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D E C I S I O N
of 1 June 2004

Case Number: T 1102/00 - 3.3.8

Application Number: 89400768.1

Publication Number: 0344024

IPC: C12N 15/81

Language of the proceedings: FR

Title of invention:

Vecteur pour l'expression des récepteurs membranaires de mammifère dans des organismes unicellulaires et procédé d'étude de ligands reconnaissant des récepteurs

Patentee:

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Opponent:

Duphar International Research B.V.

Headword:

Mammalian membrane receptors/CNRS

Relevant legal provisions:

EPC Art. 123(2), 56, 14(3)

EPC R. 1(2)

Keyword:

"Main request and auxiliary request 1 - disclaimer not allowable"

"Auxiliary requests 2 to 4 - inventive step (no)"

"Auxiliary request 5 - not admitted in the appeal proceedings"

Decisions cited:

G 0001/03, G 0002/03, J 0018/90, T 0455/91

Catchword:

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Case Number: T 1102/00 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 1 June 2004

Appellant: CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 12 September 2000
revoking European patent No. 0344024 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
C. Rennie-Smith

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division posted on 12 September 2000, whereby European patent No. 0 344 024 (European application No. 89400768.1) was revoked pursuant to Article 102(1) EPC. The patent had been opposed on the grounds of Article 100(a), namely lack of inventive step (Article 56 EPC), 100(b) and 100(c) EPC. At a later stage of the opposition proceedings the opposition ground of lack of novelty (Article 54 EPC) was introduced.

The decision was based on claims 1 to 13 as filed on 4 February 2000. The opposition division decided that the claims met the requirements of Articles 123(2), 84 and 83 EPC, and that the subject-matter of the claims, the priority rights being considered as validly claimed (Article 87 EPC), was novel. However, the subject-matter of claims 1 to 8 and 10 to 13 lacked an inventive step in view of document:

(E): Emorine, L.J. et al., Proc. Natl. Acad. Sci. USA, Vol. 84, pages 6995 to 6999, October 1987

in combination with documents:

(J): Bitter, G.A., Methods in Enzymology, Vol. 152, pages 673 to 684, 1987, and

(L): Fujita, N. et al., Biochem. Soc. Symp., Vol. 52, pages 41 to 56, 1986.

Independent claims 1, 10 and 11 of the set of claims on which the decision was based, read as follows:

"1. Vecteur répliquable dans une culture de levures contenant un insérat de nucléotides codant pour une séquence d'acides aminés contenue dans une protéine de mammifère et ayant une activité biologique de récepteur membranaire, ce vecteur étant caractérisé en ce que l'insérat est placé sous le contrôle d'une séquence, incluse dans ce vecteur autorisant l'expression de cet insérat dans les levures, et comportant notamment un promoteur reconnu par les polymérases de ces levures, et en ce que cet insérat code pour une séquence d'acides aminés contenue dans une protéine de mammifère présentant des éléments de structure en commun avec les récepteurs membranaires susdits, notamment les récepteurs α - ou β -adrénergiques, les récepteurs muscariniques, les récepteurs neuropeptidiques, en particulier la "substance K", ladite séquence d'acides aminés comportant dans la structure au sein de la membrane plasmique, sept segments transmembranaires hydrophobes entre lesquels s'intercalent des boucles extra et intracellulaires, une région aminoterminal extracellulaire et une région cytoplasmique carboxyterminale, et des sites de liaison constitués par des régions hydrophiles formées dans la membrane, l'expression de l'insérat s'accompagnant également de l'exposition à l'extérieur de ces levures des sites caractéristiques des récepteurs membranaires qui affleurent à la surface des cellules de mammifères d'origine."

"10. Procédé de détection de la capacité d'une molécule à se comporter comme ligand vis-à-vis d'un récepteur

appartenant à la classe des récepteurs normalement fixés à une protéine G, caractérisé par:

- la mise en contact de la molécule avec un organisme unicellulaire à l'exception des lignées cellulaires de mammifères, préalablement transformé par un vecteur lui-même modifié par un insérat codant pour ce récepteur membranaire, cet organisme exprimant ledit récepteur membranaire, le cas échéant après induction de l'expression de cet insérat, et portant à sa surface un ou plusieurs sites spécifiques de ce récepteur, cette mise en contact étant effectuée dans des conditions permettant la formation d'une liaison entre l'un au moins de ces sites spécifiques et la dite molécule dès lors qu'elle s'avérerait effectivement posséder une affinité pour ce récepteur;
- la détection de la formation éventuelle d'un complexe du type ligand-récepteur."

"11. Procédé pour l'étude de l'affinité d'un récepteur de mammifère appartenant à la classe de ceux qui sont couplés à une protéine G, pour un ou plusieurs ligands déterminés, caractérisé par:

- la transformation d'une culture unicellulaire avec un vecteur, à l'exception des lignées cellulaires de mammifères, notamment un plasmide ou un phage, dans lequel avait auparavant été incorporée une séquence de nucléotides codant pour le polypeptide contenu dans ce récepteur de mammifère, sous le contrôle d'éléments de régulation, notamment d'un promoteur, permettant l'expression dans la culture unicellulaire utilisée, de ladite séquence de nucléotides, et l'exposition à l'extérieur de ces hôtes unicellulaires, des sites caractéristiques des récepteurs membranaires qui

affleurent à la surface des cellules de mammifères d'origine,
— la culture des organismes unicellulaires transformés dans des conditions permettant l'expression dudit insérat,
— la mise en contact de ces organismes unicellulaires avec ces ligands déterminés,
— la détection d'une réaction affine entre lesdits organismes unicellulaires transformés et lesdits ligands déterminés."

Dependent claims 2 to 7 concerned particular embodiments of the vector according to claim 1. Independent claim 8 was directed to yeasts transformed with the claimed vector. Independent claim 9 concerned an *E. coli* cell culture (I-737) as deposited with the CNCM, and independent claim 12 was directed to a kit comprising a culture of yeasts transformed with a vector according to claims 1 to 7. Finally, independent claim 13 related to a method for expressing a mammalian receptor on the surface of bacterial or yeast cells.

- II. With the statement of grounds of appeal, the patentee (appellant) submitted five new documents in support of its inventive step arguments. The opponent (respondent) filed a response, including three additional documents, and requested that the documents filed by the appellant should not be admitted. Both parties requested oral proceedings as a subsidiary request.
- III. The parties were summoned to oral proceedings. In a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal sent with the summons, the board expressed its provisional opinion on some of

the issues to be discussed during the oral proceedings, *inter alia* the issue as to whether the disclaimer in claims 10 and 11 might contain added subject-matter contrary to Article 123(2) EPC.

IV. In reply to the board's communication, the appellant maintained claims 1 to 13, on the basis of which the decision of the opposition division was taken, as its **main request**. Additionally, it submitted four auxiliary requests, all them having in common that claim 2 of the main request was omitted, and claims 3 to 13 renumbered as claims 2 to 12. Moreover, in **auxiliary requests 2 to 4**, claim 9 was amended to replace the limitation "organisme unicellulaire à l'exception des lignées cellulaires de mammifères" by "organisme unicellulaire choisi parmi les bactéries et les levures", and the terms "la transformation d'une culture unicellulaire avec un vecteur, à l'exception des lignées cellulaires de mammifères" in claim 10 was replaced by "la transformation d'une culture unicellulaire choisi parmi les bactéries et les levures, avec un vecteur".

Claim 1 of **auxiliary request 3** differed from claim 1 of the main request in that the phrase "cet insérat code pour une séquence d'acides aminés contenue dans une protéine de mammifère..." had been replaced by "cet insérat code pour une séquence d'acides aminés d'une protéine de mammifère...". In claim 1 of **auxiliary request 4**, the claimed vector contained an insert encoding a mammalian membrane receptor having structural elements in common with particular types of receptor specified in the claim ("cet insérat code pour un récepteur membranaire de mammifère présentant des éléments de structure en commun avec notamment...").

V. Oral proceedings took place on 1 June 2004. The parties were heard on the question of the allowability of the disclaimer present in claims 10 and 11 of the main request and claims 9 and 10 of auxiliary request 1, in view of decisions G 1/03 and G 2/03 (OJ EPO 2004, 413 and 448), and on issues in connection with Articles 123(2) and (3), 84, 87, 54 and 56 EPC with respect to auxiliary requests 2 to 4.

VI. After the board expressed its intention to dismiss the appeal, the appellant requested the opportunity to file an additional request. The new request (**auxiliary request 5**) consisted of four claims, claim 1 being identical to claim 9 of the main request and claims 2 to 4 being derived from claims 10, 11 and 13 of that request and containing extensive amendments.

VII. In addition to the documents already listed in section I above, the following additional document is referred to in this decision:

(I): Fujita, N. et al, Science, Vol. 231, pages 1284 to 1287, March 1986.

VIII. The submissions made by the appellant in writing and during oral proceedings, as far as they are relevant to this decision, may be summarised as follows:

With respect to Article 123(2) EPC:

The subject-matter excluded by the disclaimer in claims 10 and 11 of the main request had a basis in the application as filed, namely on page 3, lines 21 to 25.

Although the term used in the disclaimer ("lignées cellulaires de mammifères") was not literally identical to the term used in the description ("cultures de cellules de mammifères"), it had however unambiguously the same meaning in the context.

As to the objection of lack of inventive step:

The difference between the disclosure of document (E) and the claimed subject-matter was that the G-coupled receptor was expressed in a host cell of a different origin in terms of species, thereby introducing a level of heterogeneity in the expression system which was neither disclosed nor envisaged in document (E). The cells used in document (E) were mammalian cells, in particular rabbit TP3 cells. Document (E) provided no incentive for the skilled person to depart from mammalian cell systems and to express G-coupled receptors in other types of cells. The opposition division's conclusion, that the patent provided sufficient incentive for the skilled person to formulate the problem solved by the invention, was only the result of a *ex post facto* analysis.

Document (J) was merely a cookbook guidance to the skilled person for methods that may be feasible or not in specific areas of research. Although document (J) described the successful expression of three different heterologous proteins, namely a viral glycoprotein, the alpha-subunit of the fish *Torpedo californica* and the major surface antigen of the sporozoite stage of *Plasmodium knowlesi*, in yeast, there was no indication that a mammalian G-coupled receptor with seven

hydrophobic transmembrane segments could be expressed in yeast.

The opposition division failed to consider that a skilled person would not equate the successful expression in yeast of a subunit of a nicotinic acetylcholine receptor from the electronic organs of a fish (as described in document (L)) with the successful expression in yeast of a mammalian G-coupled receptor. Since maintaining structural conformation in membrane proteins was important for ligand binding, it could not be predicted that functional expression of a particular subunit of a specific receptor would be predictive of the functional expression in yeast of any receptor having transmembrane domains but with a different conformation.

IX. The respondent's submissions may be summarized as follows:

The selection of yeast for the production of mammalian G-coupled membrane receptors was obviously derivable from a combination of document (E) with document (L) and/or document (J). The same standards had to be applied when assessing the sufficiency of the disclosure of the patent in suit and the disclosure of document (J). The disclosure content of the patent in suit for the expression in yeast was rather poor; reference was made only to standard plasmids and promoter regions already known at the priority date, and the yeast "leader sequence" or "signal sequence" was described only in very general terms without any specific exemplification. In addition, the examples in the experimental section of the specification pertained

exclusively to bacteria and no experimental results were given for yeasts. Document (J) not only provided a motivation to consider yeasts as an alternative eukaryotic unicellular host cell, but also provided even more guidance to the skilled person than the patent specification itself.

No prejudice existed in the art against the applicability of the disclosure of documents (L) and (J) to the problem defined on the basis of document (E), ie the expression of a complete functional receptor in an alternative unicellular host cell. There was also no indication in the prior art that the expectation of success was ill-founded. If the skilled person had replaced the subunit of the pentameric receptor of document (L) by the desired heptameric receptor and followed the instructions given in documents (J) and/or (L), he/she would have arrived at the solution proposed in the patent.

- X. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of either the main request or auxiliary requests 1 to 4, all filed on 30 April 2004, or auxiliary request 5 filed during the oral proceedings.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

Formal issues

1. Although the language of the proceedings is French (cf Article 14(3) EPC), the parties agreed that the English language be used during the oral proceedings, and that the decision be issued in this language (see J 18/90, OJ EPO 1992, 511). Nevertheless, in compliance with Rule 1(2) EPC, amendments to the claims were submitted in French.
2. In order to support their arguments on inventive step, both parties relied on new citations including, in part, post-published documents. The respondent requested that the documents filed by the appellant should be held inadmissible by the board.

The board, having examined the newly filed documents as to their relevance, finds that none of these documents either contains information more relevant to the assessment of inventive step than the information contained in the documents already on file, nor discloses any matter which could change the outcome of the decision. Since the board sees no reason not to admit them, all documents filed in the appeal proceedings, either by the appellant or by the respondent, are admitted in the proceedings.

Main request and auxiliary request 1 - Article 123(2) EPC

3. In its decision, the opposition decision held that the disclaimer present in claims 10 and 11 of the main request ("à l'exception des lignées cellulaires de

mammifères") correctly excluded the novelty-destroying matter disclosed in the prior art. The opposition division apparently did not examine the question as to whether the disclaimer in claims 10 and 11 had a basis in the application as filed, this question being decisive for the criteria to be applied in assessing its allowability.

4. The board is not convinced that the passage in the application as filed cited by the appellant (see section VIII above) provides a basis for the disclaimer in issue. Even if it were acknowledged that the subject-matter defined by the expression "lignées cellulaires de mammifères" (as in the disclaimer) corresponded exactly to that defined by the expression "cultures de cellules de mammifères" (as in the application), it cannot be inferred from the disclosure of the application as filed that the applicant intended to exclude such subject-matter from the scope of protection it was seeking. Thus, the board comes to the conclusion that the disclaimer in claims 10 and 11 has no basis in the application as filed.

5. The criteria to be applied in assessing the allowability of a disclaimer which is not disclosed in an application as filed have been established by the Enlarged Board of Appeal in decisions G 1/03 and G 2/03 (*supra*). According to these decisions, an undisclosed disclaimer may be allowable in order to restore novelty by delimiting a claim against an accidental anticipation under Article 54(2) EPC. An anticipation is considered to be accidental if it is so unrelated to and remote from the claimed invention that the person skilled in the art would never have taken it into

consideration when making the invention (see point II of the Headnote). If a disclaimer is or becomes relevant for the assessment of inventive step or sufficiency of disclosure, it will be considered to add subject-matter contrary to Article 123(2) EPC (see point II.3 of the Headnote).

6. In the present case, the disclaimer at issue was introduced in order to restore novelty by delimiting claims 10 and 11 of the main request against the subject-matter disclosed in document (E). In the assessment of inventive step made by the opposition division (see in particular point 7.4 of the contested decision), document (E) was considered as the closest prior art for claims 10 and 11, ie as the prior art document disclosing subject-matter aiming at the same objective (production of a mammalian membrane receptor in an heterologous expression system) as the claimed methods, which would be taken by the skilled person as the starting point for further development (see Case Law of the Boards of Appeal of the European Patent Office, 4th edition 2001, Section I.D.3). This finding has not been contested by the appellant and the board sees no reason to differ.

7. It follows from the above that document (E), being relevant for the assessment of inventive step, cannot be considered as an accidental anticipation under Article 54(2) EPC for the subject-matter of claims 10 and 11 of the main request, and that the disclaimer included in these claims is not allowable as it adds subject-matter contrary to Article 123(2) EPC. The same applies to claims 9 and 10 of auxiliary request 1.

Therefore, the main request and auxiliary request 1 must fail.

Auxiliary requests 2 to 4

8. In view of the findings on Article 56 EPC (see points 19 and 20 below), the board does not deem it necessary to discuss the issues under Articles 123(2), 84 and 83 EPC with respect to auxiliary requests 2 to 4. Novelty (Article 54 EPC) of the claimed subject-matter has not been contested by the respondent.

Inventive step (Article 56 EPC)

9. The patent was revoked by the opposition division on the grounds of lack of inventive step for the subject-matter of claims 1 to 8 and 12, as well as of claims 10, 11 and 13 of the sole request then on file (main request in appeal proceedings), insofar as these claims referred to yeast. The set of claims of the present second auxiliary request differs from the set of claims examined by the opposition division only in that claim 2 has been omitted and the disclaimer in the renumbered claims 9 and 10 has been replaced by the limitation "organisme unicellulaire **choisi parmi les bactéries et les levures**".
10. For the assessment of inventive step, document (E) is considered as the closest prior art. Document (E) describes the heterologous expression of a functional human β_2 -adrenergic receptor in the rabbit splenocyte line TP3, this cell line having been transfected with a plasmid that contains a nucleotide sequence encoding the receptor.

11. Starting from document (E), the objective technical problem to be solved is to provide an alternative expression system for the production of a mammalian membrane receptor coupled to a guanine nucleotide regulatory protein, the receptor being inserted into the cell membrane in a manner that allows binding of its ligands.

12. This problem is allegedly solved by an expression system based on a vector according to claim 1, which is replicable in yeast, or an *E. coli* vector as described in the examples of the patent, both types of vector containing a nucleotide sequence that encodes a protein with the activity of a mammalian membrane receptor. The proposed expression system can be used for screening potential ligands of the membrane receptor (see claim 9) or assessing the affinity of the receptor for certain ligands (see claim 10). A kit relying on the yeast expression system is also provided (see claim 11).

13. The question at issue is whether the production of a protein with the activity of a mammalian G-coupled receptor in yeast was obvious within the meaning of Article 56 EPC, ie whether the skilled person, having regard to document (E) alone or in combination with other prior art documents, would have tried to produce the protein in yeast, and whether he/she would have had a reasonable expectation of success.

14. The appellant has argued that none of the documents cited provides an incentive to the skilled person to depart from a mammalian cell system for the expression of the membrane receptor as described in document (E).

The board, however, notes that, if the problem is merely to find an alternative, the skilled person does not in principle need an incentive to try alternatives which are part of the common general knowledge in the pertinent technical field, in this case the expression of heterologous genes. The skilled person working in a certain field does not remain inactive, but always seeks alternatives or changes in known processes or/and products when little work and no risks are involved using routine measures and without applying inventive skills (cf eg T 455/91, OJ EPO 1995, 684).

15. Nonetheless, it is noted that the disadvantages of mammalian cells as an expression system were well known in the art, and that it was obvious to the skilled person to try to find an expression system which did not present such disadvantages. Moreover, since mammalian cells possess their own receptor and effector proteins which may interfere with the analysis of the binding of a ligand to a certain receptor (see in this respect document (E), page 6995, sentence bridging the left and right column), the skilled person would in fact have found a reason in the prior art to seek an alternative expression system without such a drawback.

16. At the priority date, yeast was known in the art as a suitable expression system for heterologous genes, and in particular for genes encoding hydrophobic membrane proteins (see page 675, first full paragraph of document (J), which exemplifies the general common knowledge at the time the priority application was filed). Having this in mind, the skilled person would have readily looked for documents in the field of membrane receptor expression in yeast, and in

document (J) he/she would have found a reference to document (I), which described the expression of a gene encoding the alpha subunit of a fish membrane receptor in yeast, and the successful insertion of the protein subunit thereby produced into the membrane. The receptor retained the ability to bind to ligands (see document (I), page 1286, right column). This was confirmed by the disclosure of document (L).

17. In view of these encouraging results, the skilled person seeking to produce the membrane receptor of document (E) in yeast, would have considered replacing the nucleotide sequence encoding the alpha subunit of the fish receptor in the vector pYTc α 1 disclosed in documents (I) and (L), by the sequence encoding a receptor with seven transmembrane domains disclosed in document (E), thus arriving at the subject-matter of claim 1 of the main request without applying any inventive skill. The board concurs with the opposition division in that, having regard to the teachings of documents (L) or (J), the successful production of the membrane receptor in yeast could reasonably be expected when using the vector disclosed in these documents with the sequence encoding a mammalian G-coupled membrane receptor inserted therein.

18. In sum, the mere choice of yeast as expression system for a mammalian G-coupled membrane receptor is considered to be obvious having regard to a combination of documents (E) and (I) and, therefore, not to involve an inventive step in the meaning of Article 56 EPC. The board also notes that the patent in suit does not provide any additional information or particular technical detail which goes beyond the common general

knowledge in the field of yeast expression systems, and which might have contributed to an inventive step over the prior art.

19. For these reasons, the claims of auxiliary request 2, as far as they relate to the expression of the receptor in yeast, do not involve an inventive step.
20. Since the claims of the auxiliary requests 3 and 4 differ from those of auxiliary request 2 solely in amendments that aim at compliance with Article 84 EPC rather than at establishing an inventive step over the prior art, this finding also applies *mutatis mutandis* to them.

Auxiliary request 5 - Late filing

21. Auxiliary request 5, having been filed during the oral proceedings when the debate on all requests then on file had been concluded, was undoubtedly "late-filed". The question to be decided is whether, in spite of its late-filing, auxiliary request 5 should be taken into consideration by the board.
22. In order to decide whether amended claim requests filed at a late stage of appeal proceedings can be taken into consideration, the boards of appeal have applied different criteria, *inter alia*, whether the late filing is justified, whether the new requests represent a *bona fide* attempt at overcoming objections raised by the opponent(s) or the board, or whether the requests can be quickly checked for their compliance with the EPC, in particular with the requirements of Articles 123 and 84 EPC (see Case Law of the Boards of Appeal of the

European Patent Office, 4th edition 2001, Section VII, D.14.)

23. In the present case, the appellant did not put forward any arguments to justify the late filing of its additional auxiliary request, and the board cannot see any reasons why the appellant did not submit this request at an earlier stage of the appeal proceedings, especially taking into account that the objection which the appellant's new request tries to overcome, namely the lack of inventive step with respect to the expression of the mammalian membrane receptor in yeast, had been raised early in the opposition proceedings and led to the revocation of the patent by the opposition division.
24. Additionally, because of the numerous amendments introduced in the claims corresponding to claims 10, 11 and 13 of the main request, there must be serious doubts as to whether the new auxiliary request would fulfil the requirements of Articles 123(2) and 84 EPC.
25. Accordingly, exercising its discretion to disregard amended claim requests which have been late filed and are *prima facie* not allowable, the board decides not to admit auxiliary request 5 in the appeal proceedings.

Conclusion

26. The board sees no reason to set aside the decision of the opposition division, as neither the main request nor the auxiliary requests 1 to 4 filed on appeal meet the requirements of the EPC. The request for

maintenance of the patent on the basis of any of these requests cannot be granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani