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Datasheet for the decision of 18 April 2013

Case Number: T 0288/09 - 3.3.08

Application Number: 91914376.8

Publication Number: 542830

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Assay methods and compositions for detecting and evaluating the intracellular transduction of an extracellular signal

Patent Proprietor:
Merck Sharp & Dohme Corp.

Opponents:
Cadus Technologies, Inc.
Soames, Candida Jane
Lawrence, John
Oser, Andreas
Glaxo Group Ltd.

Headword:
Intracellular transduction/MERCK

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2)
RPBA Art. 13(1)

Keyword:
"Admissibility of a new document (no)"
"Amendments - added subject-matter (no)"
"Disclosure - sufficiency (yes)"
"Novelty and inventive step (yes)"

Decisions cited:
T 0226/85, T 0743/97

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0288/09 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 18 April 2013

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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 1 December 2008 concerning maintenance of European patent No. 542830 in amended form.

Composition of the Board:

Chairman: M. Wieser
Members: T. J. H. Mennessier
J. Geschwind

Summary of Facts and Submissions

I. Opponent 02 (appellant I), opponent 04 (appellant II) and opponent 05 (appellant III) each lodged an appeal against the interlocutory decision of the opposition division dated 1 December 2008, whereby European patent No. 0 542 830, which had been granted on European application No. 91914376.8 (published under the international publication number WO 92/02639), was maintained in an amended form on the basis of the third auxiliary request (claims 1 to 11) filed at the oral proceedings held on 15 July 2008.

II. The main request (filed with letter of 16 January 2007), and the first and second auxiliary requests (filed with letter of 13 June 2008), all with the same set of claims as the third auxiliary request, were refused for lack of compliance with Article 123(2) EPC due to the presence of added matter in the amended description being part of each request.

III. The patent had been opposed by five opponents, including opponent 01 and opponent 03 which/who are parties to the appeal proceedings as of right, on the grounds as set forth in Article 100(a) EPC (lack of novelty and lack of inventive step), Article 100(b) EPC (insufficient disclosure) and Article 100(c) EPC (extension beyond the content of the application as filed).

IV. The patent proprietor (respondent) replied to the three statements of grounds of appeal with a letter of 1 September 2009. The third auxiliary request (claims 1

to 11) filed at the oral proceedings held on 15 July 2008 was its only claim request.

Claim 1 read as follows:

"1. A method of assaying test compounds to determine the agonist or antagonist activity of each of said compounds with respect to a cell-surface G-protein coupled receptor comprising the following steps:

a) contacting a eukaryotic cell which comprises a heterologous G-protein coupled receptor expressed from a heterologous gene and a heterologous reporter gene construct, with the compound, wherein the reporter gene construct comprises a reporter gene under the control of at least one transcriptional control element responsive to an intracellular condition that occurs when said receptor interacts with the compound;
b) measuring the amount of transcription or translation of the reporter gene;
c) comparing the difference in the amount of transcription or translation of a reporter gene in a eukaryotic cell in the presence of the test compound with the amount of transcription or translation in the absence of compound, or with the amount of transcription in the absence of the G-protein coupled receptor, whereby test compounds that modulate said receptor mediated activity are identified."

Claims 2 to 11 were dependent on claim 1.

V. On 8 March 2012, the Board issued a communication pursuant to Rule 100(2) EPC asking the parties to inform the Board whether they requested a continuation

of the appeal proceedings, although the patent had lapsed. Appellants II and III as well as opponent O3 replied positively.

VI. On 21 November 2012, the Board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) in which provisional and non-binding opinions were expressed. Summons to oral proceedings were issued.

VII. In reply to the Board's communication, appellant III filed on 18 March 2013 further submissions which were accompanied by a new prior art document (WO 89/08149) which will be referred to below as document D77.

VIII. With a letter dated 4 April 2013, the respondent requested that this newly-filed document be not admitted into the proceedings.

IX. The following documents are referred to in the present decision:

(D4) WO 89/09834 (published on 19 October 1989)

(D11) H. A. Lester, Science, Vol. 241, 26 August 1988, Pages 1057 to 1063

(D39) P. Payette et al., FEBS, Vol. 266, N° 1-2, June 1990, Pages 21 to 25

(D41) S. J. Dowell and A. J. Brown, Receptors and Channels, Vol. 8, 2002, Pages 343 to 352

(D63) Declaration of Dr. Harpold dated 2 June 2003

(D77) WO 89/08149 (published on 8 September 1989)

X. The submissions made by the appellants, insofar as they are relevant to the present decision, can be summarised as follows:

Admissibility of document D77

A review by appellant III of document D11 and the documents cited herein resulted in the discovery of document D77. Although it did not explicitly refer to assaying for the agonist or antagonist activity of test compounds, document D77 was directed to a method of screening for drugs that specifically interact and bind to the serotonin 5HT1c receptor, a G-protein coupled receptor. Therefore, it was highly relevant and was believed to represent the closest prior art. Furthermore, it was a relatively short, readily-understandable document.

