a new claim request (claims 1 to 38) on 19 April 2006. Independent claims 1, 9, 19, 25 and 32 read as follows:

"1. A composition comprising a plurality of cells containing a diverse population of expressible oligonucleotides contained within vectors, each of said oligonucleotides encoding a peptide, said oligonucleotides containing randomized codons and at least two codons encoding amino acids capable of forming a covalent bond that is not a backbone peptide bond, wherein each of said oligonucleotides is operationally linked to expression elements contained within each vector.

9. A composition comprising a plurality of cells containing a diverse population of expressible oligonucleotides contained within vectors, each of said oligonucleotides encoding a peptide, said oligonucleotides containing at least two codons encoding amino acids capable of forming a covalent bond that is not a backbone peptide bond, wherein each of said oligonucleotides is operationally linked to expression elements contained within each vector, said expressible oligonucleotides containing random codon sequences produced from random combination of first and second oligonucleotide precursor populations, each or

either of said first and second oligonucleotide precursors containing random codon sequences.

19. A method of constructing vectors containing a diverse population of expressible oligonucleotides, comprising:

(a) operationally linking sequences from a diverse population of first precursor oligonucleotides to a first vector, said first vector having a cloning site for a population of first precursor oligonucleotides and a pair of restriction sites for operationally combining said first precursor oligonucleotides with a population of second precursor oligonucleotides;

(b) operationally linking sequences from a diverse population of second precursor oligonucleotides to a second vector, said second vector having a cloning site for said second precursor oligonucleotides and a pair of restriction sites complementary to those on said first vector, one or both vectors containing expression elements capable of being operationally linked to said first and second precursor oligonucleotides, wherein said first or second precursor oligonucleotides have at least two codons encoding amino acids capable of forming a covalent bond that is not a backbone peptide bond, or said first and second precursor oligonucleotides have at least one codon encoding an amino acid capable of forming a covalent bond that is not a backbone peptide bond, wherein each or either of said first and second precursor oligonucleotides contain random codon sequences;

(c) combining the vector products of step (a) and (b) under conditions where said populations of first and second precursor oligonucleotides are joined together into a population of combined vectors containing said diverse population of expressible oligonucleotides.

25. A cloning system comprising a set of first vectors containing a diverse population of first precursor oligonucleotides and a second set of vectors containing a diverse population of second precursor oligonucleotides, wherein said first or second precursor oligonucleotides have at least two codons encoding amino acids capable of forming a covalent bond that is not a backbone peptide bond, or said first and second precursor oligonucleotides have at least one codon capable of forming a covalent bond that is not a backbone peptide bond, said first and second vectors each having a pair of restriction sites allowing the operational combination of said oligonucleotides into a contiguous oligonucleotide encoding a peptide, wherein each or either of said first or second precursor oligonucleotides contain random codon sequences.

32. A population of vectors comprising a diverse population of expressible oligonucleotides, each of said oligonucleotides encoding a peptide, said oligonucleotides containing randomized codons and at least two codons, encoding amino acids capable of forming a covalent bond that is not a backbone peptide bond, wherein each of said oligonucleotide is operationally linked to expression elements contained within each vector."

Dependent claims 2 to 8, 10 to 18, 20 to 24, 26 to 30 related to further features of respectively the compositions of claims 1 or 9, the method of claim 19 and the cloning system of claim 25. Claim 31 related to host cells containing the cloning system of claims 25 to 30. Dependent claims 33 to 37 related to further features of the population of vectors of claim 32. Claim 38 related to host cells containing the population of vectors of any one of claims 32 to 37.

IX. The following documents are mentioned in the present decision:

(1): WO 92/06176;

(2): Jemmerson, R. and Hutchinson, R.M., Eur.J.Immunol., Vol.20, pages 579 to 585, 1990;

(5): Pierschbacher, M.D. and Ruoslahti, E., J. Biol.Chem., Vol. 262, No.36, pages 17294 to 17298, December 1987;

(6): O'Neil, K.T. et al., PROTEINS: Structure, Function, and Genetics, Vol.14, pages 509 to 515, December 1992;

(8): Hruby, V.J. et al., Biochem.J., Vol. 268, pages 249 to 262, 1990.

X. The appellant's arguments may be summarized as follows:

Article 56 EPC; inventive step

The decision of the examining division that the claimed invention was obvious in the light of the combined teachings of document (1) with documents (2) or (5) was based on hindsight. Specifically, the person skilled in the art would not have combined these teachings in the expectation of some improvement or advantage of the claimed libraries over the libraries of document (1).

Document (2) did not contain the information that higher binding properties would be provided through the introduction of constraints within a peptide (see, in particular, page 579, right-hand column, Figure 4). Document (5) related to the preparation of single cyclic RGD containing peptides (passage bridging pages 17296 and 17297) but did not provide generalizable information. Indeed, the authors found that although the cyclic peptide was able to inhibit cell attachment to fibronectin at a lower molar concentration than the linear peptide, no inhibition was observed with respect to vibronectin where the linear peptide was effective (Figure 5).

If no generalizable predictions could be made with respect to the binding properties of a single peptide, how could the skilled artisan make any predictions with respect to a plurality of cyclic peptides ?

Furthermore, post-published document (6) emphasized the potential of phage peptide libraries for the identification of pharmaceutically active lead compounds. It confirmed that the library of cyclic peptides provided many more clones that bound test

receptor than the library containing linear peptides (page 152).

For these reasons, the claimed subject-matter involved an inventive step.

XI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the request filed on 19 April 2006.

Reasons for the decision

Claim request filed on 19 April 2006

Articles 123(2) and 84 EPC; amendments; clarity and support in the description.

1. In its notice of appeal, the appellant had requested that a patent be granted on the basis of the same claim request as was refused by the examining division. This request comprising 63 claims had been filed on 11 February 2003 with submissions which clearly identified the passages in the application as filed which served as basis for the claimed subject-matter (Section II of these submissions, Table of concordance). The claim request filed on 19 April 2006 now for consideration is distinctly different from the claim request refused by the examining division. It contains 38 claims, 31 claims were deleted, independent claim 32 and dependent claims 2, 10, 20, 26 and 33 were added. Some of the claims which were retained from the set of claims dated 11 February 2003 were amended.

2. A basis for the amendments is found in the following passages of the application as filed:

   - The feature in claims 1, 9 and 19 that the expressible oligonucleotides are contained within vectors is found eg. in the passage bridging pages 19 and 20 and on pages 21 to 24.

   - The feature in claims 1, 9, 11, 12, 19, 25, 32 that the covalent bound is not a backbone peptide bond is mentioned on page 11.

   - The feature in claims 22, 28 and 35 that the expressible oligonucleotides are expressible as peptide fusion proteins on the surface of a filamentous bacteriophage is mentioned eg. in the passage bridging pages 27 and 28 and original claim 36.

3. New independent claim 32 (Section VIII, supra) finds a basis in particular in the passage bridging pages 19 and 20. New dependent claims 2, 10, 20 ,26 and 33 respectively relating to cell compositions/a method for constructing vectors/ a cloning system/ a population of vectors comprising expressible oligonucleotides all encoding peptides of the same length find a basis in the description of the method used to produce the compositions on pages 12 and 13, in the passage bridging pages 21 and 22, on page 22 and in the passage bridging pages 27 and 28.

4. Moreover, in the board's judgment, the claimed subject-matter is clear and supported by the description.

5. The requirements of Articles 123(2) and 84 EPC are, thus, fulfilled.

Articles 54, 57 and 83 EPC; novelty, industrial applicability and sufficiency of disclosure

6. There are no documents on file describing a plurality of cells containing a population of expressible oligonucleotides with the now claimed features, namely contained within vectors and encoding peptides wherein at least two codons encode amino acids capable of forming a covalent bond that is not a backbone peptide bond. Nor is a method or a cloning system or a population of vectors, for producing the said expressible oligonucleotides, disclosed. Novelty is acknowledged.

7. Industrial applicability is to be seen in the field of producing peptides having biologically useful binding affinities. One way to test their properties is described on page 28, lines 24 to 34. The high affinity of some peptides expressed from randomly synthesized oligonucleotides for anti-tetanus toxin antibody is disclosed in Example VII. The requirements of Article 57 EPC are fulfilled.

8. The successive steps which need to be carried out to obtain a composition such as claimed are described in detail from pages 6 to 28. Examples are provided to illustrate these steps. In the absence of any evidence to the contrary, the board concludes that the requirements of Article 83 EPC are fulfilled.

Article 56 EPC; inventive step of the subject-matter of claim 1

9. The closest prior art is document (1) which teaches the production of a DNA library (composition) which contains the population of oligonucleotides which encodes **all** peptides of a certain given length which can "theoretically" be made from the 20 natural amino acids. Each peptide resulting from the expression of these oligonucleotides, of course, adopts a secondary structure in solution (linear, circular etc...) which depends, in particular, on the nature of the amino acids it contains. From pages 48 to 54 of the description, it is explained how to retrieve from the composition those recombinant vectors (recombinant filamentous phages) which contain oligonucleotides expressing peptides which are capable of binding a protein of interest (protein-binding ligands). The ultimate aim of the work is expressed on page 5 as: *"The oligonucleotides produced are therefore useful for generating an unlimited amount of pharmaceutical and research products."*

10. Starting from the closest prior art, the problem to be solved can be defined as producing another population of oligonucleotides encoding peptides biologically useful as protein-binding ligands.

11. Neither document (1) nor any of the other documents on file (which, in any case, are not concerned with high-scale recombinant production of protein-binding ligands) suggest the possibility of obtaining another such population. Yet, taking into account that it is the normal task of the skilled person to be constantly

occupied with furthering the existing state of the art (see, eg, T 195/84, OJ EPO 1986, 121), the formulation of this problem is per se obvious.

12. The solution proposed in the present case is a composition comprising a plurality of cells containing a diverse population of oligonucleotides which contain randomized codons but, unlike those described in document (1), all of them contain at least two codons encoding amino acids capable of forming a covalent bond other than the peptidic bond. Otherwise stated, the provided solution is a population of oligonucleotides wherein **all** oligonucleotides encode peptides which have the potential of adopting a constrained secondary structure by cyclization.

13. At the priority date, it was already known that changing the conformation of a peptide may alter its affinity for its ligand. Document (8) is a review of the kind of alterations which had been envisaged (see, in particular, the passage bridging pages 249 and 250). Isolating a cyclic analogue was only one of the many available methods. Enantiomeric substitutions of one or more amino acid residues, changes in the chemistry of one residue, varying the size of the peptide were also commonly carried out by chemical synthesis starting with the knowledge of the sequence of the relevant peptide.

14. In the art, there was document (2) which presents a study of the inhibitory capacity of analogues to residues 41-48 of horse CytC on the binding of an anti-41-48 monoclonal antibody to the peptide 41-48. On page 582 (right-hand column, last paragraph), it is

described that: "*The cyclized dimer of Cys-41-48 Cys was about 80-fold* ***less effective*** *than the reduced and alkylated form in binding the anti-41-48 antibodies,.... The cyclized monomer was about* ***1200-fold less*** *effective than the reduced and alkylated form.*" (emphasis added by the board) but it is also disclosed on page 584 (right-hand column, last paragraph) in relation to bovine myoglobin that *"the cyclized peptide 26-54 was about 1000-fold* ***more effective*** *at binding anti-myoglobin antibodies than was the uncyclized peptide"* (emphasis added by the board). As for document (5), it relates to the influence of stereochemistry of the sequence Arg-Glu-Asp-Xaa in the binding specificity in cell adhesion. It is mentioned in the passage bridging pages 17296 and 17297: "*When the cyclic peptide from HPLC fraction 2 was tested for its ability to inhibit cell adhesion, it was* ***found to inhibit*** *attachment to vitronectin at a ten-fold lower molar concentration than did the same peptide before cyclisation, but it was* ***ineffective at inhibiting*** *attachment to fibronectin"* (emphasis added by the board). In the last paragraph, on page 17297, it is emphasized how cyclization of a peptide can have an opposite effect on its binding capacity depending on the protein it is meant to bind to.

15. In summary, the overall teaching of the state of the art at the priority date was that many different chemical alterations could be envisaged as means to provide a "better" peptide analogue and also, most importantly, that each and every kind of alterations had to be tested separately for each and every peptide as it could not be predicted from the existing bulk of

data which alteration would give which effect or even that an alteration would have any effect.

16. In contrast, the present invention enables the specific choice of isolating cyclic analogues and allows to test all of them "in one go" for their protein-binding capacity. This is undoubtedly a great simplification of the task of identifying protein-binding ligands.

17. Document (6) provides post-published evidence that many more protein-binding peptides are expressed from the oligonucleotide library encoding cyclic peptides than from the one encoding linear peptides. On page 512, right-hand column, it is stated that: *"As shown in Table I, the second round of selection yielded a 500-fold increase in the percentage of phage recovered from the C-X6-C library* (circular) *as compared to the X6 library* (linear)*. This suggest the C-X6-C library gives rise to far more clones that bound to the IIb/IIIa receptor."* (qualifications in brackets added by the board for better understanding).

18. For the reasons developed in points 9 to 17, the board concludes that the composition of claim 1 provides the hitherto unforeseeable possibility of producing in high yields peptides suited as protein-binding ligands. Inventive step is, thus, acknowledged in the subject-matter of said claim.

19. Independent claims 9, 19, 25 and 32 respectively relate to a further cell composition/a method of constructing vectors/a cloning system/ a population of vectors, containing expressible oligonucleotides which are all capable of adopting a constrained secondary structure.

Their subject-matter is inventive for the same reasons as given in relation to that of claim 1.

20. The requirements for patentability under the EPC are fulfilled by the claim request filed on 19 April 2006.

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 grant a patent on the basis of:

   - claims 1 to 38 filed with the submissions dated 19 April 2006, and

   - a description to be adapted thereto, and

   - Figures 1 to 10 as originally filed.

The Registrar: The Chairman:

A. Wolinski L. Galligani