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Case Number: T 0188/09 - 3.3.04

Application Number: 99937576.9

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Title of invention:
Nucleic acids encoding a G-protein coupled receptor involved in sensory transduction

Applicant:
The Regents of The University of California, et al.

Headword:
G-protein coupled receptor/UNIVERSITY OF CALIFORNIA

Relevant legal provisions:
EPC Art. 56

Keyword:
"Sole request - inventive step (no)"

Decisions cited:
T 0465/92, T 0039/93, T 0387/05, T 0818/05, T 1333/07,

Catchword:
see Reasons, points 1 to 8, 16, 17

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Case Number: T 0188/09 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 21 July 2011

Appellant: The Regents of The University of California et al.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 2 September 2008 refusing European application No. 99937576.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
B. Claes

Summary of facts and submissions

I. The appeal is against the decision of the examining division whereby the European patent application No. 99 937 576.9 was refused. The application has the title "Nucleic acids encoding a G-protein coupled receptor involved in sensory transduction". The European patent application originates from an international patent application under the Patent Cooperation Treaty published as WO 00/06592.

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

D4 Journal of Neuroscience, vol. 16, no. 12, 1996, 3817-3826, Chaudhari, N. et al.

D7 Current Opinion in Neurobiology, vol. 10, 2000, 519-527, Gilbertson, T. et al.

D8 Cell, vol. 96, 1999, 541-551, Hoon, M.A. et al.

D9 FEBS, vol. 316, no. 3, 1993, 253-256, Abe, K. et al.

D10 The Journal of Biological Chemistry, vol. 268, no. 16, 1993, 12033-12039, Abe, K. et al.

D11 Biochemical and Biophysical Research Communications, vol. 194, no. 1, 1993, 504-511, Matsuoka, I. et al.

D12 Cell, vol. 100, 2000, 703-711, Chandrashekar, J. et al.

D13 Nature advance online publication, DOI 10.1038/nature726, 24, February 2002, Nelson, G. et al.

D16 TIPS, vol. 18, 1997, 430-436, Stadel, J.M. et al. (introduced by the board pursuant to Articles 111(1) and 114(1) EPC)

III. The examining division based the refusal of the application on the finding that the subject-matter of claims 1 to 19 lacked an inventive step pursuant to Article 56 EPC. The examining division considered any one of documents D9 to D11 to represent the closest prior document and the problem to be solved in their light as being the "cloning of an additional taste receptor". This problem was considered not to be solved by the claimed subject-matter because there was evidence in post-published documents D7, D12 and D13 that the claimed polypeptide was not a functional taste receptor. The examining division further took the view that in the present case reformulation of the problem should not be allowed because the reformulated problem did not represent the objective technical problem formulated according to the problem-solution approach. A second reason for refusal was that the claimed subject-matter lacked industrial applicability pursuant to Article 57 EPC.

IV. With the statement of the grounds of appeal the appellant submitted a single claim request (referred to as "main request" hereinafter) which was identical with the one dealt with in the decision under appeal. The main request comprised 19 claims related to nucleic

acids and the proteins which they encode, antibodies thereto, expression vectors, host cells and methods of making taste cell specific G-protein coupled receptor polypeptides, recombinant cells and recombinant expression vectors.

Claims 1 and 9 of this main request read:

"1. An isolated nucleic acid encoding a taste cell specific G-protein coupled receptor polypeptide, the polypeptide comprising greater than about 70% amino acid identity to the amino acid sequence of SEQ ID NO: 1.

9. An isolated taste cell specific G-protein coupled receptor polypeptide encoded by the nucleic acid of any of claims 1 to 8."

The appellant requested that the decision of the examining division be set aside and that a patent be granted on the basis of the claims of the main request. In case an adverse decision was envisaged it requested oral proceedings.

V. By a letter of 8 July 2011 the appellant informed the board that it withdrew its request for oral proceedings and asked for a decision on the basis of the written submissions on file.

VI. The board cancelled the oral proceedings to which the appellant had already been summoned.

VII. The appellant's arguments, insofar as they are relevant to the present decision, may be summarized as follows:

Inventive step

Although the so-called "problem and solution approach" was used as a tool to provide a consistent approach to the assessment of inventive step, there were cases where its application was not appropriate because it hindered rather than assisted in answering the ultimate question of whether or not the claimed subject-matter was obvious over the prior art. This was acknowledged in decision T 465/92 of 26 November 1993 where the board for that reason avoided use of the "problem and solution approach".

When the question of whether or not the claimed invention solved a technical problem was asked in the course of the "problem and solution approach" it should not be allowed to obscure the fundamental question in the assessment of inventive step, namely whether or not the claimed subject-matter was obvious over the prior art.

The protein of the application, denoted therein as "GPCR-B3", was now known as "T1R1".

T1R1 formed a taste receptor by making a heteromer with another polypeptide chain, i.e. T1R3. This was for example derivable from the disclosure in post-published document D13.

The problem had to be formulated on an objective basis. Therefore, in view of the post-published evidence in the present case the problem should not be formulated so as to require a functional receptor. Rather the

problem should be formulated as the provision of an isolated nucleic acid encoding a polypeptide of a taste cell specific G-protein coupled receptor. This problem was clearly solved by the claimed subject-matter as evidenced by Example II, Figures 2 to 5 and the description on page 8, lines 4 to 12.

Since the claimed polypeptide had no substantial overall sequence identity to any known polypeptide of a G-protein coupled receptor there was no straightforward route for cloning the claimed nucleic acid molecules.

Moreover, the skilled person would not have expected to isolate successfully a G-protein coupled receptor specifically expressed in taste cells because, as evidenced by documents D9 to D11, other groups had failed to do so.

Reasons for the decision

Main Request

Inventive step

1. The "problem and solution approach" is regularly applied as an auxiliary means by the instances of the European Patent Office in the course of deciding whether or not claimed subject-matter fulfils the requirements of Article 56 EPC.

2. The appellant, referring to decision T 465/92 of 26 November 1993, observes that there are however cases where the "problem and solution approach" hinders,

rather than assists answering the question of whether claimed subject-matter is obvious over the prior art.

3. In decision T 465/92 the board explicitly decided not to use the "problem and solution approach" (see points 6 to 9.6 of the Reasons). Thus, the board understands the appellant's reference to this decision as an argument that the present case is one where the "problem and solution approach" should not be used.

4. The board notes first that whatever approach is applied as an auxiliary means for the evaluation of inventive step of claimed subject-matter, in a given evidential situation it must provide the same result, be it either in favour of or against inventive step. Therefore, in the present case, even if the "problem and solution approach" was applied, the decision on inventiveness should be the same as if it was not used.

5. Moreover, according to the reasons of decision T 465/92, the board decided to avoid the "problem and solution approach" because it considered that the seven relevant citations were all equally close to the claimed invention and that therefore, the opponent "ought not to be tied down by having to select one or more citations as being closer than others" (see points 9.3 and 9.4 of the Reasons). Consequently, the board considered them all individually without selecting one as the closest prior art document.

6. The board in decision T 465/92 also notes in point 9.5 of the Reasons that there may be situations which "can result in a complicated multi-step reasoning where the facts were clear, either for or against inventiveness.

Thus, if an inventions breaks new ground it may suffice to say that there is no close prior art rather than constructing a problem based on what is tenuously regarded as the closest prior art."

7. None of the circumstances for the avoidance of the classical "problem and solution approach" referred to in decision T 465/92 is present in the case at hand, i.e. neither can the claimed subject-matter be considered as breaking new ground, since document D4 describes a G-protein coupled receptor specifically located in taste cells nor is there a large number of equally close prior art documents (see points 9 to 13 below).

8. Thus, having considered the rationale in decision T 465/92 the present board does not see a reason to apply the approach adopted by the board in that decision rather than the classical "problem and solution approach".

Closest prior art

9. The first step in the "problem and solution approach" is the determination of the closest prior art document. According to established case law the closest prior art is a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as, and having the most structural features in common with, the claimed invention (Case Law of the Boards of appeal of the EPO, 6th edition 2010, I.D.3.1).

10. The objective derivable from the present application as a whole is the provision of a receptor involved in the

transduction of taste and which is, due to this function, specifically expressed in taste cells. It is for example stated on page 3, lines 14 to 18: "However, little is known about specific membrane receptors involved in taste transduction, [...]. Identification of such molecules is important given the numerous pharmacological and food industry applications for bitter antagonists, sweet antagonists, and modulators of salty and sour taste".

11. Document D4 aims at providing nucleic acid encoding a taste receptor. Reverse-transcriptase (RT)-PCR with degenerate primers specific for the family of metabotropic glutamate receptors (mGluRs), a family belonging to the superfamily of G-protein coupled receptors with seven transmembrane domains, was carried out. The primers span one-third of the extracellular N-terminus and the first three transmembrane helices (page 3820, under the heading "mGluRs").

RNA from rat taste bud-enriched lingual tissue, but not from lingual tissue lacking taste buds, yielded an amplification product of the expected size. Several amplified nucleic acid fragments were obtained and cloned. Two of the clones were sequenced and were found to be 100% identical to the corresponding region of the mGluR4 from rat brain (page 3820, under the heading "mGluRs").

It is therefore concluded in document D4 that mGluR4 is specifically expressed in taste-cells and that it is a member of the family of G-protein coupled receptors (see the abstract or under the heading "Discussion").

12. Documents D9 to D11 which were considered to represent the closest prior art in the decision under appeal, also aim at the cloning of G-protein coupled taste receptors. The obtained molecules are however not, or at least not exclusively, expressed in taste buds. Therefore, there is a presumption that the obtained nucleic acids do not encode taste receptors. This presumption is confirmed in document D4, page 3817, second column, end of first paragraph: "Receptors, similar to those in olfactory neurons, have been cloned from lingual epithelia, but do not appear to be expressed in taste buds (Abe et al., 1993; Matsuoka et al., 1993). Thus, to date no membrane receptors for sweet or bitter taste have been identified by molecular cloning".(The board notes that the two references are documents D10 and D11 in these proceedings, document D10 being a follow-up document to document D9).

13. Therefore, the board considers document D4 as the closest prior art document.

Problem and solution

14. In view of the closest prior art document D4 and the disclosure in the application, for example on page 3, lines 14 to 18 (see point 10 above), the problem to be solved by the application is formulated as the provision of a nucleic acid encoding a G-protein coupled taste receptor.

15. The solution to this problem as provided in claim 1 is "[a]n isolated nucleic acid encoding a taste cell specific G-protein coupled receptor polypeptide, the polypeptides comprising greater than about 70% amino

acid identity to the amino acid sequence of SEQ ID No. 1".

Evidence that the problem is solved

16. The nucleic acid specifically provided in the application encodes a protein denoted as "GPCR-B3" which has the typical motifs of a seven-transmembrane G-protein coupled receptor (see point 24 below). Since this type of polypeptide was considered as a candidate for taste receptors (see point 26 below), alone the structural information about "GPCR-B3" in the application - there are no data relating to the function of the disclosed protein in the application - could be considered as prima facie establishing that the formulated problem is solved by the claimed subject-matter.

However, post-published document D13 identifies the mammalian taste receptor "T1R1+3" which is a heteromer of the T1R1 and T1R3 G-protein coupled receptors. According to the appellant "T1R1" is the new name for the "GPCR-B3" protein of the application. Document D13 demonstrates that only in combination do T1R1 and T1R3 function as a taste receptor, i.e. one which specifically responds to most of the L-enantiomers of the 20 standard amino acids, but not to their D-enantiomers or other compounds.

Also the appellant admits that "GPCR-B3" forms a functional taste receptor only by making a heteromer with another polypeptide chain.

17. Thus, evidence published after the priority date of application establishes that the claimed subject-matter does not have the function ascribed to it in the application. On the basis of this evidence the board comes to the conclusion that the claimed subject-matter cannot be considered as solving the problem formulated on the basis of the application and the closest prior art document.

Reformulation of the problem

18. Normally, if an initially formulated problem is found not to be solved, the problem is reformulated to one which is considered as having been solved and the obviousness of the claimed subject-matter is then assessed on that new basis (for example decision T 1333/07, points 4.2 to 4.4.3 of the Reasons; T 387/05, points 5.1 to 5.5.6 of the Reasons; T 818/05, points 2.3 to 2.5 of the Reasons). Thus, generally, the board does not agree with the appellant's view that there may be the risk that problem-solution approach "obscures" the question of whether or not the claimed subject-matter was obvious over the prior art.

19. The examining division considered that the reformulation of the problem should not be allowed in the present case because the reformulated problem does not represent the "objective technical problem" formulated according to the "problem and solution approach".

20. The meaning of the notion "objective technical problem" is for example explained in decision T 39/93 of 14 February 1996.

It is stated in points 5.3.2 and 5.3.3 of the Reasons:

"5.3.2 [...] In both cases, reformulation of the technical problem as originally disclosed, in accordance with Rule 27(1)(c) EPC, in the application or patent in suit (the "subjective" technical problem), on the basis of objectively relevant elements originally not taken into account by the Applicant or Patentee, yields a definition of the "objective" technical problem.

5.3.3 The "objective" technical problem thus established represents the ultimate residue (effect), corresponding to the objective contribution provided by the subjectmatter [sic] defined in the relevant claim (features)."

21. Thus, in contrast to the examining division's view, it is in fact the reformulated problem which is considered as the "objective technical problem".

22. According to established case law any effect provided by the claimed subject-matter may be used as a basis for reformulating the technical problem to a less ambitious one as long as that effect is derivable from the application as filed (Case Law, I.D.4.4, first paragraph).

23. A less ambitious problem which is derivable from the application as filed is, as suggested by the appellant
- the "provision of an isolated nucleic acid encoding a polypeptide of a taste cell-specific G-protein coupled receptor."

24. The application establishes that the claimed subject-matter solves this problem. SEQ ID No. 1 shows structural motifs identifying the polypeptide with this sequence as a G-protein coupled receptor polypeptide, for example a seven-helix motif (Figure 1; page 7, lines 20 to 28; page 57, lines 29 to 31). The polypeptide is expressed specifically in taste buds of the tongue (see Example II and Figures 2 and 3).

Obviousness

25. G-protein coupled receptors are proteins known to be generally involved in the transmission of signals across the membrane. They are present in many tissues of the body and considered to be involved in many diseases.

26. The sensation of taste is mediated by specialized neuroepithelial cells of the tongue that are clustered into onion-shaped end organs called taste buds (see for example first sentence of document D1). At the priority date of the application G-protein coupled receptors, and in particular those of the family with seven transmembrane domains, were postulated as candidates for the transduction of different sensory stimuli, including taste (see for example document D4, page 3817, first column, second paragraph).

27. In line with this postulate, document D4 discloses nucleic acid fragments encoding parts of a seven transmembrane domain G-protein coupled receptor. The receptor is specifically located in taste cells (see also point 11 above). On the basis of behavioural

assays it is suggested it is responsible, in part, for the taste of monosodium glutamate.

28. It is for example mentioned in document D4 (page 3817, second column, last sentence of first paragraph) that "to date no membrane receptors for sweet or bitter taste have been identified by molecular cloning".

29. In the board's view, the general importance of G-protein coupled receptors, and in particular the apparently scarce knowledge about their role in relation to the transduction of taste, would give the skilled person the motivation to provide nucleic acids encoding G-protein coupled receptor polypeptides in general and in particular those specifically expressed in taste cells.

30. According to the application the specific nucleic acid encoding the protein having SEQ ID No. 1 was isolated from rat taste-cell tissue. Due to its availability rat tissue is an obvious source as an experimental tissue, i.e. also as a source for taste cells. Moreover, rat tissue is not infrequently used for research purposes in relation to taste. For example, the application refers to a "method of Dulac & Axel, Cell 83:195-206 (1995)" for the isolation of individually isolated taste receptor cells and taste buds from rat and mouse circumvallate, foliate and fungiform papillae (see page 56, lines 8 to 11). Also the assays of document D4 were carried out with taste cells from rat (page 3820, first column, first sentence of the paragraph headed "mGluRs": "We also used RT-PCR to test for the presence of mRNAs for mGluRs in rat taste buds.").

31. The members of the family of the seven transmembrane domain G-protein coupled receptors have several conserved structural elements and sequence motifs, such as a series of conserved cysteine residues in the extracellular domain, several conserved short sequence motifs scattered throughout the molecule or seven hydrophobic transmembrane domains (see document D8, page 542, second column, last sentence of first paragraph, cited as an expert opinion) which can serve to specifically "hook" polypeptides which belong to this family of G-protein coupled receptors.

32. The methodology for achieving the provision of G-protein coupled receptor polypeptides was known to the skilled person. It is stated in document D16, a review article about orphan G protein-coupled receptors, on page 433 in the middle of the second column: "As the nucleotide sequences for GPCRs begin to accumulate and be analysed, additional receptors can be cloned by homology screening, by positional cloning, and by polymerase chain reaction (PCR) methodologies that use oligonucleotide primers based on nucleotide sequences conserved within the seven transmembrane domains of the GPCR family."

33. Thus, the skilled person wanting to provide a taste cell-specific G protein coupled receptor would be able to do so following routine methods.

34. Particularly in view of the statement in document D16 as cited in point 32 above, the board is not convinced by the appellant's argument that the claimed G-protein coupled receptor encoding nucleic acids could not have been be obtained by a sequence-based approach due to

their low identity with other G-protein coupled receptor proteins. G-protein coupled receptor proteins can be traced by virtue of their conserved sequence structure (see point 31 above), despite an overall low sequence identity.

35. Moreover, the board is not persuaded by the appellant's argument during the examination proceedings that the skilled person would not have expected to isolate successfully a G-protein coupled receptor protein specifically expressed in taste cells because, as evidenced by documents D9 to D11, other groups had failed to do so. In the board's view, the disclosure in these documents would have influenced the skilled person only insofar as it would have indicated that the methods used in documents D9 to D11 are not suited to solve the formulated problem. The evidence does not support the view that the skilled person would have expected difficulties when using a different method from among those commonly available. In fact, document D4, which is published about 3 years after documents D9 to D11, discloses the identification of a taste-cell specific G protein coupled receptor by relying on taste cell-enriched tissue and the amplification of a region different from the one disclosed in documents D9 to D11.

36. Thus, the board concludes that the subject-matter of claim 1 does not involve an inventive step.

37. The main request does not fulfil the requirements of Article 56 EPC.

38. In view of this decision the further reason for refusal given in the decision under appeal, lack of industrial applicability, need not be dealt with.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith