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Datasheet for the decision of 13 April 2021

Case Number: T 2945/18 - 3.3.04

Application Number: 15188991.2

Publication Number: 3009142

IPC: A61K38/08, A61K38/55, A61P25/04

Language of the proceedings: EN

Title of invention:
Opiorphin for use as analgesic agent

Applicant:
Institut Pasteur

Headword:
Opiorphin as analgesic/INSTITUT PASTEUR

Relevant legal provisions:
EPC Art. 76(1)

Keyword:
Divisional application - subject-matter extends beyond content of earlier application (yes)

Decisions cited:

Catchword:

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Case Number: T 2945/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 13 April 2021

Appellant: (Applicant)	Institut Pasteur 28, Rue du Docteur Roux 75724 Paris Cedex 15 (FR)
Representative:	Plasseraud IP 66, rue de la Chaussée d'Antin 75440 Paris Cedex 09 (FR)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 18 July 2018 refusing European patent application No. 15188991.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chair	G. Alt
Members:	B. Rutz
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the applicant ("appellant") lies from the decision of the examining division refusing European patent application No. 15 188 991.2 entitled "*Opiorphin for use as analgesic agent*". The application was filed as a divisional application of European patent application No. 09 761 603.1 published as international application under the PCT with No. WO2009/150040 ("the earlier application").

II. In the decision under appeal, the examining division held that the subject-matter of claims 1 to 7 of the sole request extended beyond the content of the earlier application as filed and thus contravened the requirements of Article 76(1) EPC. The examining division held that "*the parent application does not clearly and unambiguously disclose the use of pyroglutamate-opiorphin in the treatment of pain, wherein repeated administration of such peptides do* [sic] *not induce pharmacodependence*" (see point 14.5 of the Reasons).

III. With the statement setting out the grounds of appeal, the appellant submitted a set of claims of a new main request (identical to the claims on which the decision under appeal was based with the exception of a corrected claim dependency in claim 7) and auxiliary requests 1 and 2.

IV. The board summoned the appellant to oral proceedings and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA.

V. In points 8 to 15 of this communication, the board stated that it preliminarily considered that the subject-matter of claim 1 of the main request and auxiliary request 1, both relating to the peptide pyroglutamate-RFSR "for use as an analgesic agent for treatment of pain", contravened the requirements of Article 76(1) EPC.

Furthermore, in points 18 to 24 of this communication, the board stated that it preliminarily considered that also claims 3 to 7 of all requests contravened the requirements of Article 76(1) EPC.

VI. The appellant replied by providing further arguments, a new main request and new auxiliary requests 1 and 3 in which claims 3 to 7 had been deleted. These requests were to replace the main request and auxiliary requests 1 and 2 on file. In addition, a new auxiliary request 2 was submitted in which claim 1 had been amended *vis-à-vis* claim 1 of the main request by replacement of "pyroglutamate-RFSR" with the expression "a modified sequence SEQ ID NO: 2 comprising one or more chemical modifications improving its stability or bioavailability".

VII. Claim 1 of the main request reads as follows:

"1. A peptide for use as an analgesic agent for treatment of pain, wherein said peptide consists of the sequence QRFSR (SEQ ID NO: 2), or pyroglutamate-RFSR, and wherein said treatment comprises repeated administrations of the peptide and does not induce pharmacodependence."

VIII. Oral proceedings before the board took place on 13 April 2021, as requested by the appellant, in the

form of a videoconference. During the oral proceedings, the appellant withdrew their three auxiliary requests. At the end of the oral proceedings, the chair announced the board's decision.

IX. The appellant's arguments submitted in writing and during oral proceedings may be summarised as follows.

Main request (sole request)

Divisional application - content (Article 76(1) EPC)

The earlier application explicitly disclosed pyroglutamate-RFSR as a preferred peptide according to the invention and further disclosed that the peptides of the sequences QRFSR (SEQ ID NO: 2) and pyroglutamate-RFSR formed "*a preferred pair of peptides according to the invention*" (see statement of grounds of appeal, page 11, last paragraph and page 13, point 2.3.3, citing page 6, lines 27 to 33 and page 7, lines 1 and 2 of the earlier application).

The earlier application disclosed the use of all peptides of the invention for treating pain via the activation of an opioidergic pathway depending on μ-opioid receptors (see page 16, lines 14 to 16 and 20 to 21 and page 17, lines 7 to 9). The results laid out in the examples corroborated the mechanism of action of the peptides according to the invention as stated in the description on page 5, lines 20 to 26: "*Without being limited by a particular theory, the inventors believe that the peptides according to the invention by inhibiting degradation of enkephalins by these two metallo-ectopeptidases (NEP and APN), potentialize their physiological action in terms of amplitude of action and of duration of action and thereby activates*

the opioid pathways, more particularly the enkephalin-dependent μ- and δ-opioid receptors."

