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File Number: W 41/90 - 3.3.2

Application No.: PCT/EP 90/00617

Publication No.: WO 90/12879

Title of invention: Expression of human apolipoprotein AI-Milano in yeast and pharmaceutical compositions containing them

Classification: C12N 15/81

D E C I S I O N
of 16 December 1991

Applicant: SIRTORI, Cesare

Headword: Apolipoprotein/SIRTORI

PCT: Article 17(3)(a) and Rules 13.1 and 40.1

Keyword: "Non-unity a posteriori (no) - Deficient reasons in the invitation - No evidence for lack of novelty"

Headnote



Case Number : W 41/90 - 3.3.2
International Application No. PCT/EP 90/00617

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 16 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 2 July 1991.

Composition of the Board :

Chairman : P. Lançon
Members : U. Kinkeldey
C. Holtz

Summary of Facts and Submissions

- I. The applicants filed international patent application PCT/EP 90/00617 with ten claims.

Claims 1, 2 and 6 read as follows:

"1. An expression vector capable of expressing, in a transformed yeast, apolipoprotein AI and apolipoprotein AI-M (Milano) comprising a promoter sequence autologous to the yeast to be transformed, a DNA sequence coding for Apo AI or Apo AI-M, a sequence coding for a leader peptide able to induce secretion of the expression product in the culture medium, a transcription terminator sequence autologous to the yeasts to be transformed.

2. An expression vector according to claim 1 wherein the leader sequence is the modified MF α 1 leader sequence encoding for the residue His Gly Ser Leu Asp Lys Arg."

6. A DNA sequence coding for apolipoprotein AI-Milano obtainable by:

- a) amplification of the fragment between nucleotides 1792- and 2240 of DNA coding for Apo AI using as primers the synthetic oligonucleotides of formula

5'-CTGAGGCAAGAGATGAGCAA-3';

5'-CTCAGGAAGCTGACCTTGAA-3';

- b) digestion of the fragment obtained in a) with the restriction enzymes Xho II and StuI;
c) ligation of the fragment obtained in b) with the fragments 1-1791 and 2241-2396."

- II. The EPO acting as an International Search Authority (ISA) sent to the applicants an invitation to pay an additional search fee in accordance with Article 17(3)(a) and Rule 40.1 PCT. In this invitation the ISA stated that the

application did not comply with the requirements of unity of invention but related to the following two groups of invention:

"1. Claims 1;3 (part.); 6;7-10 (part.):

A yeast expression vector comprising a promoter sequence, an Apo AI(-MI) sequence, a leader sequence and a transcription terminator.

Host yeast transformed with this expression vector.

DNA sequence coding for apolipoprotein AI-Milano.

Protein obtainable from this host.

Pharmaceutical compositions.

2. Claims 2;3 (part.); 4;5;7-10 (part.):

A yeast expression vector comprising a promoter sequence, an Apo AI(-MI) sequence, a MODIFIED MF-alpha leader sequence and a transcription terminator. Synthetic DNA encoding the MODIFIED MF-alpha leader/Apo AI junction.

Host yeast transformed with this expression vector.

Protein obtainable from this host.

Pharmaceutical compositions."

The consideration of these two groups of inventions was based on an a posteriori objection of unity in the light of the prior art document WO 87/02062 from which already was known an expression vector for the production of apolipoprotein AI(-M) in yeast, comprising a promoter sequence, an Apo AI sequence, a leader sequence and a transcription terminator.

III. The applicant paid the additional search fee under protest, stating that Claim 2, defining a more restricted scope of the invention, namely the use of a particular

leader sequence, did not represent a separate invention. It was not believed that a complete new search was to be carried out only for one element characterising the expression vector disclosed in the application and claimed in Claim 1. A search on the expression of apolipoproteins in yeast had certainly already covered the particular aspect of the leader sequence. It was understood that the leader sequence of Claim 2 could possibly also be used for expression of proteins other than apolipoproteins, but this was of no relevance to the present invention, since it was otherwise known that leader sequences did not have general applicability. The request for payment of a complete additional search fee was thus excessive, in particular because the references for the natural, unmodified leader sequence were already cited in the specification.

Reasons for the Decision

1. The protest is admissible.

2. Non-unity "a posteriori" was considered in the light of the disclosure of the prior art document WO 87/02067 with the result that there were two inventions, the one being essentially represented by Claims 1 and 6, directed to the expression of certain apolipoproteins as such and the other one represented essentially by Claims 2, 4 and 5 being directed to a certain modified leader sequence. As it was held in a decision of the Enlarged Board of Appeal (G 1/89, OJ EPO 1991, 155), such an "a posteriori" consideration, however, should only be applied with a view to giving the applicant fair treatment and that additional fees should only be charged in clear cases.

3. The invitation does not contain any detailed information concerning the specific parts of the cited document which could be detrimental to the patentability of Claim 1, finally the invitation does not set out why the case should be regarded as clear within the meaning of the above-mentioned decision of the Enlarged Board of Appeal.
4. It has been repeatedly decided (see e.g. W 4/85, OJ EPO 1987, 63 and W 7/86, OJ EPO 1987, 67 among many other decisions) that only in very exceptional and clear cases the reasoning of an invitation may be based on mere allegations without being sufficiently detailed to be readily understood by the person to whom it is addressed without further investigations and assumptions.
5. From the reasons of the invitation given by the ISA, using the words "... was known ..." the Board concludes that the invitation is based on the sole ground that the search has revealed a document which was regarded as prejudicial to novelty of the subject-matter of Claim 1 of the application.

Claim 1 of the application under consideration refers to an expression vector capable of expressing, in a transformed yeast two different genes coding for apolipoprotein AI and apolipoprotein AI-M and containing certain regulatory elements. Claim 2 relates to a developed regulatory element, namely the leader sequence. Claim 6 relates to a DNA sequence coding for apolipoprotein AI-M, defined by its process to be prepared and thus, like Claim 2, represents a certain embodiment of one element contained in Claim 1.

6. Document WO 87/02062, cited by the ISA in support of the stated non-unity, relates to recombinant apolipoproteins and methods and, according to Example V, (which was not

mentioned by the ISA in its reasons of the invitation to pay an additional fee but at least is mentioned in the search report), to the construction and expression of apolipoprotein AI in yeast. From a careful analysis of Example V which is the only place in the document dealing with expression in yeast and thus of possible relevance for the question of novelty, it is apparent that the gene for apolipoprotein AI is not complete but rather is missing the first seven, N-terminal amino acids. There is no mention in the whole document of the apolipoprotein AI-M. It is thus clear that Claim 1 of the present application is novel with regard to document WO 87/02062.

7. Since the reasons given in the invitation are focused on a novelty objection only (see point 5 above) and since the Board came to a different result as to the novelty question the protest is justified and the fee has to be refunded.

Order

For these reasons, it is decided that:

Refund of the additional search fee is ordered.

The Registrar:

The Chairman:

P. Martorana

P. Lançon