DECISION
of 18 October 2005

Case Number: T 0255/05 - 3.3.08
Application Number: 01981441.7
Publication Number: 1330522
IPC: C12N 15/12
Language of the proceedings: EN

Title of invention:
Isolated human G-protein coupled receptors, nucleic acid molecules encoding human GPCR proteins, and uses thereof

Applicant: Applera Corporation

Opponent: -

Headword: Human GPCR protein/APPLERA

Relevant legal provisions: EPC Art. 56, 113(1)

Keyword: "Main request - inventive step (no)"
"Auxiliary request - unclear - disregarded"

Decisions cited: T 0382/96

Catchword: -
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DECISION
of the Technical Board of Appeal 3.3.08
of 18 October 2005

Appellant: Applera Corporation
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Representative: Thomson, Paul Anthony
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Decision under appeal: Decision of the Examining Division of the European Patent Office posted 22 October 2004 refusing European application No. 01981441.7 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
          B. Günzel
Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division posted on 22 October 2004, whereby the European patent application No. 01 981 441.7 was refused pursuant to Article 97(1) EPC. The European patent application originated from an international application under the Patent Cooperation Treaty published as WO 02/34914, and claimed the priority of two US patent applications of 25 October 2000 and 31 May 2001. The refusal was based on the finding that the subject-matter of claims 1 to 8 filed on 16 September 2004, did not involve an inventive step as defined in Article 56 EPC, and lacked industrial applicability within the meaning of Article 57 EPC.

II. On 22 February 2005, the appellant filed a statement setting out the grounds of appeal, maintaining as its main request the request on the basis of which the application had been refused by the examining division. As an auxiliary request, the appellant requested "that the application proceed to grant on the basis of all, or at least one, of the four alternative claim sets as per the attached Annex 1". In brackets the appellant added that it appreciated "that if more than 1 set of such claims is allowed then it may be necessary to file divisional applications accordingly" (cf. point 2 of the statement of grounds of appeal). Oral proceedings were requested under Article 116 EPC, in the event that the board did not intend to grant the appellant's requests in written proceedings.
III. Claims 1 and 6 of the main request read as follows:

"1. An isolated nucleic acid molecule consisting [sic] the sequence of SEQ ID NO 1 or SEQ ID NO 3, wherein the molecule encodes a Human Mas-related G-Protein coupled receptor.

6. A biological assay to identify compounds, which bind to Mas-related G Protein-coupled Receptor proteins, for use as potential modulating agents of said Mas-related G Protein-coupled Receptor proteins, said assay comprising one or more of the peptides encoded by either of the nucleotide sequences of claim 1."

Independent claims 2, 3 and 4 were directed to a nucleic acid array, a transgenic non-human animal and a nucleic acid vector, respectively, each comprising a nucleic acid molecule as defined in claim 1. Independent claim 5 related to a host cell containing the vector of claim 4, and dependent claims 7 and 8 related to further embodiments of the assay of claim 6.

IV. The first alternative amended claim set filed with the statement of grounds of appeal consisted of a single claim which was essentially identical to claim 6 of the main request (cf. Section III above), except for the term "Mas-related" characterizing the receptor proteins having been deleted, and the back-reference to claim 1 replaced by a reference to the specific sequences SEQ ID NO 1 and SEQ ID NO 3.

V. The second alternative amended claim set consisted also of a single claim reading as follows:
"1. A tissue sample identification kit to identify whether a sample tissue is one of the following tissue types: testis or human erythroleukemia cells; characterised in that the kit gives a positive result if a peptide encoded by either of the nucleotide sequences of SEQ ID NO 1 or SEQ ID NO 3 is found to be present in the tissue sample."

VI. The third alternative amended claim set consisted of two claims which read as follows:

"1. Use of an isolated nucleic acid molecule consisting of the sequence of SEQ ID NO 1 or SEQ ID NO 3 as part of a diagnostic kit for identifying cells or tissues that express a GPCR protein.

2. A diagnostic test kit for identifying cells or tissues comprising a GPCR protein, comprising an isolated nucleic acid molecule consisting of the sequence of SEQ ID NO 1 or SEQ ID NO 3."

VII. The fourth alternative amended claim set consisted of three claims:

1. Use of an isolated nucleic acid molecule consisting of the sequence of SEQ ID NO 1 or SEQ ID NO 3 for measuring a level of a G-protein receptor-encoding nucleic acid in a sample of cells from a subject.

2. Use of claim 1, wherein the cells are human erythroleukemia and/or testis cells.
3. Use of claims 1 or 2, wherein the measured level determines if a G-protein receptor gene has been mutated."

VIII. The examining division did not rectify its decision and, pursuant to Article 109(2) EPC, remitted the appeal to the boards of appeal.

IX. On 5 August 2005, the appellant was summoned to oral proceedings. In a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal dated 17 August 2005 following the summons, the board drew the attention of the appellant to the fact that its auxiliary request was not clear. The board also expressed its preliminary opinion on the issue of inventive step, this opinion being adverse to the position of the appellant.

X. On 17 August 2005, the appellant requested that the appointed oral proceedings be cancelled and a decision be taken on the basis of the written submissions. No substantive reply to the points raised by the board was filed, neither was the question of the auxiliary request clarified. The oral proceedings were cancelled.

XI. The following documents are cited in the present decision:

D2: WO 99/32519, published on 1 July 1999;

D5: WO 00/20455, published on 13 April 2000;

The arguments of the appellant, insofar as they are relevant to the present decision, may be summarised as follows:

Main request

The genesis of the invention lay in the worldwide effort to sequence the entire human genome. The specific sequences with which the application was concerned were G-protein coupled receptors, a class of proteins of substantial biological interest. The application disclosed a further Mas-related G protein-coupled receptor, and its technical contribution lay in a different solution to a problem than that offered by the prior art, rather than an improved version of the same solution.

The difference between D2 and the present application lay first in the fact that the relevant sequences were different, but also in the greater technical contribution to the art made by the application as regards the relationship of the claimed sequence to human erythroleukemia and testis cells. The objective problem solved by the invention was the provision of novel Mas-related G protein coupled receptors (alternatively, the provision of a novel Mas-related G protein coupled receptor which was, or was likely to be, expressed in human erythroleukemia and testis cells in particular). Since D2 was exclusively concerned with G protein coupled receptors located in dorsal root ganglia, the skilled reader would not have been prompted to investigate the expression of the claimed sequence in anything other than dorsal root ganglia.
The obvious way forward from D2, if anything, was to examine why the sequence of D2 was only expressed in foetal dorsal root ganglia rather than foetal spinal cord or any adult cells at all.

There was no hint or incentive to arrive at the claimed invention. Document D10 described orphan G protein-coupled receptors as potential drug targets, but it did so by making it clear that these were a neglected opportunity. There was no particular reason why, absent knowledge of the invention, the skilled addressee would have been interested in taking up such neglected opportunities. Nor could one see any logical reason why the skilled addressee would have combined what were described as neglected opportunities in a review article published in 1997 (ie D10) with very specific teaching re dorsal root ganglia published in July 1999 (ie D2).

**Auxiliary request**

The claim sets of the auxiliary request were narrower still than the claims of the main request and more clearly distinguished from the prior art. They related to four separate uses of the nucleic acids claimed in the main request, each being the solution to a correspondingly narrower formulation of the relevant problem. For instance, the 1st claim set provided a solution to the problem of providing a biological assay to identify compounds which bind to G protein-coupled Receptor proteins, for use as potential modulating agents of said G protein-coupled Receptor proteins. The 2nd claim set provided a solution to the problem of providing a tissue sample identification kit to
identify whether a sample tissue was one of the following tissue types: testis or human erythroleukemia cells, and so on. None of these claim sets were either anticipated by, or obvious in the light of, the cited prior art.

XIII. The appellant requests that the decision of the examining division be set aside and a patent be granted on the basis of claims 1 to 8 as filed on 16 September 2004. As auxiliary request, the appellant requests, literally, "that the application proceed to grant on the basis of all, or at least one, of the four alternative claim sets" filed with the statement setting out the grounds of appeal.

Reasons for the Decision

Main request - Inventive step (Article 56 EPC)

1. Claim 1 of the main request is directed to an isolated nucleic acid molecule having the nucleotide sequence of either SEQ ID NO 1 or SEQ ID NO 3 as shown in the Sequence Listing and in Figures 1 and 3 of the published application. SEQ ID NOs 1 and 3 are said to represent, respectively, cDNA/transcript and genomic sequences encoding a human G-Protein coupled receptor protein related to the rat *Mas* protein (cf. page 14, lines 23 to 28). The amino acid sequence of the encoded protein (SEQ ID NO 2; amino acids 1 to 337) is shown in Figure 2 of the application.

2. In the decision under appeal, the examining division found that the claimed subject-matter was obvious in
view of documents D2 and D10 (cf. point 2.4 of the decision) and, absent a confirmed function of the encoded protein, did not provide a solution to a technically meaningful problem (cf. point 2.3 of the decision). Consequently, the claims were considered to not fulfil the requirements of Article 56 EPC.

3. For the assessment of inventive step applying the problem-solution approach, the examining division identified document D2 as the closest prior art. However, in view of the structural similarities between the nucleic acid molecules and the encoded receptor protein disclosed in the present application and those described in document D5, the board considers this prior art document to be a more adequate starting point.

4. Document D5, which concerns the international application PCT/JP99/05366, was published in Japanese language under the Patent Cooperation Treaty on 13 April 2000, ie before the first priority date claimed in the present application. Thus, this document constitutes prior art within the meaning of Article 54(2) EPC and is relevant to the assessment of inventive step pursuant to Article 56 EPC.

5. D5 describes a human Mas-related G protein-coupled receptor with about 30% homology at the amino acid sequence level, to the rat Mas protein (cf. page 19, lines 27-28 of the English translation of the international application PCT/JP99/05366, published in accordance with Article 158(3) EPC as EP 1 118 620 A1). It should be noted that the amino acid sequence of the G protein-coupled receptor described in document D5 (cf. SEQ ID NO 1 in the Sequence Listing) is, to a
great extent, identical to the amino acid sequence of the protein encoded by either of the nucleotide sequences SEQ ID NO 1 and SEQ ID NO 3 of the present application (cf. amino acid sequence between positions 15 and 337 in SEQ ID NO 2 and Figure 2 of the application), the sole difference between these two amino acid sequences being the initial 15 amino acids present in the protein disclosed in the application, which are, however, absent from the protein described in document D5.

6. Furthermore, document D5 describes an isolated nucleic acid molecule encoding said Mas-related G protein-coupled receptor, the nucleotide sequence of this molecule (cf. SEQ ID NO 3 in D5) showing 100% identity with the nucleotide sequence between nucleotides 492 and 1460 in SEQ ID NO 1 of the present application. A vector, a host cell and a transgenic non-human animal containing the nucleic acid molecule are also described (cf. page 3, line 45; page 12, lines 46 to 49; and page 15, lines 57 to 58 of EP 1 118 620 A1). An assay for identifying ligands of the Mas-related G protein-coupled receptor is described on page 16, under the heading "Determination of a ligand (agonist) for the present G protein coupled receptor protein".

7. Starting from document D5 as closest prior art, the objective technical problem to be solved may be formulated as the isolation of further nucleic acid molecules encoding the amino acid sequence of the human Mas-related G protein-coupled receptor described in the prior art document. According to claim 1, this problem is solved by a nucleic acid molecule consisting of the sequence of SEQ ID NO 1 or SEQ ID NO 3 as disclosed in
the application. These sequences include the nucleotide sequence described in D5, flanked by additional sequences at the 3' and 5' end. The genomic sequence specified in SEQ ID NO 3 of the application further includes non-coding intervening (intron) sequences.

8. The question to be decided is whether, having regard to document D5, either alone or in combination with further prior art documents on file, it would have been obvious to a person skilled in the art to try to identify further human nucleic acid molecules encoding the Mas-related G protein-coupled receptor described in D5, and, if so, whether the skilled person could have reasonably expected to succeed.

9. In the decision under appeal, document D10 was cited as prior art relevant to inventive step in the present case. The examining division held that, in view of the teachings of documents D2 and D10, and taking into account the availability of various sequence analysis tools, the identification of a further cDNA encoding a G protein-coupled receptor would have been straightforward to a person skilled in the art.

10. In the board's view, the same is true when the teachings of documents D5 and D10 are combined. Document D10, a review article which describes orphan G protein-coupled receptors as potential drug targets, provides not only the motivation to identify further nucleic acid molecules encoding such receptor proteins, but also suggests various methodologies to achieve this goal, such as homology screening, positional cloning, PCR or, as applied in the present application, computational and bioinformatic methodologies (cf.
The feasibility of identifying the desired nucleic acid molecules using any of these methodologies has not been questioned by the appellant.

11. The board considers that, contrary to the appellant's view, the person skilled in the art would not have been discouraged by G protein-coupled receptors being described in D10 as a "neglected opportunity". Rather, throughout document D10 G protein-coupled receptors are presented as promising targets for pioneer drug discovery, to which, in the view of the authors, not enough attention had been paid up to then. The prospect of better characterising drug targets already known or identifying new ones provides a strong motivation for the skilled person to seek further nucleic acid molecules from which G-coupled receptor proteins can be produced. There is also no doubt that the skilled person would have combined the teachings of documents D5 and D10, as these prior art documents belong to exactly the same technical field and have been published within a few years.

12. The appellant has pointed out that the scope of protection claimed is very narrow, since it is limited to the specific sequences disclosed in the application. In its communication, the board expressed the opinion that, even if the scope of claim 1 might be narrow, the claimed nucleic acid molecules would not appear to be anything but an arbitrary selection, among all other possible choices, of a fragment of the human genome encoding the Mas-related G protein-coupled receptor of document D5, the specific fragment lacking any
unexpected properties or effects on which an inventive step could be based. No arguments have been put forward by the appellant in this respect, except for the allegedly novel expression pattern of the nucleic acid molecules described in the application. However, the board notes that a possible expression of the described molecules in erythroleukemia cells and testis, which has been computationally predicted on the basis of a virtual Northern blot and a PCR-based screening panel, does not constitute a property or an effect on which an inventive step for the claimed nucleic acid molecules could be based.

13. The board thus concludes that, having regard to the teachings of documents D5 and D10 the subject-matter of claim 1 was obvious to a person skilled in the art. The subject-matter of claims 2 to 8 relies on the isolation of the nucleic acid molecules of claim 1, and does not contain any further elements beyond the teaching of document D5 (cf. point 6 above). Since the requirements of Article 56 EPC are not fulfilled, the main request cannot be granted.

Auxiliary request

14. In the communication sent in preparation of the oral proceedings, the board indicated that the "auxiliary request" put forward in the statement of grounds of appeal was not clear. Furthermore, the board expressed its doubts as to whether the subject-matter of the amended claims filed with the statement of grounds of appeal involved an inventive step. The appellant did not reply to the board's communication.
15. As "auxiliary request" the appellant requested that "the application proceed to grant on the basis of all or at least one of the four alternative claim sets". In brackets the appellant added that it appreciated "that if more than 1 set of such claims is allowed then it may be necessary to file divisional applications accordingly".

16. The appellant's "auxiliary request" is thus not one single request but encompasses numerous requests. These are not only the four alternative claim sets filed, but also any possible combination of more than one of these claim sets up to all of them taken together. It is, however, totally undefined in which order these four requests and any such combination requests should be considered by the board.

17. According to Article 113(2) EPC, the European Patent Office shall consider or decide upon the European patent application only in the text submitted to it, or agreed, by the applicant. It is therefore the applicant's responsibility to define the text on the basis of which it requests a patent to be granted. In the case of auxiliary requests this includes that the applicant must indicate also the order in which the requests are to be examined. This is so because filing an auxiliary request means that such a request is only filed in the event that the preceding request is not allowed by the board.

18. As a consequence, when the appellant, even after having been invited to do so by the board, does not clearly indicate the order in which its several requests are
submitted and what the exact content of each of these requests is, there is no text submitted or agreed by the applicant within the meaning of Article 113(2) EPC and no request which could be considered by the board. Therefore, the appellant's "auxiliary request" must be disregarded.

**Article 113(1) EPC**

19. The reasons given by the board in the present decision were apparent from the communication sent in preparation for the oral proceedings. Nevertheless, the appellant chose not to file a reply to the board's communication or amended requests, and withdrew its request for oral proceedings. Thus, the provisions of Article 113(1) EPC are complied with.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:                The Chairman:

A. Wolinski                   L. Galligani