Article 123(2) EPC

The objection was raised in writing by appellant I. The only part of the original description from which a method involving G-protein coupled receptors could be derived was at page 22, lines 23 to 24. However, the 'G-protein coupled receptor' feature was not disclosed in the application as filed in combination with all the other features of claim 1. Moreover, by using the term 'any one of the preceding claims' in claims 3 to 6, as well as 'any of claims 1 to X' in claims 7 to 9, multiple further combinations of subject-matter were created which were not disclosed in the application as

filed. The additional subject-matter arose at least from combining individual elements disclosed separately in various parts of the application as filed, regardless of whether these elements were a part of multiple lists or not.

Article 83 EPC

The objection was raised in writing by appellant I and discussed by appellant III at the oral proceedings before the Board. While the method of claim 1 required that any heterologous G-protein coupled receptor coupled to a G-protein in any eukaryotic cell, the patent described in its experimental part genetically engineering of a single mammalian receptor in two different mammalian cells only. Document D39 showed that in a transformed *Saccharomyces cerevisiae* a heterologous G-protein coupled receptor could not couple to the endogenous yeast G-protein and document D41 confirmed that modification of the yeast G-protein alpha subunit was required in order to achieve functional coupling. As the patent was silent in this respect and did not describe any technique for coupling functionally to the corresponding G-protein any G-protein coupled receptor in any eukaryotic cell, the claimed invention was not sufficiently disclosed for it to be reproduced over the whole scope of claim 1.

Article 54 EPC

The objection was raised in writing by appellant I. Document D63 - a declaration of one of the inventors - made it clear that the invention was disclosed to third parties prior to the relevant filing date. It was up to

the respondent to prove otherwise, or to provide evidence that such disclosures were confidential.

Article 56 EPC

Document D11 represented the closest prior art. It discussed in a prospective way the use of heterologous expression of G-protein coupled receptors, also referred to therein as seven-helix receptors, as a tool for testing candidate agonists. Table 2 (see page 1060) provided information about receptors which had been cloned and successfully expressed in a heterologous eukaryotic cell. The *in vivo* signal pathway in which G-protein coupled proteins participated was described on page 1061 (see the paragraph entitled "Coupling to second messengers"). The question of how much of this pathway would have to be reconstituted to provide meaningful assessments of the interaction between a candidate ligand (agonist) and an expressed receptor was raised. The proposition was made in this respect that ligand screening could be conducted in cells that express the appropriate G protein and, with little regard for subsequent steps, the assessment of an expressing cell's complement of endogenous G-proteins by the ability to activate various second messenger systems was suggested (see page 1062, left-hand column, first and second sentences).

The technical problem to be solved over the disclosure of document D11 was seen in the provision of a functional assay for determining the agonist or antagonist activity of a compound with respect to a G-protein coupled receptor. The proposed solution according to claim 1 differed from the prospective

method of document D11 only in that the eukaryotic cell was transformed with a heterologous reporter gene construct comprising a reporter gene under the control of a transcriptional control element responsible to an intracellular condition occurring when said receptor interacted with the compound to be tested.

As document D11 was exploring the potential interest of using heterologous expression of not only G-protein coupled receptors but also other excitability proteins, in particular ion channels (see the introduction on page 1057 as well as Tables 1 and 2), the skilled person would have had an incentive to turn to document D4, which differed from the subject-matter of claim 1 only in so far as the cell surface protein dealt with in D4 was a calcium channel.

Therefore, the method of claim 1 was obvious over the combination of document D11 and D4.

XI. The submissions made by the respondent, insofar as they are relevant to the present decision, can be summarised as follows:

Admissibility of document D77

D77 was filed very late in the procedure. It has been submitted more than seven years after the end of the opposition period and represented a clear amendment to appellant III's case as given in the statement setting out the grounds of appeal. There was absolutely no reason why D77 could not have been identified prior to the filing of the opposition by appellant III. Document

D77 added nothing of technical relevance to the disclosure of document D11.

Article 123(2) EPC

The claimed subject-matter was clearly and unambiguously derivable from the application as filed since the features of all the claims were present in the description in a manner which made it clear to the skilled person that all combinations were intended. The transcription based-assay, used for testing functional ligand-receptor interactions for at least four categories of cell surface-localized receptors, including G-protein coupled receptors, as referred to on page 22, lines 8 to 15 was the same as the transcription-based assay, using recombinant cells "to detect extracellular signals that act as agonists and antagonists of the activity of the cell surface proteins", as discussed from page 13, line 29 to page 15, line 7, of the original application. Therefore, there was direct and unambiguous basis for the subject-matter of claim 1.

Article 83 EPC

Document D39, the sole prior art document relied on by appellant I, referred exclusively to *Saccharomyces cerevisiae* and taught nothing about the situation in other yeasts. The absence of growth in the halo assay reported in document D39 was no proof that signal transduction was not happening at all. It could well be working at a low level so that it would have been detectable with a sensitive reporter gene method according to claim 1. Post-published document D41 did

not state that the yeast G-protein alpha sub-unit (Gpa1p) did not couple with mammalian G-coupled protein receptors. The appellants had failed to provide any conclusive evidence that the claimed method would not work with yeasts, let alone with any other sort of eukaryotic cells.

Article 54 EPC

The phrase "under appropriate confidentiality" used in document D63 meant that presentations were made in such a way that a disclosure prejudicial to patentability did not take place. Appellant I did not provide any evidence that public disclosure of the claimed invention took place before the priority date and had therefore failed to discharge its burden of proof.

Article 56 EPC

Document D11 represented the closest state of the art. The technical problem to be solved was the provision of a functional assay for determining the agonist or antagonist activity of a compound with respect to a G-protein coupled receptor.

Document D4 described a method for assaying compounds agonist or antagonist activity vis-à-vis a calcium channel by using a cell expressing a heterologous calcium channel which cell included a reporter gene linked to a promoter that activated the reporter in response to an ion or molecule entering the cell through the channel. There was no reference to any second messenger signal transduction system.

Document D11 disclosed that G-protein coupled receptors participate in a complex signal pathway involving the coupling to second messengers, which messengers in turn activated kinases or channels. However, it did not say that second messengers activated gene transcription and so by itself did not provide the information necessary to conclude that the transcription-based assay of document D4 was suitable for G-protein coupled receptors.

The skilled person would have turned to document D4 only with the impermissible use of hindsight. Therefore, starting from document D11, the skilled person would not have arrived at the invention of claim 1 in an obvious way.

XII. Oral proceedings took place on 18 April 2013 in presence of the respondent and appellant III. Of the non-attending parties only opponent 03 had announced with letter of 14 March 2012 that he will not be present.

XIII. The appellants requested that the decision under appeal be set aside and that the patent be revoked.

XIV. The respondent requested that document D77 not be admitted into the procedure and that the appeals be dismissed.

Reasons for the decision

Admissibility of document D77

1. Document D77 was submitted by appellant III one month before the oral proceedings together with its letter of 18 March 2013. Thus, the submission took place four years after the filing of appellant III's statement of grounds of appeal, i.e. not only at a very late stage of the appeal proceedings but also more than seven years after the end of the nine month period for filing an opposition.

2. Appellant III's argument that the Board should admit document D77 because it was so highly relevant that it should be regarded as the closest prior art is a clear signal that its admission into the proceedings, whereas it has never been considered by the first instance, would create **a fresh case**. The Board has also noticed that document D77 could not have been discovered as the result of a review of document D11, as put forward by appellant III, for the simple reason that it was not mentioned therein.

3. Under these circumstances and in view of the fact that the function of the Boards of appeal is to give a judicial decision upon the correctness of a separate earlier decision taken by a department of first instance, using the discretional power conferred to it by Article 114(2) EPC and Article 13(1) and (3) RPBA, the Board does not admit document D77 into the appeal procedure.

Article 123(2) EPC

4. According to appellant I, the claims did not comply with the requirements of Article 123(2) EPC as there was no basis for the combination of features in claim 1 and, as a consequence thereof, also in dependent claims 2 to 11. G-protein coupled receptors (hereinafter referred to as GPCR(s)) were disclosed on page 22, lines 23 to 24 of the original description only.

5. While it is true that claim 1 is restricted to GPCRs while the original application also refers to other surface proteins, this restriction represents a selection of one out of four preferred embodiments referred to in the description (page 22 lines 10 to 15 of the original description). Each one of these alternative embodiments is explicitly disclosed in the application as filed. Therefore, the requirements of Article 123(2) EPC are fulfilled by claim 1.

6. The additional technical features of dependent claims 2, 4 to 11 are unambiguously described in the context of all alternative embodiments including GPCRs (see page 13, lines 1 to 4 (for claim 11), page 14, lines 27 to 33 (for claims 4 to 6), page 22, lines 1 to 5 (for claim 10), and page 25, lines 16 to 29 (for claims 2 and 7 to 9)). Also the additional features of claim 3 have a clear support in the application as filed (see pages 14 and 18). Consequently, the objection that claims 2 to 11 represent combinations of subject-matter which has been artificially created is not tenable. Therefore, the requirements of Article 123(2) EPC are also fulfilled by claims 2 to 11.

Articles 84 and 123(3) EPC

7. No objections under Articles 84 and 123(3) EPC have been raised by the appellants. The Board is satisfied that the claims are clear and supported by the description and that the amendments to the claims do not extend the protection conferred by the patent. Thus, the requirements of Articles 84 and 123(3) are met.

Article 83 EPC

8. Appellant I, in its statement of grounds, and appellant III, at the oral proceedings, have argued that it was derivable from documents D39 and D41 that the method of claim 1 could not be carried out over its entire scope, at least as regards embodiments involving a yeast cell comprising an heterologous GPCR, for the reason that the receptor would not couple to the endogenous yeast G-protein, unless said protein has been modified.

9. Document D39 reports the results of experiments in which a cloned gene encoding the M1 subtype of human muscarinic receptor - which is the only receptor referred to in the experimental part of the patent specification - was transformed into *Saccharomyces cerevisiae*. It was hypothesized that the receptor did not couple to the endogenous G yeast protein (see page 23, right-hand column, last but one sentence reading "*Based on the present findings,* ***it would appear*** *that recombinant HM1 expressed in S. Cerevisiae* ***does not couple*** *to the endogenous G protein homologue responsible for signal transduction by receptors for mating pheromones*"; in bold emphasis added by the Board). Document D41 is a post-published review article

reporting on yeast assays for G-protein-coupled receptors. On page 343, in the right-hand column, it is stated that "*The functional coupling of a broad range of [heterologous] CPCRs has been achieved typically by* ***modifications*** *to the G-protein alpha subunit, Gpa1p.*" (in bold emphasis added by the Board).

10. Firstly, it could very well be, as argued by the respondent, that the negative result reported in document D39 was caused by the use of a detector method, which, contrary to the one of the present invention, was not sensitive enough.

11. Secondly, it certainly cannot be extrapolated from the teaching of documents D39 and D41 that **any** heterologous receptor will not be capable of successfully coupling with the corresponding native (unmodified) endogenous yeast G-protein.

12. It is established case law that occasional failure is part of any scientific work and does not impair the reproducibility of an invention if no evidence showing that the claimed technical effect can definitely not be achieved within the whole range of application or that it can be achieved only with undue burden (see decision T 743/97 of 26 July 2000; point (20) of the Reasons). This is exactly the present situation: whereas document D39 teaches no more than a (possible) occasional failure, no such evidence has been provided by the appellants. Therefore, the appellants' objection is not correctly founded. The Board concludes that the requirement that "substantially any embodiment falling within the scope of the claims can be realised" as formulated in decision T 226/85 (OJ EPO 1988, 336; see

point (2) of the Reasons) is fulfilled. Therefore, the requirements of Article 83 EPC are met.

Article 54 EPC

13. An objection of lack of novelty has been raised by appellant I only who argued that a prior public disclosure was made by an inventor. This was derivable from a passage in document D63, a declaration of this inventor submitted by the respondent in the course of the opposition proceedings. This passage, at the end of the first full paragraph of page 5, reads: "*Having a primary responsability for presenting, under appropriate confidentiality, the transcription-based drug screening assay methods to management and scientists in many pharmaceutical companies in the late 1980's and early 1990's, I can personally attest to observing such doubts and skepticism amongst what seemed like the majority of scientists involved in drug screening.*"

14. While the author explicitly indicates that his presentations of the transcription-based drug screening assay methods were made **under appropriate confidentiality**, appellant I has failed to provide any evidence at all that any non-confidential disclosure of the invention took place before the priority date and, therefore, has not discharged its burden of proof.

15. In view of this the Board concludes that the claimed subject-matter is new and that the requirements of Article 54 EPC are met.

Article 56 EPC

16. Whereas in their written submissions appellants I and III have considered document D4 to be the closest prior art, appellant II (see its statement of grounds in which document 11 was regarded as a valuable alternative to document D4) and the respondent (see its reply to the statements of grounds), took the view that the disclosure of document D11 represented the closest prior art. Document D11 is concerned with the problem of screening for novel pharmaceuticals against cell surface receptors, including GPCRs, whereas document D4 is primarily concerned with the cloning of a 'new' calcium channel and succinctly refers to a method of testing a compound for its activity as an agonist or antagonist vis-à-vis this calcium channel (see point (21) infra). The Board, therefore, concludes that document D11 constitutes the most promising starting point for the assessment of inventive step in the present case.

17. Document D11 is a prospective journal article discussing whether the heterologous expression of ion channels, receptors, and ion pumps in biological membranes (collectively referred to as excitability proteins) may become a tool for testing drugs acting thereon. Information is given regarding *inter alia* cloning and expression of those proteins (see in particular Table 2 on page 1060, in which some GPCRs, namely adrenergic receptors, muscarinic receptors, serotonin receptor and substance K receptor, are listed). The *in vivo* signal pathway in which seven-helix receptors, which indeed are GPCRs, participate in the presence of an agonist is described

in the Section entitled "*Coupling to second messengers*": (i) the agonist activates the receptor; (ii) the receptor activates a G-protein; (iii) the G-protein in turn activates or inhibits an effector enzyme or ion channel; (iv) second messengers activate kinases or channels; and (v) possible last events include down-regulation and phosphorylation-induced desensitization of the receptor itself (see last paragraph on the right-hand column of page 1061). In the same section the author asked "[h]ow much this pathway must be reconstituted to provide meaningful absolute or relative assessments of the interaction between a candidate ligand and an expressed receptor" and hypothesizes that "*ligand screening can be conducted in cells that express (or can be induced to express) the appropriate G protein,* ***with little regard for subsequent steps.***" (see page 1062, left-hand column, first sentence; in bold emphasis added by the Board). Thus, in the section entitled "*Coupling to second messengers*" on pages 1061 and 1062 document D11 gives some prospective considerations for the design of a ligand screening based on the *in vivo* complex signal pathway in which seven-helix receptors, i.e. GPCRs, participate.

18. In the light of the disclosure in document D11, the technical problem to be solved is seen in the provision of a functional assay for the determination of the agonist or antagonist activity of a compound with respect to a GPCR. As a solution to this problem the patent proposes a method according to claim 1 comprising a step of contacting a eukaryotic cell transformed with a heterologous gene expressing a heterologous GPCR and a heterologous reporter gene

construct. The reporter gene construct comprises a reporter gene under the control of at least one transcriptional control element responsive to an intracellular condition that occurs when said receptor interacts with the compound. In view of the disclosure of the invention in the general part of the description and of the results presented in the experimental part thereof, describing in detail one way of carrying out the claimed screening method with respect to the HM1 muscarinic receptor, the Board is convinced that the technical problem has been solved over the entire scope of claim 1.

19. It remains to be answered whether, starting from the disclosure of document D11 and in view of the prior art documents on file, a skilled person would have arrived at the claimed solution in an obvious way.

20. Appellant III has argued that the skilled person, in an obvious way, would have turned to document D4 and would have supplemented the method based on steps (i) to (iv) of the *in vivo* signal pathway referred to in point (17) supra with a step involving a heterologous reporter gene construct.

21. Document D4 is primarily concerned with the cloning of a 'new' two-subunit voltage-dependent calcium channel. There is also a succinct description (without details and without any experimental illustration) of a method of testing a compound for its activity as an agonist or antagonist vis-à-vis said calcium channel (see page 9, line 35 to page 10, line 32). The method involves a eukaryotic cell transformed with a first heterologous gene encoding the calcium channel and with a second

heterologous gene comprising a transcriptional control element operatively linked to a structural gene for the expression of an indicator protein. It is required that the transcriptional activity of the transcription control element responds to an ion or molecule capable of entering said cell through a functional calcium channel. However, the precise **second messenger signal transduction system** underlying the method is not described.

22. Thus, document D4 refers to calcium channels and not to seven-helix receptors, i.e. GPCRs, and, most importantly, it does not disclose the second messenger system on which the method of claim 1 relies (see paragraph [0020] on page 5 of the patent specification).

23. Consequently, the skilled person facing the technical problem as formulated in point (18) supra, would not have had any incentive to turn to document D4. Only with hindsight, after having read the application on which the present patent has been granted, the skilled person could have conceived the idea to use a heterologous reporter gene and to attempt to combine it with a method based on steps (i) to (iv) of the *in vivo* signal pathway of GPCRs (see point (16) supra). Moreover, in view of the succinct description offered by document D4, he/she would not have had any expectation of success.

24. Therefore, the skilled person would not have arrived in an obvious way at the method of claim 1. The subject-matter of claims 1 to 11 of respondent's request involve an inventive step and meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar The Chairman

A. Wolinski M. Wieser