BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Publication in the Official Journal ~~Yes~~ / No

File Number: W 31/91 - 3.3.2

Application No.: PCT/US90/06483

Publication No.: WO 9107483

Title of invention: Mammalian Pancreatic Cholesterol Esterase

Classification: C12N 9/18

D E C I S I O N
of 20 December 1991

Applicant: LANGE, Louis George III et al.

Headword:

PCT Article 17(3)(a) and Rules 13 and 40

Keyword: "Non-unity a posteriori - yes"

Headnote

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Case Number : W 31/91 - 3.3.2
International Application No. PCT/US90/06483

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 20 December 1991

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Subject of the Decision : Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fee) of the European Patent Office (branch at The Hague) dated 25 March 1991.

Composition of the Board :

Chairman : P.A.M. Lançon
Members : U. Kinkeldey
F. Benussi

Summary of Facts and Submissions

I. The applicant filed an international patent application PCT/US 90/06483 with 24 claims.

Claims 1, 2 and 3 read as follows:

"1. A method for purifying useful quantities of a mammalian pancreatic cholesterol esterase to homogeneity, the method comprising the following steps:

(a) loading a solution comprising the cholesterol esterase onto a sulfated matrix, wherein the concentration of salt and the pH of the solution comprising the cholesterol esterase is sufficient to allow the cholesterol esterase to bind the sulfated matrix and benzamidine is included in the solution to inhibit proteolysis;

(b) removing non-binding protein impurities by washing the matrix with a solution comprising a concentration of salt and pH sufficient to allow continued binding of the cholesterol esterase to the matrix; and

(c) eluting the cholesterol esterase from the matrix by washing the matrix with a solution comprising a concentration of salt and pH sufficient to inhibit binding of the cholesterol esterase to the matrix.

2. A homogeneous composition of a 72 kilodalton bovine pancreatic cholesterol esterase or derivative thereof, wherein the amino acid sequence of the cholesterol esterase or derivative thereof, comprises a sequence shown in Figure 1.

3. A homogeneous composition of a mammalian pancreatic cholesterol esterase purified according to the method of Claim 1."

Claim 4 relates to DNA sequences encoding a mammalian pancreatic cholesterol esterase;

Claims 10, 11 and 12 are independent process claims relating to the production of cholesterol esterase by expression of a respective gene in a prokaryotic cell culture and lysing the cells (Claim 10), in a prokaryotic cell culture and collecting the supernatant (Claim 11) and in a eukaryotic cell (Claim 12);

Claim 13 relates to the production of antibodies;

Claim 15 relates to a method of screening inhibitors of a mammalian pancreatic cholesterol esterase;

Claim 17 relates to a method for modifying the ester composition of foodstuffs;

Claim 20 relates to certain oligopeptides.

II. The EPO acting as an International Search Authority (ISA) sent to the Applicant an invitation to pay five additional search fees pursuant to Article 17(3)(a) and Rule 40.1 PCT.

III. The invitation stated that claims to a product, claims concerning derivatives in direct relation with the claimed product, different (new) uses of said product and/or close derivatives were to be considered as being part of the same inventive concept, if the product is new. In view of the prior art cited in the partial search report (patent document WO 89/08456), the claimed product was not new, so that the above-mentioned application related to the following groups of subject-matter which did not satisfy the criteria of unity of invention:

1. Claims 1 to 3:
Method for purifying a mammalian pancreatic cholesterol esterase; homogeneous composition of said protein.

2. Claims 4 to 12:
DNA sequences encoding a mammalian pancreatic cholesterol esterase; cloning vector and expression in a host cell.

3. Claims 13 to 14:
Production of antibodies to a mammalian pancreatic cholesterol esterase.

4. Claims 15 to 16:
Method for screening inhibitors of a mammalian pancreatic cholesterol esterase.

5. Claims 17 to 19:
Method for modifying the ester composition of foodstuffs by action of the cholesterol esterase.

6. Claims 20 to 23:
Oligopeptides binding to sulfated agents that bind to and do/do not inhibit human pancreatic cholesterol esterase and uses of said oligopeptides.

Claim 24 which relates to non-patentable subject-matter was not searched, in accordance with Rule 39.1(iv) PCT.

IV. The Applicant paid the additional fees under protest pursuant to Rule 40.2(c) PCT. In support of the protest, the Applicant submitted that the claimed product should be considered new, in view of the fact that the method for purifying pancreatic cholesterol esterase described in the

instant application was not the same as, nor equivalent to, the method described in WO 89/08456. In particular, the invention disclosed the use of sulfated matrices which were not equivalent to the heparin-Sepharose used in WO 89/08456. The sulfated matrices of the invention gave faster and less expensive purification, together with a purification factor five to ten fold greater. Only the purification factor attained with the method of the invention allowed for the first time the preparation of a sufficient amount of an adequately pure quantity of pancreatic cholesterol esterase to permit amino acid sequencing and hence, the cloning and expression of cDNA coding for cholesterol esterase and the different uses of the cholesterol esterase thus produced, as claimed in Claims 4 to 23.

Reasons for the Decision

1. The protest is admissible.

2. According to Rule 13.1 PCT, the international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. If the ISA considers that the claims lack this unity, it is empowered, under Article 17(3)(a) PCT, to invite the Applicant to pay additional fees.

3. Lack of unity may be directly evident "a priori", i.e. before considering the claims in relation to any prior art. Alternatively, having regard to decision G 1/89 of the Enlarged Board of Appeal, dated 2 May 1990 (OJ EPO 1991, 155), the ISA is also empowered to raise an objection a posteriori, i.e. after having taken the prior art into consideration. The Enlarged Board indicated that this represented only a provisional opinion on novelty and

inventive step which was in no way binding upon the authorities subsequently responsible for the substantive examination of the application (point 8.1 of the grounds for the decision).

However, the Enlarged Board in point 8.2 of the reasons mentioned that such invitation to pay additional fees should always be made with a view to giving the Applicant fair treatment and should only be made in clear cases.

4. The invitation to pay additional fees cites patent document WO 89/08456 for considering that the subject-matter of Claims 1, 2 and 3 is not novel. Although the reasons for the invitation given by the ISA are stringent the Board concludes that they may be considered to be sufficient within the meaning of Rule 40.1 PCT.

5. Document WO 89/08456 cited by the ISA discloses on page 6, lines 23 to 32 a general method for the isolation and purification of pancreatic cholesterol esterase that results in homogeneous enzyme from human, porcine, or rat pancreas, said method relying upon the observation that cholesterol esterase binds to heparin-Sepharose, heparin being a sulfated agent. The addition of benzamidine to the solution to inhibit proteolysis is disclosed in the prior art document on page 6, lines 29 and 30 and the elution of the cholesterol esterase from the matrix is, for example, disclosed on page 7, lines 10 and 11. A more detailed disclosure of the method of purifying pancreatic cholesterol esterase by binding it on heparine-agarose and removing impurities by washing and adding benzamidine and finally eluting 90% of the applied cholesterol esterase activity is provided in document WO 89/08456 on page 12 in Example I.

6. Compared with this prior art, the method of Claim 1 of the present application, relating to the provision of purified pancreatic cholesterol esterase by a purification process by binding the cholesterol esterase onto a sulfated matrix, and adding benzamidine to inhibit proteolysis, the removing of impurities and eluting the cholesterol esterase, can be regarded as being anticipated.

7. The Applicants emphasised in their protest that the present invention utilised sulfated matrices which were different from heparin-Sepharose. However, the description of the present patent application defines on page 6, lines 31 to 33 heparine-agarose as a most preferred embodiment to be used as the affinity matrix as claimed in Claim 1. As mentioned above, it is also heparine-agarose which is disclosed in document WO 89/08456.

8. The Board thus does not follow the argument put forward by the Applicants that purifying pancreatic cholesterol esterase as described in the instant application is not the same as the method described in WO 89/08456.

9. Claims 2 and 3 relate to a homogeneous composition of cholesterol esterase, defined by its amino acid sequence and the process of Claim 1 respectively.

Claim 3, being worded as "product-by-process" claim, relates to a product being purified by the method of Claim 1, which is the same as that disclosed in document WO89/08456 (see above points 5-7). One may assume that same processes result in same products. Claim 3 consequently may be regarded as being anticipated by document WO89/08456.

Claim 2, being an independent product claim relates to a more narrowly defined 72 kilodalton bovine pancreatic cholesterol esterase specified by its amino acid sequence.

It is comprised in the "homogenous composition" claimed in Claim 3, which is anticipated by document WO 89/08456.

10. The reasoning given by the ISA in its invitation that Claims 1 to 3 are anticipated by document WO 89/08456 may be confirmed at that stage of proceedings.

11. It now should be considered whether or not the remaining claims nevertheless could possibly represent one single inventive concept. This second requirement for the examination of unity has already been developed in detail in a decision of the Board of Appeal W 10/89 of 27 September 1991.

12. The problem to be solved in the light of document WO 89/08456 can be seen in providing alternative means for producing homogeneous cholesterol esterase. A solution to this problem is represented by the product of Claim 4, relating to a DNA sequence comprising a nucleotide sequence encoding a mammalian pancreatic esterase.

13. Claims 5 to 12, relating to DNA sequences, cloning vectors, cell cultures transformed with the vectors and the processes for expression may be considered as to belong to a single inventive concept, if product Claim 4 is patentable.

14. Document WO89/08456 does not relate to the production of cholesterol esterase by a recombinant DNA technique, as analysed above. The provision of DNA sequences and vectors containing them (Claims 4-7), cell cultures producing cholesterol esterase and the actual expression of pancreatic cholesterol esterase in a prokaryotic cell (Claims 10 and 11) or eukaryotic cell (Claim 12) may be considered to be novel. Whether or not these claims are also inventive in the light of the prior art mentioned is

certainly a question which cannot be answered easily and clearly and, therefore, the Board considers this situation as being the one which is addressed in the Enlarged Board of Appeal's decision mentioned above where restraint should be applied in objecting non-unity to give the Applicants fair treatment.

The Board concludes, thus, that the ISA correctly grouped Claims 4 to 12 in one single group of invention.

15. It remains to be considered whether the ISA's grouping of Claims 13 to 14, 15 and 16, 17 to 19 and 20 to 23 in four further groups of invention is correct.

The subject-matter of the four groups as claimed established by the ISA could be considered as being linked to a common inventive concept, within the meaning of Rule 13.1 PCT, if a highly homogeneous and pure pancreatic cholesterol esterase were novel. A homogeneous pancreatic cholesterol esterase being suitable for the methods and subject-matters claimed in groups 3 to 6, was already provided by the method for purifying pancreatic cholesterol esterase utilising sulfated matrices. This process, and the respective product, however, was shown not to be novel over the prior art document WO 89/08456. The homogeneously purified pancreatic cholesterol esterase belonging to the state of the art, thus cannot be the connecting link causing a single inventive concept for the remaining claims.

16. With regard to the prior art document WO 89/08456 the Board defines for each subject-matter mentioned in groups 3 to 6 different problems. These different problems become apparent from the definition of the subject-matter of the certain groups as correctly carried out by the ISA (see paragraph III above). The Board further cannot

recognise a common link between the solutions, be it by a structure or an effect (see decision W 6/90, OJ EPO 1991, 439). These criteria, which may serve for an examination of unity are also not fulfilled by the subject-matters mentioned in groups 3 to 6.

Thus, the claims grouped by the ISA in groups 2 to 6 do not represent one single general inventive concept but rather represent those different groups of invention as identified by the ISA and, therefore, the invitation by the ISA to pay five additional search fees was justified.

Order

For these reasons, it is decided that:

The protest according to Rule 40.2(c) PCT is dismissed.

The Registrar: The Chairman:

P. Martorana P. Lançon