The link between activation of the enkephalin-dependent μ-opioid receptors and the anti-pain effect was disclosed in Example 2 (pages 21 to 24), in particular on page 23, lines 3 to 10 and in the Conclusion of Example 7 on page 37, in particular, lines 1 to 7 and lines 23 to 26.

The earlier application therefore disclosed the use of pyroglutamate-RFSR for treating pain via the activation of an opioidergic pathway depending on μ-opioid receptors.

Requests

X. The appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request filed by letter of 11 June 2020.

Reasons for the Decision

Main request (sole request)

Divisional application - content (Article 76(1) EPC)

1. Claim 1 is directed to a "peptide for use as an analgesic agent for treatment of pain, wherein said peptide consists of the sequence QRFSR (SEQ ID NO: 2), or pyroglutamate-RFSR, and wherein said treatment comprises repeated administrations of the peptide and does not induce pharmacodependence".

2. In view of the examining division's decision (see section II above), the issue is whether the skilled person would have derived from the earlier application, directly and unambiguously, using common general knowledge and seen objectively and relative to the date of filing, the disclosure of the "*use of pyroglutamate-RFSR as an analgesic agent for treatment of pain, and wherein said treatment comprises repeated administrations of the peptide and does not induce pharmacodependence*".

3. The first question to arise is whether the application generally discloses the use of the peptides of the invention for the treatment of pain.

4. The title of the earlier application is "*OPIORPHIN FOR USE AS A PSYCHOSTIMULANT AGENT*", and its first sentence on page 1 reads: "The present *invention relates to peptides derived from human BPLP (Basic Proline-rich Lacrimal Protein) protein coded by the Prol1 gene, notably opiorphin, for use as psychostimulating agents.*"

5. The first reference to "*analgesic*" effects or properties can be found in the introductory section on page 2 with regard to prior art on sialorphin (a rat hormonal peptide) and opiorphin (its human homologue).

It is stated on page 2, lines 17 to 20: "*Therefore, sialorphin is the first physiological inhibitor of NEP enkephalinase to have been identified in mammals (European Patent Application EP 1 216 707) and that displayed a potent analgesic effect in rat models of pain.*"

It is further stated on page 2, lines 28 to 32: "*European Patent Application EP 1 577 320 indicates that opiorphin has analgesic properties and that it may notably be used for treating or preventing pain. The analgesic effect of opiorphin was confirmed subsequently by Rougeout and Messaoudi (Med. Sci. (Paris) 2007; 23(1):37-9).*"

6. At the end of the introductory part on page 3, lines 4 to 15, the following is stated: "*The inventors have found that, surprisingly, opiorphin not only has analgesic properties, but also a psychostimulant effect. Further, this psychostimulant effect is not associated with any adverse effect on amnesia, sedation, hyperactivity or addiction type. Finally, it was found that the analgesic potency of opiorphin is as powerful as that of morphine and that its psychostimulant potency is as powerful as that of imipramine.*

Therefore, opiorphin and derived peptides may advantageously be used as psychostimulants for treating or preventing diseases such as narcolepsy, hypersomnia, vigilance drop, attention deficit in adults and in children, hyperactivity in adults and in children, attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorders (OCD), and mood disorders such as depression, bipolar disease, dysthymic disorder and cyclothymic disorder."

7. Moreover, neither the aforementioned list of diseases, nor such a list in the claims (see claims 8 to 10), nor the definition of diseases on page 14, lines 7 to 14 and page 16, line 29 to page 17, line 4 mention use in the treatment of pain or as an analgesic agent.

8. From the passages on page 1 and page 3 cited above, the skilled person would have derived that the invention is concerned with the newly discovered use of opiorphin as a psychostimulant. From the passage on page 2, the skilled person would have derived that this is a recapitulation of what was known about opiorphin in the prior art, namely that it was useful as an analgesic and that the application adds the following to this knowledge (see point 6. above): "*Finally it was found that the analgesic potency of opiorphin is as powerful as that of morphine*".

9. In the board's view, from the cited passages, it remains at least ambiguous whether a medical use relating to the analgesic properties of opiorphin was part of the invention. None of the diseases listed on page 3, page 14 and page 16 to 17 and in the claims include pain.

10. The only further references to analgesic activity/ effect or pain in the earlier application are in the context of the examples carried out with opiorphin (see the figure legends on page 20; Examples 2, 5, 6 and 7 and Figures 2 and 3).

11. However, the skilled person, when considering the examples in the context of the earlier application as a whole, would have understood them as attempts to dissect the μ- and δ-opioid receptor pathways (Examples 2 to 4) and obtain further information on the pharmacodependence and tolerance of the agent (Examples 5 and 6). Thus, the skilled person would not have considered them as a direct and unambiguous disclosure of a use of all the peptides of the invention as analgesic agents for the treatment of pain.

12. The appellant referred to page 16, lines 14 to 16 which discloses the "*use in vivo of peptides according to the invention for activating an opioidergic pathway depending on μ- and/or δ-opioid receptors*". According to the appellant, it would have been clear from the examples that the μ-opioid receptors were responsible for the anti-pain activity of the peptides of the invention. It would therefore have been immediately apparent and implicit for the skilled person that potentialising the activation of the opioidergic pathway depending on μ-opioid receptors by the peptides of the invention, including Glp-RFSR, was equivalent to the treatment of pain.

13. Indeed, the earlier application provides evidence that the analgesic effect of opiorphin is primarily mediated by μ-opioid receptors (see page 23, Table 1 and lines 3 to 10: "*the analgesic effect of opiorphin in the 'formalin test' is abolished in the presence of Naloxone or CTPA, a specific antagonist of μ-opioid receptors*" and Example 7: "*opiorphin exerts at 1 mg/kg i.v. a potent and tonic antinociceptive activity via activation of opioidergic pathways dependent on endogenous μ-opioid receptors*"), while the antidepressant and psychostimulant activity is primarily mediated through opioid receptors of the δ subtype (see page 29, lines 8 to 10).

14. The earlier application also discloses that the effect exerted by opiorphin (and other peptides of the invention, including pyroglutamate-opiorphin) takes place upstream of the enkephalin-receptor interaction, i.e. by inhibiting enkephalin degrading metallo-ectopeptidases and thus potentialising the physiological action of the enkephalins (see page 5, lines 17 to 26).

15. The board further notes that the peptides of the invention can have such an indirect effect on endogenous μ- and δ-opioid receptors but not on κ-receptors (see e.g. page 14, lines 2 to 6). Which receptor class (μ- or δ-opioid) is activated depends on the physiological status of the patient to be treated. In other words, in a patient experiencing pain, the same enkephalins regulated by the same metallo-ectopeptidases can bind to a different receptor than in a patient experiencing stress or emotions. This is, *inter alia*, disclosed on page 37, lines 23 to 26: "*The anti-pain, antidepressant and psychostimulant effects of opiorphin are dependent on the activation of the endogenous μ- and δ-opioid receptors which transmit the action of the endogenous enkephalins released in response to the stimulus (pain, stress, emotions ...)*".

16. However, the board is not persuaded by the appellant's line of argument that it would have been immediately apparent and implicit for the skilled person that potentialising the activation of the opioidergic pathway depending on μ-opioid receptors by the peptides of the invention was equivalent to the treatment of pain. This is because the earlier application does not unambiguously disclose that the activation of endogenous μ-receptors is exclusively linked with the treatment of pain.

17. In fact, several passages in the earlier application disclose that antidepressant and psychostimulant effects are, at least partially, also transmitted through the endogenous μ-receptors (highlighting added by the board):

page 5, lines 13 to 26: "*The peptides according to the invention exert a psychostimulant activity. By 'peptide exerting a psychostimulant activity' is meant a peptide which:* [...] *activates the opioid pathways, more particularly the enkephalin dependent μ-* ***and*** *δ-opioid receptors*"

page 13, lines 30 to 32: "*the antidepressant effect and the psychostimulant effect of opiorphin are dependent on the activation of the endogenous μ-* ***and*** *δ-opioid receptors, but not on activation of endogenous κ-opioid receptors*"

page 14, lines 1 to 4: "*Therefore, the invention relates to peptides according to the invention, described in the above paragraph, for a use as psychostimulants. Such peptides according to the invention may be used for activating an opioidergic pathway dependent on μ-* ***and****/or δ-opioid receptors.*"

page 14, lines 15 to 18: "*Within the scope of treating one of these diseases* [not including pain]*, the peptides according to the invention are preferably administered to a sub-group of patients needing a psychostimulant and/or activation of an opioidergic pathway depending on μ-* ***of*** [sic] *δ-opioid receptors.*"

18. Thus, the mere disclosure of an *in vivo* use of the peptides for activation of the μ-opioid receptor pathway would not have led the skilled person to conclude that the peptides were to be used as analgesic agents for the treatment of pain.

19. In conclusion, a general disclosure of "a peptide for use as an analgesic agent for treatment of pain" is lacking from the earlier application as filed, even for

the compound opiorphin - and thus even more for the compound pyroglutamate-opiorphin.

20. The board therefore finds the subject-matter of the claims to extend beyond the content of the earlier application as filed (Article 76(1) EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated