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Datasheet for the decision of 11 October 2007

Case Number: T 0250/06 - 3.3.08

Application Number: 93920068.9

Publication Number: 0656007

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Language of the proceedings: EN

Title of invention:
Delta opioid receptor genes

Patentee:
The Regents of the University of California

Opponents:
PFIZER LIMITED
JANSSEN PHARMACEUTICA N.V.

Headword:
Opioid receptor genes/UNIVERSITY OF CALIFORNIA

Relevant legal provisions:
EPC Art. 87, 88, 56

Keyword:
"Main request - entitlement to priority - no"
"Novelty - no"
"First auxiliary request - inventive step - no"
"Second auxiliary request - entitlement to priority - yes; inventive step - yes"

Decisions cited:
T 0923/92, T 0412/93, T 0190/99

Catchword:
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Case Number: T 0250/06 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 11 October 2007

Appellant I: (Opponent 1)
PFIZER LIMITED
Ramsgate Road
SANDWICH, KENT CT13 9NJ (GB)

Representative:
Courgeon, Antoine
Pfizer Limited, UK Patent Department
Ramsgate Road
Sandwich, Kent CT13 9NJ (GB)

Appellant II: (Opponent 2)
JANSSEN PHARMACEUTICA N.V.
Turnhoutseweg 30
B-2340 Beerse (BE)

Representative:
von Menges, Albrecht
UEXKÜLL & STOLBERG
Patentanwälte
Beselerstrasse 4
D-22607 Hamburg (DE)

Respondent: (Patent Proprietor)
The Regents of the University of California
1111 Franklin Street
12th Floor
Oakland
CA 94607-5200 (US)

Representative:
Campbell, Patrick John Henry
J.A. Kemp & Co.
14 South Square
Gray's Inn
London WC1R 5JJ (GB)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 20 December 2005 concerning maintenance of European patent No. 0656007 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
C. Heath

Summary of Facts and Submissions

I. European patent No. 0 656 007 with the title "Delta opioid receptor genes" was granted with nine claims for all Designated Contracting States based on the International patent application published under No. WO 94/04552, claiming priority from the document US 929200 filed on 13 August 1992.

Granted claims 1 to 3 read as follows:

"1. A recombinant nucleic acid molecule comprising a nucleotide sequence encoding a delta opioid receptor which hybridizes under conditions of low stringency to a probe consisting of the nucleotide sequence shown in Figure 5 or to its complement.

2. The nucleic acid molecule of claim 1 which encodes human delta opioid receptor or murine delta opioid receptor.

3. The nucleic acid molecule of claim 2 which encodes the murine delta opioid receptor, wherein the murine delta opioid receptor comprises the amino acid sequence encoded by the nucleotide sequence of Figure 5."

Claims 4 and 5 were respectively directed to an expression system comprising a nucleotide sequence as defined in the previous claims and to a host cell comprising this system.
Claims 6 and 7 were respectively directed a method to produce a cell that displays an opioid receptor at its surface and to a cell prepared by this method. Claims 8 and 9 respectively related to a method to screen opioid

antagonists or agonists and to an in vitro method for modulating the expression of a nucleic acid encoding an opioid receptor.

II. Two oppositions were filed under Articles 100(a) to (c) EPC, for reasons of lack of novelty and inventive step, insufficiency of disclosure, added subject-matter. The main request (granted claims) was rejected by the opposition division for the reason that the subject-matter of claim 1 did not enjoy priority insofar as it comprised recombinant DNA molecules encoding delta opioid receptors of non-vertebrate origin and that, consequently, some of the documents published within the priority interval were detrimental to novelty. The patent was, however, maintained in amended form pursuant to Article 102(3) EPC on the basis of the auxiliary request then on file. Claim 1 of this request read as follows:

"1. A recombinant nucleic acid molecule comprising a nucleotide sequence encoding a **vertebrate** delta opioid receptor which hybridizes under conditions of low stringency to a probe consisting of the nucleotide sequence shown in Figure 5 or to its complement." (difference with granted claim 1 emphasized by the board).

Claims 2 to 9 remained identical to granted claims 2 to 9.

III. The appellants (opponents) filed notices of appeal, paid the appeal fee and submitted statements of grounds of appeal.

IV. The respondent (patentee) filed a submission in answer to these statements of grounds of appeal accompanied by a main request (claims as maintained by the opposition division) and three auxiliary requests.

V. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA) indicating its preliminary non-binding opinion.

VI. Both appellants filed further submissions in answer to the board's communication.

VII. Oral proceedings took place on 11 October 2007. A main and two auxiliary requests came under consideration. The main request was the request maintained by the opposition division (see Section II, supra).

Claim 1 of auxiliary request 1 (claims 1 to 8) read as follows:

"1. A recombinant nucleic acid molecule comprising a nucleotide sequence encoding a **human or murine** delta opioid receptor which hybridizes under conditions of low stringency to a probe consisting of the nucleotide sequence shown in Figure 5 or to its complement." (emphasis added by the board)

Claim 1 of auxiliary request 2 (claims 1 to 7) read as follows:

"1. A recombinant nucleic acid molecule comprising a nucleotide sequence encoding a **murine** delta opioid receptor which hybridizes under conditions of low stringency to a probe consisting of the nucleotide

sequence shown in Figure 5 or to its complement."
(emphasis added by the board)

The remaining claims of these requests corresponded respectively to granted claims 3 to 9 and 3 to 8.

VIII. The following documents are mentioned in the present decision:

(P1) : US patent application No. 929200 with a filing date of 13 August 1992;

(2) : Cabon, F. et al., Proceedings of the International Narcotics Research Conference, 8 to 13 July 1989, Abstract S.5.4, pages 282 to 284, Publisher: Elsevier Science Publishers B.V., 1990.

(4) : Knapp, R.J. et al., Life Sci. Vol. 54, No. 25, pages PL-463 to PL-469, 1994;

(5) : Simonin, F. et al., Mol. Pharmacol., Vol. 46, pages 1015 to 1021, December 1994;

(13) : Yasuda, K. et al., Proc.Natl.Acad.Sci.USA, Vol. 90, pages 6736 to 6740, July 1993;

(14) : Fukuda, K. et al., FEBS Letters, Vol. 327, No. 3, pages 311 to 314, 2 August 1993;

(20) : Evans, C.J. et al., Science, Vol. 258, pages 1952 to 1955, 18 December 1992;

(22) : Wollemann, M., J. Neurochem., Vol.54, No.4, pages 1095 to 1101, 1990;

(24) : Barinaga, M., Science, Vol. 258, pages 1882 to 1884, 18 December 1992;

(30) : Cabon, F. et al., J. Neurochemical Research, Vol. 18, No. 7, pages 795 to 800, 1993;

(32) : Declaration of Dr. C. Evans dated 4 April 1994;

(36) : Smith, A.P. and Loh, H.H., NIDA Research Monogr. 111, pages 69 to 84, 1991;

(38) : Miller, R.J. et al., Life Sciences, Vol. 22, No. 5, pages 379 to 388, 1978.

IX. The appellants' submissions in writing and during oral proceedings insofar as relevant to the present decision may be summarised as follows:

Main request; claim 1
Articles 87 and 88 EPC; entitlement to priority

The subject-matter of claim 1 did not enjoy priority because it was only enabling as regards the isolation of mouse delta opiate receptor (DOR) DNA and not as regards, more generally, the isolation of a vertebrate DOR DNA.

- Evidence thereto came from the priority document (P1) itself wherein Example 6 which allegedly illustrated the isolation of DOR DNA of vertebrate origin (human)

starting with the mouse DOR DNA as a probe mistakenly led to the identification of a human partial DNA sequence encoding the μ opiate receptor (μOR). The skilled person would have had no way to realize that this partial DNA identified as DOR DNA was wrong (see, in particular, page 41, lines 22 to 29 of the priority document). Furthermore, no teaching was provided of how to isolate a full-length opiate receptor (OR) DNA. Had this sequence been retrieved using the partial allegedly human DOR sequence (in fact μOR), the skilled person testing the pharmaceutical properties of the protein encoded by it would have had to conclude that it was not the DOR DNA. The cloning of the DOR nucleotide sequence would have had to be re-started de novo without any help from (P1) (which had proven wrong). This meant that a new research program needed to be initiated which clearly amounted to undue burden.

- There was a second reason why document (P1) was not enabling for the retrieval of the group of recombinant molecules such as claimed. These molecules were defined by their property of hybridising to the nucleotide sequence shown in Figure 5 of the patent in suit. The priority document also contained a Figure 5. Yet, the nucleotide sequences presented in these two figures were different by seven bases. As the hybridising probes were different, it followed that the two groups of recombinant molecules retrievable by hybridisation would necessarily be different. This, in turn, implied that (P1) was not enabling as regards the isolation of the group of recombinant DNA molecules retrievable by hybridisation to the hybridising probe mentioned in the claim.

Otherwise expressed, lack of enablement resulted from the fact that the sequences disclosed in the two Figures were different. This situation was identical to that dealt with in T 923/92 (OJ EPO 1996, 564) where priority was refused to the then claimed tissue plasminogen activator molecule defined by its sequence because this sequence differed by three amino acids from the sequence disclosed in the priority document.

- Furthermore, (P1) failed to give sufficient information as regards the specific ligand-binding properties to be expected from the DOR protein. By analogy to the findings in T 923/92 (supra) that lack of enablement could result from the fact that the functional features used to define a claimed molecule were insufficiently defined, it had to be concluded that (P1) was not enabling.

- Finally, whereas document (14) prima facie described a successful attempt at cloning rat DOR DNA using a mouse cDNA probe, this result should not be taken as evidence that (P1) - disclosing such a probe - was enabling as regards obtaining vertebrate DOR DNA. The mouse probe used in document (14) was of a shorter size than the one disclosed in (P1), which shorter size enhanced binding specificity. And besides, the rat species was closer to the mouse species than the human species, thus facilitating the cloning. In any case, (P1) presented a failed attempt at cloning other vertebrate DNA (human) than mouse DNA.

For these reasons, the subject-matter of claim 1 only enjoyed priority from the filing date of the application, namely 13 August 1993.

Article 54 EPC, novelty

There were numerous documents published in the priority interval which disclosed the cloning of vertebrate DOR DNA, for example document (14) which, as already mentioned, described the cloning of rat DOR DNA using a mouse DNA probe. The subject-matter of claim 1, thus, lacked novelty.

First auxiliary request; claim 1 to recombinant DNA molecules comprising a nucleotide sequence encoding ***human*** *DOR DNA.*
Article 56 EPC, inventive step

As already established when assessing priority in relation to vertebrate DOR DNA, the specific human DOR DNA enjoyed priority rights from the filing date of the application. Documents published between the priority and the filing dates were relevant to the assessment of inventive step.

- Document (14) could be regarded as the closest prior art. By showing that the full-length rat DOR DNA could be obtained using a mouse DOR DNA as a probe, this document gave the motivation to use the mouse DOR DNA - which had then been disclosed in document (20) - for the cross- species cloning of the human DOR DNA and, also, provided evidence that one would have a reasonable expectation of success in doing so. Furthermore, document (14) also disclosed μOR DNA, and the κOR DNA was known from document (13). Accordingly, the task of identifying an isolated DOR DNA as being a

bona fide DOR DNA had been made trivial by these disclosures in the priority interval.

- Alternatively, document (20) could be taken as the closest prior art as it showed (Fig.4) that the murine DOR sequence hybridized to DNA extracted from human tissues, which, of course, provided evidence that it could be used as a probe to isolate the human DOR DNA from a human cDNA library. Once this DNA was isolated, it became trivial to check that it was indeed DOR DNA by comparing its sequence to that of μOR and κOR DNAs respectively known from documents (14) and (13).

Claim 1 of the first auxiliary request relating to human DOR DNA lacked inventive step.

Second auxiliary request
Admissibility in the proceedings

This request should not be admitted in the proceedings as it was very late filed.

Articles 87 and 88 EPC, entitlement to priority

Claim 1 did not enjoy priority for reasons already given as regards claim 1 of the main request (see supra), namely the group of mouse DOR DNA sequences defined by reference to Figure 5 in (P1) had to be different from the group of sequences defined by reference to Figure 5 in the patent in suit. And also, (P1) failed to give a clear definition of the properties to be expected from a protein encoded by a mouse DOR DNA.

Article 56 EPC, inventive step

- Document (2) which disclosed a prior attempt at cloning mouse DOR DNA could be taken as closest prior art. The problem to be solved could be regarded as finding an improved method for obtaining this receptor. In this framework, it would be obvious in order to identify the clones encoding the DOR protein, to express the DOR DNA in COS cells rather than use an in vitro cell free transcription system because it was a matter of common general knowledge that receptors best functioned when part of a cell membrane. As for the use of ^{125}I-DADDLE as a screening agent for the DOR protein expressed in COS cells, it would equally be obvious insofar as it had long been known (document (38)) that this compound was much more efficient at detecting opiate receptors than any other forms of DADDLE. Besides, other screening agents were known which could have been used for screening.

- Alternatively, document (36) could be regarded as the closest prior art as it disclosed a cloning method for DOR DNA (page 79). This cloning method in combination with the obvious use of ^{125}I-DADDLE (document (38)) rendered non-inventive the claimed recombinant molecules.

X. The respondent's submissions in writing and during oral proceedings insofar as relevant to the present decision may be summarised as follows:

Main request; claim 1
Articles 87 and 88 EPC; entitlement to priority

- Prior to the priority date, there had been numerous attempts at cloning the DOR DNA, which had all failed. It was only after the inventors had disclosed the mouse DOR DNA sequence ((P1), Figure 5) that the isolation of DOR DNA from other organisms had become possible (documents (4), (5) and (14)). Figure 5 gave a very clear pointer has to the kind of DNA which should be looked for and, indeed, the human DOR DNA turned out to be very similar to the mouse DOR DNA. The confirmation that the cloned DNA was DOR DNA could easily be obtained by testing the ligand-binding properties of the DOR protein. At the priority date, this would have been routine work. Document (22), page 1097 showed that there were numerous ligands available. Therefore, the teachings of the priority document were enabling as regards isolating DOR DNA other than the mouse DNA.

- The scope of claim 1 extended to DNAs hybridising to the mouse DOR DNA. In accordance with the case law, once a DNA encoding a specific protein had been obtained, it was allowable to claim all sequences hybridising to it (eg. T 412/93 of 21 November 1994). The argument that (P1) was not enabling because in Example 6, the human DOR DNA had been mistaken for the μOR DNA did not hold. In fact, what simply happened was that the inventors had obtained several clones when cloning the human DOR DNA and the μOR DNA was the first one to be sequenced. Yet, this did not change the fact that amongst the other clones subsequently sequenced, there was a DOR clone. It was also not correct that the DOR clone could only be identified by comparison to the

μOR or κOR DNA sequences which had been published in the priority interval. Documents (4), (5) and (14) reported the cloning of other DOR DNAs than the mouse DOR DNA without any hint that they relied on sequence comparison.

- The differences in sequence (seven bases) between the mouse DOR DNA probe shown in Figure 5 of the priority document and that shown in Figure 5 of the patent in suit did not make the group of recombinant DNA molecules which was claimed different from the group of recombinant DNA molecules which may have been obtained by hybridisation to the earlier Figure 5, all the more so that hybridisation was to be carried out under low stringency conditions. In order to be convincing that they were meaningful, the appellants would have had to show that hybridisation carried out under low stringency conditions led to a DOR DNA being identified as hybridising to one of the probes and not to the other.
This case was clearly different from that dealt with in T 923/92 (supra) where a specific and individualized molecule was the claimed subject-matter and differed from that disclosed in the priority document. Here, the errors were not in the claimed DNA molecules but in the reference molecule used for identifying them.

The claimed subject-matter enjoyed priority from 13 August 1992.

First auxiliary request; claim 1 to recombinant DNA molecules comprising a nucleotide sequence encoding ***human*** *DOR DNA.*
Article 56 EPC, inventive step

- Document (14), identified as the closest prior art, described the cross-species cloning of rat DOR DNA starting with the mouse DOR DNA probe (document (20)). Yet, the fact that both DNAs would hybridize had already been described in (P1) (example 4). If (P1) was to be disregarded as non-enabling as regards cross-species cloning, then by analogy it had to be concluded that the combination of the teaching of document (14) with that of document (20), which did not provide more information than that found in the priority document, had to be disregarded when assessing the inventive step of cloning human DNA. In particular, the fact that document (14) provided the μOR DNA sequence was not meaningful. It did not transform the ability of the skilled person from not being able to clone human DOR DNA to being able to do so. For these reasons, inventive step was not affected.

- One came to the same conclusion taking as closest prior art document (20) which was the scientific publication corresponding to the priority document. Document (14) did not bring any information further to that contained in document (20) which would render obvious the cloning of human DOR DNA.

Second auxiliary request
Admissibility in the proceedings

This request was submitted in direct answer to the board's findings as regards the earlier requests. It differed from the first auxiliary request only by a very simple amendment (deletion), raised no new issues as the claimed subject-matter was already in the granted claim request. Although late filed, it was, thus, admissible.

Articles 87 and 88 EPC, entitlement to priority

The mouse DOR sequence was disclosed in the priority document. The arguments presented as regards the priority rights to be attributed to claim 1 of the main request (see supra, third and fourth paragraphs) equally applied to claim 1 of this request. The claimed subject-matter enjoyed the priority date of 13 August 1992.

Article 56 EPC, inventive step

- Prior to the priority date, there had been numerous reports of failure in cloning the mouse DOR DNA. Document (2), identified as the closest prior art, was an example of such a failure. In order to obtain the mouse DOR DNA, the present inventors had proceeded in quite a different manner from the one therein described, insofar as they had used a different expression screening method i.e. that of expressing the cloned DNA into mammalian cells. Furthermore, they had chosen random priming of the cDNA library and, besides, they had used ^{125}I-DADDLE as the ligand to identify the

clones expressing the DOR protein. This last change was not trivial because of the increase in screening efficiency which resulted therefrom, nor was it obvious in view of the number of ligands available. In particular, arguing that it would have been obvious to use ^{125}I-DADDLE in view of the teachings of document (38) was not convincing as ^{125}I-labelled compounds were known to be dangerous and would not be used if there was a choice. The cloning method used in the patent in suit was not in any way suggested in document (2) even if combined with document (38) and the claimed subject-matter was thus inventive.

- Document (36) also cited as possible closest prior art, described another failed attempt at cloning DOR DNA. There was evidence on file (document (32)) that the cloning method therein described was flawed. Document (36) was not relevant for inventive step even if combined with the teachings of ^{125}I-DADDLE as an efficient screening ligand in document (38).

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

The respondent requested that the appeals be dismissed (main request) or that the patent be maintained on the basis of one of the auxiliary requests 1 or 2 as filed during the oral proceedings.

Reasons for the decision

Main request, claim 1
Articles 87 and 88 EPC, entitlement to priority

1. Claim 1 relates to a group of recombinant DNA molecules comprising a nucleotide sequence encoding a **vertebrate** delta opioid receptor (DOR) defined by its property of hybridising under conditions of low stringency to a probe consisting of the nucleotide sequence shown in Figure 5 or its complement. In the priority document (P1), the following statement is found in the passage bridging pages 13 and 14:

"Illustrated hereinbelow is the obtention of a cdNA encoding murine delta opioid receptor ... The availability of this cDNA permits the retrieval of the corresponding delta opioid receptors-encoding DNA from other vertebrate species... Thus the cDNA of Figure 5,...,may be used as a probe to identify that portion of vertebrate genomic DNA which encodes the corresponding delta opioid receptor protein."

On page 24, it is mentioned that cDNA libraries can be screened at low stringency for obtaining additional clones encoding other regions of the protein in order to assemble a full length DOR DNA. In Example 6, conditions of fairly low stringency are used to obtain opioid receptor human genomic clones using mouse DNA as a probe.

2. On this basis and even taking into consideration further passages of the priority document, it can be said that this document does not provide an **expressis**

verbis disclosure of the subject-matter of claim 1. Nonetheless, it must be kept in mind that in accordance with the case law, a patent must be construed by a mind willing to understand, not a mind desirous of misunderstanding (see eg. T 190/99 of 6 March 2001). This, of course, also applies to the contents of the priority document of a patent. In the board's judgement, applying this principle to the present case leaves no doubt that (P1) provides **formal support** for a group of recombinant DNA molecules such as claimed.

3. However, as pointed out in the case law (cf. Case Law of the Boards of Appeal of the EPO, 5th edition 2006. see IV, B.3), for priority to be acknowledged, it is not sufficient that a formal support for the claimed subject-matter be found in the priority document; on the contrary, it pre-supposes that the priority document also provides an adequate technical teaching in respect of said subject-matter and that this be the "same" teaching as that of the European patent. The question which needs to be addressed is, thus: is such a teaching found in (P1)?

4. (P1) teaches the cloning of the mouse DOR DNA and its sequence. The respondent repeatedly emphasized that this was the key to cloning further vertebrate DOR DNAs, relying on the fact that many previous attempts - without the help of that DNA - had failed. The board agrees that the provision of the mouse DOR DNA sequence was **one** essential element in the cloning of further DOR DNAs of different origins. However, it is readily apparent from the priority document per se that this teaching on its own is not sufficient to obtain other vertebrate DOR DNAs. In Example 6, a human DOR DNA is

allegedly identified (DOR-h1, page 41)) by probing a human DNA library with mouse DOR DNA. Yet, the partial opiate receptor DNA clone which is so isolated turned out to be μOR DNA.

5. This result has severe implications. Firstly, had the skilled person proceeded as taught in the priority document, he/she would have obtained partial DNA sequences without any means to identify them as DOR sequences and, when combining them in order to obtain a full DOR sequence would most probably have obtained a patchwork of sequences of different opiate receptor DNAs. Secondly, had the skilled person used the provided partial human opiate receptor DOR DNA sequence (in fact, μOR DNA) to retrieve full-length human DOR DNA, he/she would clearly have been misled. Once realising that a mistake had occurred, the only course of action would have been to re-start the cloning experiment, which in the absence of any guidance, amounts to undue burden. For this reason, the board concludes that the teaching of the priority document is not sufficient to establish priority for the cloning of recombinant DNA molecules encoding a vertebrate DOR.

6. Further arguments were provided by the respondent in favour of acknowledging priority. One of them was that by proceeding as taught in (P1), one would necessarily get some clones carrying DOR DNA as was shown later on in the patent application per se. This may well be true but the priority document must be read on its face value and is mistaken as to which DNA is DOR DNA. Another argument was that post-published documents (4) and (5) described the cloning of human DOR DNA and document (14) published in the priority interval

described the cloning of rat DOR DNA, using mouse DNA as a probe. Yet, document (4) emphasizes that special measures had to be taken to isolate a clone carrying full-length human DOR DNA (page PL-467) whereas the work disclosed in document (5) (published in 1994) was done in the full knowledge of μ, κ and DOR DNA sequences of other organisms (see passage bridging pages 1015 and 1016). These teachings do not amount to a satisfactory - even if post-published - evidence that the recombinant DNA molecules encoding vertebrate DOR DNA could be obtained without undue burden on the sole basis of the teaching in the priority document. The cloning described in document (14) involved a cDNA library from rat tissues, rats being phylogenetically closer to mice than any other vertebrates, and the experimental conditions which were used for the cloning were distinctly different from those described in (P1): use of a short mouse probe, direct selection of full-length rat DOR DNA. There again, document (14) does not reflect an enablement to be drawn from the priority document.

7. It is observed that the European patent discloses the isolation of μ, κ and DOR clones and their unambiguous characterisation, in particular by comparison with sequences then available in the art. Thus, it can be said to contain a technical teaching which is different (more complete) from that of the priority document. For this reason, it is concluded that the subject-matter of claim 1 enjoys priority from the filing date of the patent application, namely 13 August 1993.

Article 54 EPC; novelty

8. In view of the conclusion reached on priority, all documents published before the filing date of the patent in suit are to be taken into consideration under Article 54 EPC. Document (14) teaches the isolation of full-length cDNA encoding the rat opioid receptor as well as the sequence of the rat DOR protein. The mouse and rat DOR proteins share 97% homology (page 312, right-hand column) and, therefore, their encoding DNAs will hybridize under conditions of low stringency. The subject-matter of claim 1 is not novel. The main request is rejected for failing to fulfil the requirements of Article 54 EPC.

First auxiliary request; claim 1 to recombinant DNA molecules comprising a nucleotide sequence encoding ***human*** *DOR DNA.*

9. The above reasoning which led to the conclusion that the subject-matter of claim 1 relating to nucleotide sequences encoding a vertebrate DOR did not enjoy priority was developed in relation to the human DOR DNA (see points 4 and 5 supra). It is, thus, valid for the assessment of priority of claim 1 of the first auxiliary request when relating to human DOR DNA. Accordingly, this independent embodiment of claim 1 only enjoys priority from the filing date of the patent in suit (Articles 87 and 88 EPC).

10. None of the documents on file published before the filing date discloses recombinant DNA molecules comprising a nucleotide sequence encoding the human DOR receptor. The subject-matter of claim 1 is, thus, novel (Article 54 EPC).

11. At oral proceedings, documents (14) and (20) were discussed in the framework of assessing inventive step. Either one of them was considered to be the closest prior art and its combination with the other one was argued to be detrimental to inventive step. The board agrees that either one of them may be seen as the closest prior art. The reasoning on inventive step will be developed starting from document (14).

12. Document (14) teaches the primary structures and expression from cDNAs of rat opioid DOR and μOR subtypes. In the introductory part, the importance of opioid receptors as mediators of the pharmacological actions of opioid analgesics is emphasized. The cloning of two cDNAs is then described which involves cross-species hybridisation of a rat cDNA library with a partial mouse DOR cDNA sequence.

13. Starting from the closest prior art, the problem to be solved may be defined as isolating further DOR DNA clones from other organisms.

14. The solution provided is the cloning of human DOR DNA. Taking into account the known involvement of the DOR receptors in the mode of action of opioid drugs, the choice of human tissues as starting material is considered obvious.

15. The cloning itself involved probing a human genomic DNA library with a mouse probe. The probe had already been described in the art (document (20)). It then involved the identification of those clones screened with the mouse DNA probe as being bona fide DOR DNA. This was

done by comparison of the cloned DNA sequences with the published sequences of the then known murine δ, μ and κ DNAs (see patent in suit, page 16, Example 6). Otherwise stated, the cloning of the human DOR sequence was achieved by using a known probe for screening the positive clones and comparing with known sequences for identification of the DOR clone. For this reason, the isolation of the human DOR DNA did not involve inventive step.

16. The respondent argued that if the priority document was not enabling as regards isolating human DOR DNA, then document (20) (its scientific counterpart) could not be detrimental to inventive step. This argument is, however, not convincing. Indeed, it is the combination of the teachings of document (14) with those of document (20) which is detrimental to inventive step. Contrary to the respondent, the board sees the availability of the murine DOR, μOR and κOR sequences from documents (14) and (13) as providing the extra information which made the cloning and characterisation of the human DOR DNA feasible in an obvious manner.

17. For these reasons, the first auxiliary request is rejected for failing to fulfil the requirements of Article 56 EPC.

Second auxiliary request
Admissibility in the proceedings

18. This request was filed at oral proceedings, ie it is a late filed request which may only be admitted at the board's discretion. It was filed in direct answer to the board's findings on novelty and inventive step of

the main and first auxiliary requests. Claim 1 was obtained by limiting the claimed subject-matter to murine recombinant DNA molecules. This subject-matter was already present in the granted claim request. For these reasons, the board decides to admit the second auxiliary request in the proceedings.

Articles 87 and 88 EPC, entitlement to priority
Article 54 EPC, novelty

19. It is not disputed that the cloning and sequencing of mouse DOR DNA is described in (P1). The reasoning developed in points 4, 5 or 9 supra concerning the cloning of vertebrate or human DOR DNAs does not apply. Yet, appellant II pointed out that Figure 5 of the priority document providing the mouse DOR hybridising sequence differed from Figure 5 in the patent application by the addition of seven interspersed bases in the 3' untranslated region. In his view, the reference molecules used to identify the claimed molecules being thus different, the groups of claimed molecules to be retrieved by hybridisation to these reference molecules had to be different. This led him to conclude that the priority document was not enabling for the recovery of the group of DNA molecules to be retrieved by hybridisation to the second reference molecule (claim 1).

20. The board is not convinced by this argument. Indeed the claimed group of DNA molecules is characterized as hybridizing to the DNA of Figure 5 under conditions of low stringency. Under such conditions, molecules which are strictly identical to the probe will **not be** the only ones to hybridize to it. On the contrary, these

conditions were developed for the screening of molecules which differ somewhat from the probe while nonetheless maintaining some identity. There is no evidence on file that hybridisation to the DNA of Figure 5 of the priority document would lead to a different group of molecules from that obtained by hybridisation to the DNA of Figure 5 in the patent in suit. In contrast, it is fully expected that they will not be different. In the board's judgement, such very rare molecules, if any at all, which may theoretically bind to the sequence of Figure 5 in the priority document and would not bind to the sequence of Figure 5 in the patent in suit - or vice versa - can be ignored as de minimis.

21. During oral proceedings, appellant II mentioned T 929/93 (supra) as the case law relevant to the present situation. This is, however, not the case. In this earlier decision, what was at stake was whether **a claimed defined specific protein** could enjoy priority from the disclosure in the priority document of a protein which differed by three amino acids. The then competent board decided that priority could not be acknowledged. This situation is undoubtedly different from the one encountered here where it is not the claimed subject-matter which is different from that disclosed in the priority document and, as already mentioned, the observed differences - which rather affect the reference molecule - are not meaningful.

22. For these reasons, the board decides that the differences between Figure 5 of the priority document and Figure 5 of the patent in suit have no bearing on priority.

23. It was also argued that (P1) did not provide enough information on how to test the pharmacological properties of the mouse DOR receptor. In the board's judgement, the properties specific to a DOR receptor in terms of ligand-binding had already been well characterized at the priority date. In this respect reference is made to document (22). Table 1 clearly distinguishes a DOR receptor from the other types of receptors, for example as being able to bind to DPDPE or DTLET. There again, the findings in T 929/93 (supra) that lack of enablement may result from the functional properties of a claimed compound being loosely defined do not apply. Indeed, there is no doubt that the ligand-binding properties of the DOR receptor are meant to be all of its ligand-binding properties and that, on the contrary to the earlier case, no partial characterisation of the claimed subject-matter is intended on the basis of some of the ligand-binding abilities of the protein it encodes.

24. The board, thus, concludes that the subject-matter of claim 1 and dependent claims thereof enjoys priority from the priority date, namely 13 August 1992.

25. The novelty of the claimed subject-matter was not challenged. The board is also of the opinion that none of the documents published prior to the priority date disclosed recombinant molecules such as now claimed.

Article 56 EPC, inventive step

26. In the course of oral proceedings the closest prior art was alternatively defined as document (2) or document (36).

27. Document (2) teaches an attempt to isolate the mouse DOR cDNA from the same mouse NG108-15 neuroblastoma cell line as used for the present invention. It is mentioned on page 284 that one of the isolated clone (FLOPI-20) expressed opioid binding sites "with pure δ selectivity". Under such circumstances it is difficult to see what the motivation would be to clone once more the mouse DOR DNA. If, for the sake of argument, one accepts that the skilled person would be inclined to do so, then the problem to be solved could be defined as isolating further clones encoding mouse DOR DNA.

28. The solution provided in the patent in suit is mouse DOR clones obtained by a significantly different process from that outlined in document (2). The positive clones were identified in COS cells rather than by in vitro transcription and translation. Furthermore, while document (2) does not mention the ligand used for identifying the protein encoded by the then isolated "DOR DNA" , the patent in suit teaches the use of ^{125}I-DADDLE as a ligand , which compound was acknowledged shortly after the priority date (document (24), page 1883, right-hand column) as being "a key element... in identifying cells expressing the receptor gene." In contrast, it is mentioned in document (30) that the DNA isolated in document (2) was in fact an E. coli gene. No hint of this is, of course, found in document (2) nor, a fortiori of the probable necessity

of changing the cloning protocol. Yet, it is the protocol disclosed in the patent in suit which led to the successful isolation of bona fide mouse DOR DNA. For this reason, inventive step is acknowledged.

29. The final remark should be made that the board cannot follow appellant II's argument that the use of ^{125}I-DADDLE was rendered obvious by the disclosure in document (38) of its efficiency for identifying DOR. This document was published some 14 years before the priority date and, furthermore, was followed by the disclosure of other ligands specific to DOR (document (22)). In the board's judgment, the argument can only be arrived at with the hindsight knowledge of the invention.

30. Another starting point for the assessment of inventive step was argued to be document (36), a review on the Problems and Approaches in Studying Membrane Opioid Receptors. On page 79, it is taught that an attempt has been made at cloning the mouse DOR receptor present in the NG108-15 cell line. The cloning was not attempted using standard methodology. On the contrary, it was said to involve the construction of subtraction probes used to enrich the cDNA population in DOR cDNA. The clones, thus, obtained are said to be currently under investigation. No indication is given as to the nature of the ligand to be used for their final characterisation.

31. Starting from the closest prior art, the problem to be solved could be defined as obtaining the results expected from carrying out the method described in the art.

32. The solution was to use a different cloning method involving, as already mentioned, the expression of the DOR receptor in COS cells and its identification by ^{125}I-DADDLE. There is no hint in document (36) that the cloning method may have to be changed nor that the ligand should the ^{125}I-DADDLE. In fact, as in case of document (2), there is evidence on file (document (32)) that by following the teachings of document (36), the cloning of mouse DOR DNA was never achieved.

33. For these reasons, inventive step is also acknowledged over the teaching of document (36) even if it was to be combined with that of document (38). The second auxiliary request is found to fulfil the requirements for patentability.

Order:

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The case is referred back to the first instance with the order to maintain the patent on the basis of auxiliary request 2 comprising claims 1 to 7, as filed in the oral proceedings, and a description to be adapted thereto.

The Registrar The Chairman

A. Wolinski L. Galligani