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Datasheet for the decision of 13 August 2020

Case Number: T 1726/15 - 3.3.08

Application Number: 05775484.8

Publication Number: 1778831

IPC: C12N1/15

Language of the proceedings: EN

Title of invention:
GENETICALLY MODIFIED HOST CELLS AND USE OF SAME FOR PRODUCING ISOPRENOID COMPOUNDS

Patent Proprietor:
The Regents of the University of California

Opponent:
Maiwald Patent- und Rechtsanwaltsgesellschaft mbH

Headword:
Heterologous FPPS/UNIVERSITY OF CALIFORNIA

Relevant legal provisions:
EPC Art. 123(2), 123(3)

Keyword:
Main request - extended scope of protection (yes)
Auxiliary request 1 - admission into the proceedings (yes)
Added matter (yes)

Decisions cited:
T 1018/02

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1726/15 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 13 August 2020

Appellant: (Opponent)	Maiwald Patent- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstrasse 3 80335 München (DE)
Representative:	Lasar, Andrea Gisela Maiwald Patentanwalts- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Respondent: (Patent Proprietor)	The Regents of the University of California 1111 Franklin Street, 12th Floor Oakland, CA 94607 (US)
Representative:	Hayes, Emily A.L. Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 18 June 2015 concerning maintenance of the European Patent No. 1778831 in amended form.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. R. Vega Laso
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 1 778 831 with the title "Genetically modified host cells and use of same for producing isoprenoid compounds" was granted based on the European application No. 05775484.8 which was filed under the Patent Cooperation Treaty and published as WO 2006/014837 (in the following "the application as filed").

II. Claim 1 of the patent as granted reads as follows:

"1. A *Saccharomyces cerevisiae* host cell that produces an isoprenoid precursor or isoprenoid compound via a mevalonate pathway, wherein said cell is genetically modified to comprise:

a) a heterologous nucleic acid integrated into the host cell's chromosome encoding a truncated 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGR) lacking a membrane-spanning domain and retaining its C-terminal catalytic domain;
b) a heterologous farnesyl diphosphate synthase (FPPS) integrated into the host cell's chromosome to increase the level of activity of said FPPS; and
c) a heterologous nucleic acid integrated into the host cell's chromosome to decrease the level of activity of squalene synthase;
wherein the host cell further comprises a heterologous sesquiterpene synthase and is capable of making an isoprenoid that is derived from the action of said sesquiterpene synthase, and
wherein the genetic modifications provide for production of the isoprenoid derived from the action of said sesquiterpene synthase at a level that is at least

50% higher than the level of the isoprenoid in a control cell not comprising the genetic modifications."

Dependent claim 2 is directed to an embodiment of the host cell of claim 1. Independent claim 3 is directed to a method of producing an isoprenoid precursor or isoprenoid compound which method comprises culturing a host cell of either claim 1 or 2, and isolating the isoprenoid precursor or isoprenoid compound from the culture medium.

III. The patent was opposed on the grounds for opposition of Article 100(a) in conjunction with Article 56 EPC, and Article 100(b) and (c) EPC.

IV. In an interlocutory decision posted on 18 June 2015, an opposition division found that Article 100(c) EPC prejudiced the maintenance of the patent as granted (main request). The amendments introduced into the claims of the auxiliary requests 1 to 3 were considered to offend against Article 123(2) EPC. However, the auxiliary request 4 then on file was found to conform to Article 123(2)(3) EPC and to fulfil the requirements of Articles 83 and 56 EPC. Hence, in the view of the opposition division the patent could be maintained on the basis of the auxiliary request 4 and an amended description filed during the oral proceedings.

V. Each of the patent proprietor (the present respondent, in view of the later withdrawal of the appeal, see section XII below) and the opponent (appellant) filed an appeal against the interlocutory decision.

VI. Together with its statement of grounds of appeal, the respondent filed nine sets of claims as respectively its main request and auxiliary requests 1 to 8 in

appeal proceedings, the claims according to the auxiliary request 5 being identical to those of the auxiliary request 4 underlying the decision under appeal.

VII. The appellant filed a statement of grounds of appeal including new evidence.

VIII. Each party replied to the grounds of appeal of the other party.

IX. Under cover of a letter dated 12 April 2016, the respondent filed an amended auxiliary request 4, and in a later submission put forward additional arguments.

X. Pursuant to their subsidiary request, the parties were summoned to oral proceedings before the board. Due to the coronavirus pandemic, the oral proceedings had to be re-scheduled.

XI. In preparation of the oral proceedings, the board issued a communication in which it expressed a provisional opinion on some procedural and substantive issues, in particular issues relating to Articles 100(c) and 123(2) EPC.

XII. Oral proceedings were held on 13 August 2020 in the presence of both parties. During the oral proceedings, the present respondent withdrew its appeal and all the sets of claims then on file, except for those of the auxiliary request 5 which became the main request. It also submitted an amended set of claims as auxiliary request 1.

XIII. Amended claim 1 according to the **main request** reads:

"1. A *Saccharomyces cerevisiae* host cell that produces an isoprenoid precursor or isoprenoid compound via a mevalonate pathway, wherein said cell is genetically modified to comprise:

a) a heterologous nucleic acid integrated into the host cell's chromosome encoding a truncated 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGR) lacking a membrane-spanning domain and retaining its C-terminal catalytic domain to increase the level of activity of said HMGR;

b) a heterologous nucleic acid encoding farnesyl diphosphate synthase (FPPS) integrated into the host cell's chromosome to increase the level of activity of said FPPS; and

c) a heterologous nucleic acid integrated into the host cell's chromosome to decrease the level of activity of squalene synthase;

wherein the host cell further comprises a heterologous nucleic acid encoding a terpene synthase and is capable of making an isoprenoid that is derived from the action of said terpene synthase, wherein the terpene synthase is selected from amorpha-4, 11 -diene synthase; beta-caryophyllene synthase; germacrene A synthase; 8-epicedrol synthase; valencene synthase; (+)delta-cadinene synthase; germacrene C synthase; (E) beta- farnesene synthase; vetispiradiene synthase; 5-epiaristolochene synthase; aristolchene synthase alpha-humulene synthase; (E,E)alpha-farnesene synthase; E-alpha-bisabolene synthase; (E)-gamma-bisabolene synthase; longifolene synthase, gamma-humulene synthase, Delta-selinene synthase, epi-cedrol synthase; alpha-zingiberene synthase; guaiadiene synthase; cascarilladiene synthase; cis-muuroladiene synthase; patchoulol synthase; and

wherein the genetic modifications provide for production of the isoprenoid derived from the action of

said terpene synthase at a level that is at least 50% higher than the level of the isoprenoid in a control cell not comprising the genetic modifications."

Claim 2 is identical to claim 3 of the patent as granted, except that it refers solely to claim 1.

XIV. Amended claim 1 of the **auxiliary request 1** differs from the corresponding claim of the main request in that item b) reads:

"...
b) a heterologous farnesyl diphosphate synthase (FPPS) integrated into the host cell's chromosome to increase the level of activity of said FPPS; and
...".

Claim 2 is identical to the corresponding claim of the main request.

XV. The submissions made by the appellant, as far as they are relevant to the present decision, were essentially as follows:

Main request - Article 123(3) EPC

The amendment introduced into feature b) of claim 1 was not allowable under Article 123(3) EPC. The amended claim required that, instead of the FPPS protein as in the granted claim, the nucleic acid encoding FPPS was integrated into the host cell's chromosome. Hence, the subject-matter of the claim had changed and an *aliud* had been created.

Admission of the auxiliary request 1 into the proceedings

The set of claims according to the auxiliary request 1 should not be admitted into the proceedings. No new issue concerning Article 123(3) EPC had been raised during the oral proceedings, only a new reasoning had been given. Moreover, the request was clearly not allowable.

Auxiliary request 1 – Article 123(2) EPC

The application as filed only disclosed host cells including heterologous nucleic acids, promoters or regulatory sequences, but did not disclose a cell expressing a heterologous FPPS protein. The disclosure of a heterologous nucleic acid could not be equated to the disclosure of the encoded protein being heterologous. The particular sub-group of heterologous nucleic acids encoding a heterologous FPPS protein was not directly and unambiguously derivable from the application as filed. Thus, Article 123(2) EPC was contravened.

XVI. The relevant submissions by the respondent were as follows:

Main request - Article 123(3) EPC

The opposition division had acknowledged that a person skilled in the art reading claim 1 would "directly and unambiguously" understand that it was the nucleic acid encoding FPPS that needed to the integrated into the host cell's chromosome to increase the level of activity of the FPPS. Thus, claim 1 of the patent as granted was to be construed as being directed to a host

cell comprising a heterologous nucleic acid encoding FPPS. Any other interpretation would not make technical sense. Hence, the scope of the amended claim 1 did not extend beyond that of the claim as granted.

Admission of the auxiliary request 1 into the proceedings

The amended claims had been filed as reaction to the discussion during the oral proceedings. They did not add any complexity to the case because the sole amendment consisted in re-introducing the wording of feature b) as in the patent as granted. Hence, the request should be admitted into the proceedings.

Auxiliary request 1 – Article 123(2) EPC

The subject-matter of claim 1 had a basis in the application as filed. It was apparent from paragraphs [0032] and [0034] combined with paragraph [0066] that a genetically modified host cell according to the invention had integrated into the genome a heterologous nucleic acid encoding FPPS. While the encoded FPPS protein could, in principle, be endogenous or heterologous, the more reasonable interpretation was that also the protein encoded by the heterologous nucleic acid was heterologous.

XVII. The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked.

XVIII. The respondent (patent proprietor) requested that the appeal be dismissed or, alternatively, that the decision under appeal be set aside and the patent be maintained on the basis of the set of claims of

auxiliary request 1 filed at the oral proceedings of 13 August 2020.

Reasons for the Decision

Main request – Article 123(3) EPC

1. The set of claims according to the present main request is identical to that of the auxiliary request 4 in opposition proceedings, which was regarded as meeting the requirements of the EPC.

2. In particular, in the decision under appeal it was found that the amendment introduced into feature b) of claim 1 of the auxiliary request 4 to replace "*a heterologous farnesyl diphosphate synthase (FPPS) integrated into the host cell's chromosome ...*" by "*a heterologous* ***nucleic acid encoding*** *farnesyl diphosphate synthase (FPPS) integrated into the host cell's chromosome ...*" (emphasis added) did not contravene Article 123(3) EPC. The opposition division considered the amendment to be the straightforward correction of an obvious error, and held that a person skilled in the art "*...could not have understood something different, since the integration of a heterologous FPPS protein into the host cell's chromosome makes no sense*" (see section 17.2 of the decision under appeal).

3. Contrary to the opposition division's view, the board holds that the amendment introduced into feature b) of claim 1 violates Article 123(3) EPC because the protection conferred by the patent so amended extends beyond the scope of protection of the patent as granted.

4. The opposition division correctly interpreted the wording "*farnesyl diphosphate synthase (FPPS)*" in claim 1 of the patent as granted as referring to a protein which has farnesyl diphosphate synthase activity. Also correct is its finding that, since the integration of a protein into the chromosome makes no technical sense, the technically sensible interpretation of feature b) in claim 1 as granted is that the nucleic acid encoding FPPS - rather than the FPPS protein - is integrated into the *Saccharomyces cerevisiae* host cell's chromosome.

5. However, the opposition division failed to notice that, while claim 1 of the patent as granted specifies a heterologous **FPPS protein**, in amended claim 1 the feature "*heterologous*" characterizes the **nucleic acid** encoding FPPS.

6. The patent specification does not include a definition of the term "heterologous protein" or the term "heterologous FPPS". The term "heterologous" referring to a protein has, however, a clear meaning in the art. In cell biology, a heterologous protein is, generally, a foreign protein, i.e. a protein that is not normally present in the host cell, and more specifically, a protein which is derived from a different organism. Hence, the explicit wording of feature b) of claim 1 of the patent as granted imparts to the skilled reader a clear, technically sensible teaching, namely that the claimed host cell is genetically modified to express a FPPS protein which is not normally present in the cell. The fact that, as stated below in connection with the auxiliary request 1, neither the patent nor the application as filed disclose such a host cell is immaterial because, in the absence of any definition of a feature, the description cannot be used to give a

different meaning to a claim feature which in itself has a clear meaning and imparts a credible technical teaching to the skilled person (see decision T 1018/02 of 9 December 2003, paragraph 3.8 of the reasons).

7. Amended feature b) in claim 1 of the present main request specifies that the nucleic acid encoding FPPS is heterologous (see section XIII above). The term "heterologous nucleic acid" is defined in paragraph [0025] of the patent as granted (paragraph [0026] of the application as filed) as follows:

> "*The term "heterologous nucleic acid," as used herein, refers to a nucleic acid wherein at least one of the following is true: (a)* [...]*; (b) the nucleic acid comprises a nucleotide sequence that is naturally found in (e.g., is "endogenous to") a given host microorganism or host cell (e.g., the nucleic acid comprises a nucleotide sequence endogenous to the host microorganism or host cell); however, in the context of a heterologous nucleic acid, the same nucleotide sequence as found endogenously is produced in an unnatural (e.g., greater than expected or greater than naturally found) amount in the cell, or a nucleic acid comprising a nucleotide sequence that differs in sequence from the endogenous nucleotide sequence but* ***encodes the same protein*** *(having the same or substantially the same amino acid sequence)* ***as found endogenously*** *is produced in an unnatural (e.g., greater than expected or greater than naturally found) amount in the cell; (c)* [...]." (emphasis added by the board)

8. Hence, in the light of the broad meaning given in the specification to the term "heterologous nucleic acid",

in particular the meaning specified under (b) in the passage quoted above, amended claim 1 encompasses not only a *S. cerevisiae* host cell having integrated a foreign nucleic acid encoding a foreign FPPS protein, but also a host cell in which the integrated foreign nucleic acid encodes the same protein present endogenously, but being produced in an "unnatural" (e.g. greater than naturally found) amount.

9. The meaning given in paragraph [0025] of the patent as granted to the term "heterologous nucleic acid" was confirmed by the respondent and is consistent also with the statements in paragraph [0066] of the patent (paragraph [0068] of the application as filed) concerning FPPS. In this passage, different embodiments of a genetically modified host cell having an increased level of FPPS activity are mentioned. Among these embodiments are, e.g., an embodiment in which the strength of the promoter to which the FPPS coding region is operably linked is increased (see page 11, line 14 of the patent as granted), and an embodiment in which the codon usage of FPPS is modified such that the level of translation of the FPPS mRNA is increased (see page 11, lines 21 and 22). In both embodiments, the encoded FPPS protein would be the endogenous FPPS protein.

10. It follows from the above that amended claim 1 encompasses subject-matter which is not encompassed by claim 1 nor by dependent claim 2 or independent claim 3 of the patent as granted, the latter being directed to a method which comprises culturing the host cell of claim 1 or 2.

11. As a consequence of this negative finding on Article 123(3) EPC, the decision under appeal must be set aside, as the appellant requested.

Admission of the auxiliary request 1 into the proceedings

12. The set of claims of the auxiliary request 1 was filed as a reaction to the discussion on Article 123(3) EPC during the oral proceedings. While an objection under this article had been raised by the appellant (see paragraph bridging pages 7 and 8 of the reply to the statement of grounds of appeal of the other party), the appellant's argument had been focused on the nature of the molecule being integrated into the host cell's chromosome (a protein vs. a nucleic acid), rather than on the term "heterologous". For this reason, the board decided to admit the set of claims of the auxiliary request 1 filed at the oral proceedings.

Auxiliary request 1 – Article 123(2) EPC

13. Feature b) in claim 1 of the auxiliary request 1 is identical to the corresponding feature in claim 1 of the patent as granted (see sections II and XIV above).

14. In the decision under appeal, the opposition division stated in connection with feature b) in claim 1 as granted that integration of the FPPS protein into the chromosome "*... indeed represents added subject-matter, but makes no sense, in particular in the context of the present invention*" (see section 13.1.2.3 of the decision).

15. The board shares the opposition division's view as regards the issue of integration into the chromosome. As stated in the board's communication in preparation

of the oral proceedings, a person skilled in the art with a mind willing to understand would immediately recognize that feature b) of claim 1 of the patent as granted cannot be read as requiring the integration of the FPPS protein into the chromosome. This, however, does not apply to the characterization of the FPPS protein as being heterologous which is a feature perfectly clear and technically sensible in the context of the claim (see paragraph 6. above). In the board's view, there is no direct and unambiguous disclosure in the application as filed of a *S. cerevisiae* host cell as claimed, in particular a host cell expressing a **heterologous FPPS protein** which is encoded by a nucleic acid integrated into the chromosome.

16. In the passages in paragraphs [0026], [0032], [0034] and [0073] of the application as filed indicated by the respondent, reference is made to a heterologous nucleic acid, but not to a heterologous FPPS protein. Such a protein is not mentioned in paragraph [0066] either. While it is technically plausible that a heterologous nucleic acid may encode a heterologous protein, this must not be necessarily the case. As a matter of fact, as regards FPPS all the embodiments disclosed in paragraph [0068] of the application as filed are embodiments in which the **endogenous** FPPS protein is produced in a genetically modified host cell. The same applies to the host cell according to claim 12 of the application as filed, in which a heterologous promoter is attached to the endogenous nucleotide sequence encoding FPPS.

17. Hence, the subject-matter of amended claim 1 extends beyond the content of the application as filed.

Conclusion

18. Since the amendments introduced into the claims according to the main request and auxiliary request 1 violate, respectively, Article 123(3) and (2) EPC, there is no set of claims on file on the basis of which the patent could be maintained.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated