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Datasheet for the decision of 30 January 2014

Case Number: T 2394/10 - 3.3.08

Application Number: 99125406.1

Publication Number: 1013765

IPC: C12N15/31, C12N1/21, C07K14/245, C12P13/06, C12P13/08

Language of the proceedings: EN

Title of invention:
Method for producing L-amino acids

Patent Proprietor:
Ajinomoto Co., Inc.

Opponent:
Evonik Degussa GmbH

Headword:
Producing L-amino acids/AJINOMOTO

Relevant legal provisions:
EPC Art. 84, 54(3), 56

Keyword:
Main request - requirements of the EPC met (yes)
Referral of questions to the EBA (no)

Decisions cited:
T 0459/09

Catchword:

Europäisches Patentamt
European Patent Office
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Case Number: T 2394/10 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 30 January 2014

Appellant: (Patent Proprietor)	Ajinomoto Co., Inc. 15-1, Kyobashi 1-chome, Chuo-ku Tokyo (JP)
Representative:	Tack J. Strehl Schübel-Hopf & Partner Maximilianstrasse 54 80538 München (DE)
Respondent: (Opponent)	Ioannidis J. Evonik Degussa GmbH Intellectual Property Rodenbacher Chaussee 4 63457 Hanau (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 29 September 2010 revoking European patent No. 1013765 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: M. Wieser
Members: B. Stolz
D. Rogers

Summary of Facts and Submissions

I. The patent proprietor (appellant) filed an appeal against the decision of the opposition division to revoke European patent No. 1013765. The opposition division decided that the main request before it lacked novelty (Article 54 EPC), that auxiliary request 1 did not meet the requirements of Article 84 EPC, and that auxiliary request 2 lacked an inventive step (Article 56 EPC).

II. With its grounds of appeal, the appellant filed a new main request and two auxiliary requests.

III. The opponent (respondent) submitted its observations.

IV. The parties were summoned to oral proceedings. A communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to the summons, informed them of the preliminary non-binding opinion of the board on some of the issues of the appeal proceedings.

V. In letters dated 30 December 2013, respectively, both parties submitted their final observations.

VI. Oral proceedings were held on 30 January 2014. In the course of the proceedings, the appellant filed a new main request and withdrew all requests previously on file.

VII. The patent in suit discloses methods for the production of amino acids by E. coli having enhanced activity of a protein termed RhtC (SEQ ID NOs: 3 and 4) or of RhtC in combination with RhtB (SEQ ID NOs: 1 and 2).

VIII. Independent claim 1 of the main request reads as follows:

"1. A method for producing the amino acid L-homoserine or L-threonine comprising the steps of:
cultivating a bacterium, which has the ability to produce the amino acid, in a culture medium, to produce and accumulate the amino acid in the medium, and
recovering the amino acid from the medium, said bacterium belonging to the genus Escherichia, wherein L-threonine resistance of said bacterium is enhanced by enhancing the activity of a protein as defined in the following (A) or (B) in the cells of said bacterium:
(A) a protein which comprises the amino acid sequence shown in SEQ ID NO: 4 in Sequence Listing; or
(B) a protein which comprises the amino acid sequence including deletion, substitution, insertion or addition of one or several amino acids in the amino acid sequence shown in SEQ ID NO: 4 in Sequence Listing, and which has the activity of making a bacterium having the protein L-threonine-resistant,

wherein the protein is encoded by a DNA which is defined in the following (a) or(b):
(a) a DNA which comprises the nucleotide sequence of nucleotide numbers 187 to 804 in SEQ ID NO: 3;
(b) a DNA which hybridizes with a nucleotide sequence of nucleotide numbers 187 to 804 in SEQ ID NO: 3 under a stringent condition and which codes for a protein having the

activity of making a bacterium having the protein L-threonine-resistant, wherein the stringent condition is a condition in which washing is performed at 60°C and at a salt concentration corresponding to 1 x SSC and 0.1 % SDS."

IX. Independent claim 4 comprises all features of claim 1 and the following addition:

"and wherein the L-homoserine resistance of said bacterium is further enhanced by enhancing the activity of a protein as defined in the following (C) or (D) in the cells of said bacterium:

(C) a protein which comprises the amino acid sequence shown in SEQ ID NO: 2 in Sequence Listing; or

(D) a protein which comprises the amino acid sequence including deletion, substitution, insertion or addition of one or several amino acids in the amino acid sequence shown in SEQ ID NO: 2 in Sequence Listing, and which has the activity of making a bacterium having the protein L-homoserine-resistant."

X. Dependent claims 2 and 3 refer to specific embodiments of the method of claim 1, and dependent claims 5 to 7 refer to specific embodiments of the method of claim 4.

XI. The following documents are cited in this decision:

D1: EP 994 190

D4: Zakataeva et al., Faseb Journal 11(9) 31 July 1997, page A935

D9: Sequence alignment rhtB and rhtC, submitted by patent proprietor with letter dated 11 May 2010

XII. The arguments of the appellant, as far as relevant for the present decision, can be summarized as follows:

Article 84 EPC

Part (b) of claim 1 was unambiguous and referred to double stranded DNA. Moreover, according to the case law of the boards of appeal, the objection under Article 84 EPC was not admissible since the wording of part (b) was unaltered and identical to the wording of dependent claim 6 as granted.

Article 54(3) EPC

Document D4 disclosed rhtB but not rhtC as defined in claim 1. Furthermore, document D4 did not disclose a process of producing amino acids using rhtC.

Article 56 EPC

Document D4, the closest prior art, related to the same technical field, the production of amino acids in the presence of high concentrations of homoserine and threonine, but did not disclose a method of producing amino acids using an enhanced protein RhtC. The technical problem could be defined as providing an improved method for the production of amino acids. The claimed solution was inventive because D4 contained no indication of a further resistance mechanism to threonine and homoserine. All other documents cited did not contribute anything that would have directed the skilled person to the claimed solution. Therefore,

respondent's argument that the skilled person would have expected a further gene conferring this property was flawed.

XIII. The arguments of the respondent, as far as relevant for the present decision, can be summarized as follows:

Article 84 EPC

Feature (b) of claim 1 was unclear because a strand of nucleic acid hybridizing with SEQ ID NO: 3 was antisense to SEQ ID NO: 3 and not coding for a protein with the claimed function. It was therefore unclear whether feature (b) envisaged only proteins encoded by the strand complementary to SEQ ID NO: 3.

The objection on the basis of Article 84 EPC was admissible even if the amendment resulted from the incorporation of features of dependent claim 6 into independent claim 1. In the light of decision T 459/09 of 13 December 2012, the only relevant question, when deciding on the admissibility of an objection under Article 84 EPC, was whether the amendment was substantial, which was always the case if the amendment served the purpose of overcoming an objection based on Article 100 EPC.

The following questions should be referred to the Enlarged Board of Appeal, in case the board disagreed with this view:

"1. Are the opposition division and - in case of an appeal - the board of appeal empowered to examine an amended claim with respect to the requirement of clarity (Art. 101 (3) EPC in combination with Art. 84 EPC), if the amended claim is the mere result of the

combination of the feature(s) of a dependent claim with the feature(s) of an independent claim, those dependent and independent claim being comprised by the patent as granted?

2. If question 1 is answered affirmatively: Is it admissible to examine the amended claim with respect to clarity regardless of the kind of amendments effected by the combination or are there any other prerequisites for the amendments to be fulfilled, so that the amended claim is considered as examinable with respect to clarity?"

Article 54(3) EPC

Document D1 disclosed plasmid pNZ46 comprising genes rhtB and o128. Gene o128 was identical with rhtC, and strains of E. coli used for cloning of the plasmid pNZ46 had therefore enhanced RhtB and RhtC activity. When these strains were cultivated, they secreted amino acids. Thus, claims 1 and 4 lacked novelty.

Article 56 EPC

Starting from document D4 which disclosed methods for increasing the production of threonine, the technical problem was seen in the provision of an alternative method of producing amino acids. The claimed solution was obvious, no more efficient than the solution disclosed in document D4, and thus not inventive. The skilled person, knowing from document D4 that two threonine transporters had already been located in the genome of E. coli and that genes with similar function were frequently found within a single regulon, would have screened the immediate upstream region of rhtB for the presence of a further gene encoding a threonine

exporter. In doing so, he would would have arrived at the claimed solution in an obvious way.

XIV. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the claims of the Main Request and pages 2 to 16 of the amended description, both filed at the oral proceedings before the Board of Appeal on 30 January 2014.

XV. The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The main request filed at the oral proceedings corresponds to auxiliary request II filed with the grounds of appeal. Claim 1 is a combination of claims 1, 3 and 6 as granted, and claim 4 is a combination of claims 1, 2 and 6 as granted. The opponent has not raised any objections concerning admissibility of this request and the amendments clearly aim at overcoming objections raised in the decision under appeal. The request is, therefore, admitted into the procedure.

Article 123(2),(3) EPC

2. The respondent did not raise any objections under the provisions of Articles 123(2) and (3) EPC and the board has no reason to do so on its own.

Article 84 EPC

3. The respondent submitted that the meaning of feature (b) of claims 1 and 4, referring to

"a DNA which hybridizes with a nucleotide sequence of nucleotide numbers 187 to 804 in SEQ ID NO: 3 under a stringent condition and which codes for a protein having the activity of making a bacterium having the protein L-threonine-resistant"

was unclear because the strand of a nucleic acid hybridizing with the nucleotide sequence defined by SEQ ID NO: 3 was an antisense strand which did not encode a functional protein. The skilled person was thus left in the dark as to what molecules were encompassed by the claims.

4. Feature (b) of claims 1 and 4 refers to a DNA (molecule) which hybridizes with the nucleotide sequence defined by SEQ ID NO:3 under the indicated conditions and which encodes a protein making the bacterium L-threonine resistant.

The skilled person performing a hybridization experiment knows that the antisense strand of the DNA molecule to be tested hybridizes with the sense strand of the DNA defined by SEQ ID NO: 3 (and vice versa for the respective complementary strands). The antisense strand of the test molecule is derived from a double stranded DNA molecule, and there can be no doubt that the DNA molecule referred to in claim 1(b) comprises not only an antisense strand hybridizing under stringent conditions with the sense strand of the DNA molecule defined by SEQ ID NO: 3 but also a sense strand with a high degree of sequence identity with SEQ ID NO: 3 which encodes a structurally related protein. The language of claim 1, referring to a DNA (molecule), is unambiguous in this respect and leaves no room for the respondent's interpretation that what is claimed is a protein encoded by the antisense strand of a test

molecule hybridizing with the nucleotide sequence comprising nucleotide numbers 187 to 804 of SEQ ID NO: 3.

5. The appellant argued that the objection under Article 84 EPC was not admissible at all because the alleged clarity problem arose from the incorporation of dependent claim 6 as granted into claim 1 as granted.

6. The respondent on the other hand, referring to decision T 459/09 of 13 December 2012, argued that the amendment in claim 1 was substantial and performed in order to overcome an objection in the framework of Article 100 EPC which justified an unrestricted examination. The respondent requested that certain questions of law be referred to the Enlarged Board of Appeal, should the board not be in a position to follow respondent's view.

7. Since the wording of claim 1 is clear (cf. point 4, above), this objection is substantially without merit. As it has no further consequences for the present case, the question whether the board is competent to examine the clarity of feature (b) of claim 1 at all can be left unanswered and there is no need to refer questions of law to the Enlarged Board of Appeal.

Article 54(3) EPC

8. The respondent raised a novelty objection against claim 1 in view of document D1 disclosing a gene encoding protein RhtB which provides enhanced L-homoserine resistance.

9. Document D1 enjoys the priority date of 13 October 1998, its filing date is 20 September 1999 and it was

published on 19 April 2000. The opposed patent enjoys a priority date of 23 December 1998, and the application was filed on 20 December 1999. Document D1 is thus prior art pursuant to Article 54(3) EPC.

10. As shown in document D9, filed by the appellant in opposition proceedings, the nucleic acid sequence of rhtB is about 47% identical to the nucleic acid sequence of rhtC (SEQ ID NO: 3 of the patent under appeal), and the longest uninterrupted stretch of matching sequence is only 8 base pairs in length. No evidence has been presented, that rhtB, having only 47% identity with Seq ID NO: 3 over 596 base pairs, would hybridize under the stringent conditions specified in claim 1, and the skilled person would not expect it to do so.

11. In the process of isolating rhtB from the genome of E. coli, document D1 discloses the construction of cloning vectors which comprised additional nucleic acid sequence upstream of rhtB. The gene encoding protein RhtC (Seq ID NO. 3 of the present invention) is located in this additional sequence. The only vector construct comprising rhtC and rhtB, pNPZ46, was selected only for providing increased resistance to L-homoserine (Fig. 1 of document 1). It was however not inserted into E. coli for the production of amino acids.

12. According to established case law of the boards of appeal, the purpose of a claim referring to a method is a technical feature which has to be taken into account when assessing patentability requirements (Case Law of the Boards of Appeal, 7th edition, 2013, I.C.6.3.1).

Since, according to document D1, only rhtB, which does not fall within the definition of nucleic acid sequences according to feature (b) of claim 1, was expressed in E. coli for the purpose of producing L-threonine and/or L-homoserine, the disclosure in this document does not anticipate the subject matter of claim 1.

Article 56 EPC

13. Document D4, a conference abstract, represents the closest prior art. It discloses a mutation in the chromosome of E. coli, termed rhtA23, conferring resistance to high concentrations of L-homoserine and L-threonine. Two types of inserts belonging to different chromosome regions were cloned from both rhtA23 and wild-type cells on the basis of their ability to confer resistance to L-homoserine and L-threonine. On the basis of these experiments it was concluded that E. coli comprised at least two genes, termed rhtA and rhtB, respectively, which when present in multicopy conferred resistance to L-threonine and L-homoserine. The two genes were mapped at 18.3 and 86 minutes, respectively, on the E. coli chromosome.

14. The technical problem underlying the invention is seen in the provision of alternative methods for the production of amino acids.

15. For the solution of this problem, claim 1 proposes the use of Escherichia strains comprising enhanced activity of a protein defined by Seq ID 4 (RhtC) or of a protein encoded by a DNA sequence comprising the nucleotide sequence of Seq ID 3 or hybridizing to it under the conditions specified in claim 1. Claim 4 proposes the use of a protein as defined in claim 1 in combination

with a protein defined by SEQ ID NO: 2 (RhtB) or a protein derived from SEQ ID NO: 2.

16. The results shown in Tables 2, 4 and 5 of the patent in suit demonstrate that the solutions proposed by claims 1 and 4 solve the underlying problem.

17. It remains to be established if the claimed solutions involve an inventive step.

18. Respondent's objection is in essence based on document D4 in combination with the general knowledge. It argued that, since document D4 already disclosed two genes, it would not have required inventive skills to find a further gene in E. coli which when overexpressed rendered the strain resistant to increased concentrations of L-homoserine or L-threonine. The most obvious place to look for such a gene would be the upstream region of the gene rhtB because genes with similar functions were frequently found in the same regulon, i.e. in close physical proximity.

19. According to the established case law, the question to be asked in respect of inventive step is not whether the person skilled in the art could have carried out the invention and arrived at the claimed solution, but whether the skilled person would have done so in the hope of solving the underlying technical problem, or in the expectation of some improvement or advantage. So the point is not whether the skilled person could have arrived at the invention by modifying the prior art, but rather whether, in expectation of the advantages achieved (i.e. in the light of the technical problem addressed), he would have done so because of promptings in the prior art. (Case Law of the Boards of Appeal, 7th edition, 2013, I.D.5)).

20. Apart from the map position indicated as 18.3 minutes, document D4 provides no technical information, such as a nucleic acid sequence, that would have informed the skilled person about the molecular structure of the rhtB gene itself or its immediate upstream sequence. Neither document D4 nor any of the further documents on file contain a pointer to the presence of a further gene on the chromosome of E. coli conferring the desired properties. It is correct that the fact that two genes from E. coli with similar function were already known does not rule out the possible presence of yet a further gene with similar function. However, in the absence of any technical evidence, this assumption is purely speculative and leaves the skilled person without a reasonable expectation of success.

Moreover, the two genes disclosed in document D4 are located in different parts on the chromosome of E. coli, at 18.3 and 86 minutes, respectively. This fact contradicts respondent's argument that it would have been obvious to screen the immediate vicinity of rhtB because genes of similar function were often found in close vicinity. Even if the skilled person would have looked in E. coli for a further gene with similar function, for which it had no incentive or motivation, any additional gene might as well have been located in the proximity of the second locus, or in a completely different, independent locus.

21. In the absence of any pointer in document D4 to the presence of a further gene conferring the desired properties, the claimed solution is not obvious. Therefore, the board decides that the subject matter of claim 1 is based on an inventive step. In consequence, the subject matter of claim 4, which encompasses all

features of claim 1, and of all the dependent claims, is also based on an inventive step.

Adaptation of the description

22. At the oral proceedings, the appellant submitted amended pages 2 to 16 of the description to bring it in line with the main request. The board is satisfied that this has been done in agreement with the requirements of the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent as amended in the following version:

Description: pages 2-16 filed at the oral proceedings before the Board on 30 January 2014.

Figures: 1-4 of the patent as granted.

Claims: Claims 1 to 7 of the Main Request filed at the oral proceedings before the Board on 30 January 2014.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated