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Datasheet for the decision of 20 April 2015

Case Number: T 2046/09 - 3.3.04

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Language of the proceedings: EN

Title of invention:
Urocortin-III and uses thereof

Applicant:
Research Development Foundation

Headword:
Urocortin III/RESEARCH DEVELOPMENT FOUNDATION

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - reasonable expectation of success (yes)

Decisions cited:

Catchword:

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Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 2046/09 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 April 2015

Appellant: (Applicant)	Research Development Foundation 402 North Division Street Carson City, Nevada 89703 (US)
Representative:	Rückerl, Florian Dehmel - Bettenhausen Herzogspitalstrasse, 11 D-80331 München
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 28 April 2009 refusing European patent application No. 02753685.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Claes
	K. Garnett

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application No. 02753685.3 with the title *"Urocortin-III and uses thereof"* which was published as WO02/074326. The examining division decided that the subject-matter of all the claims of the main and the sole auxiliary requests before it lacked an inventive step (Article 56 EPC).

II. With the statement of grounds of appeal the appellant submitted a main request and two auxiliary requests.

III. In a communication pursuant to Article 17(1) RPBA the board expressed its preliminary opinion that all the requests on file contravened the requirements of Articles 123(2), 83 and 56 EPC.

IV. With its reply, the appellant submitted three amended claim requests to replace all the previously filed requests, further arguments in favour of inventive step, and re-submitted three declarations from the inventors which had been already submitted during the proceedings before the department of first instance.

Claim 1 of the main request and auxiliary requests 1 and 2 read:

"1. An isolated and purified human or mouse urocortin III protein, wherein said protein has the amino acid sequence depicted in SEQ ID NO: 3 and SEQ ID NO: 5, respectively."

V. Oral proceedings were held on 20 April 2015. The board considered that the issues of added matter and lack of

sufficient disclosure pointed out in the board's communication had been overcome by the amended claims. The appellant was then heard on the issue of inventive step. At the end of the oral proceedings the chairwoman announced the decision of the board.

VI. The following documents are cited in this decision:

D1: Brunner *et al.* (2000), Chromosome Research, Vol. 8, No. 6, pages 465-476.

D2: Reyes *et al.* (2001), PNAS, vol. 98, No. 5, pages 2843-2848.

D8: Jongeneel (2000), Briefings in Bioinformatics, Vol. 1, No. 1, pages 76-92.

Declaration by Kathy Lewis dated 3 March 2009.

VII. The appellant's arguments can be summarised as follows:

All requests - claim 1 - inventive step

Starting from the closest prior art represented by document (D2) the problem to be solved was the provision of a further active human urocortin-related peptide (URP).

The relevant question was whether or not the skilled person would have had a reasonable expectation of being able to successfully identify the human peptide described in the "Note Added in Proof" on page 2848 of document (D2).

It was known that the characterisation of neuropeptides was a technical field fraught with uncertainties, and

the mere reference to a *putative* protein in a prior art document was not a guarantee that such a protein also existed. The "Note Added in Proof" in document (D2) disclosed neither the activity of the newly identified URP nor the strategy or database used to identify it. Thus, the skilled person merely had the knowledge of the *putative* existence of the peptide of interest. This however did not confer any expectation of success on the skilled person that such a protein could actually be identified, as this required that the skilled person could rationally predict the successful conclusion of the identification process. Accordingly, the skilled person would have had no reason to embark on the project of solving the formulated problem.

Even if the skilled person had tried to identify the new peptide referred to in "Note Added in Proof" in document (D2) then the selection of the appropriate database to be searched combined with the appropriate algorithm would require a level of expertise beyond that in the relevant technical field.

As a first step to identify a further URP, the skilled person would have searched human genome databases, as this was the approach also taken in document (D2) (see the paragraph bridging pages 2844 and 2845). As explained on paragraph 4 of the declaration of the inventor Kathy Lewis dated 3 March 2009, the skilled person would then however have failed to identify the peptide referred to in the "Note Added in Proof" in document (D2) and would thus have come to a dead end in the search for the peptide. At this point the skilled person would abandon the attempt to identify the desired peptide as claimed.

After the failure with human genome databases the skilled person would have been reluctant to search in human EST databases which, in view of the drawbacks indicated on page 78 of document (D8), would not be considered to constitute the best starting point for the identification process. Moreover, even if the skilled person had then tried human EST databases, the selection of the appropriate algorithm and search parameters which allowed the identification of sequence AW293249 would still not have been straightforward, and would have gone beyond the usual level of experience of the skilled person.

Assuming nevertheless that the skilled person would have identified the AW293249 sequence, he would still not have concluded that this constituted a partial clone only. After realising that the AW293249 sequence had 68% instead of 77% sequence identity with the pufferfish sequence, as mentioned in the "Note Added in Proof" in document (D2), the person skilled in the art would have classified the result as an artifact and would have abandoned the identification process at that point.

Moreover, even if the skilled person had realised that AW293249 represented an incomplete sequence, he would then have failed to identify the full-length clone since the final step of extending the partial sequence required numerous PCR experiments. Finally, the identification of the cleavage sites within the primary translation products encoded by the full length coding regions went beyond the skilled person's expertise.

Both the examining division in its decision and the board in its preliminary opinion contained in the communication pursuant to Article 17(1) RPBA had used a

hindsight in their assessment of inventive step by drawing on the knowledge of the invention, including the examples disclosed therein, and overlooking the numerous difficulties encountered by the inventors in the finding of the claimed sequence.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request, alternatively auxiliary request 1 or 2, all as filed with its letter dated 31 July 2014.

Reasons for the Decision

1. The appeal is admissible.

All requests - claim 1

Added matter and sufficiency of disclosure

2. The board is satisfied that the concerns under Articles 83 and 123(2) EPC raised in the communication pursuant to Article 17(1) RPBA have been overcome. It is however not necessary for the board to give any reasons for this conclusion in view of its decision on the issue of inventive step (see below).

Inventive step (Article 56 EPC)

3. The application relates to the identification of urocortin III, a further member of the CRF (corticotropin-releasing factor) neuropeptide family. Claim 1 describes this isolated and purified human and mouse protein by its amino-acid sequence.

Closest prior art

4. The board can concur with both the examining division and the appellant that document (D2) represents the closest prior art with respect to the subject-matter claimed. It describes the cloning of urocortin II and mentions, in a "Note Added in Proof" on page 2848, the identification of a further gene encoding the precursor of another human urocortin-related peptide (URP). This "Note Added in Proof" reads: *"We have identified (K. L. et al., unpublished work) a gene encoding the precursor of a second human URP. The putative 38 amino acid mature peptide has, at the amino acid level, 77, 41, 44, 23, and 33% identity to the pufferfish URP, human URP, mouse Ucn II, rat urocortin, and rat/human CRF sequences shown in Fig. 1".*

Problem to be solved

5. Starting from the relevant disclosure in document (D2) reporting on the identification of a further human urocortin-related peptide, of which the putative mature peptide has a length of 38 amino acids and a high percentage identity with various known mature peptides of the urocortin family (in particular 77% identity to the pufferfish URP), the subject-matter of claim 1 differs in that the human (and corresponding mouse) amino acid sequence of the announced mature peptide is revealed. Accordingly, the problem to be solved is the identification of the sequence of the human peptide as announced in document (D2), thereby providing the claimed subject-matter.

6. During the oral proceedings before the board, the appellant formulated the problem to be solved as the provision of "a further active human URP", since the

application as filed disclosed the claimed peptide's activities of binding with several CRF receptors (see example 6). The board notes however that the "Note Added in Proof" in document (D2) refers to a "*second human URP*", thereby implying that the peptide is biologically active. Moreover, the board cannot concur with the appellant that the task with which the skilled person was confronted was the provision of "a" (unspecified) further active human URP peptide, because the starting point in document (D2) refers explicitly to the particular and specific peptide which had been identified. Hence the board is satisfied that, appropriately formulated, the problem to be solved was the identification of the sequence of "the" specific human peptide referred to in the "Note Added in Proof" in document (D2), as established above.

7. The board is satisfied that this problem is solved by the subject-matter of claim 1 in view of the examples in the application, which confirm the particular amino acid sequence and the binding of the peptide to the CRF receptors with a similar pattern as urocortin II.

Obviousness

8. It is established case law of the boards of appeal that a course of action is considered obvious within the meaning of Article 56 EPC if the skilled person would have carried it out in expectation of some advantage or improvement. In other words, obviousness is not only present when the results are clearly predictable but also when there is a "reasonable expectation of success" (not to be confused with a "hope to succeed"), which implies the ability of the skilled person to predict rationally, on the basis of the knowledge existing before a research project is started, the

successful conclusion thereof, within an acceptable amount of time (see Case Law of the Boards of Appeal of the EPO, 7th edition, 2013, point I.D.7.1).

9. When examining the obviousness of the claimed subject-matter in the present case, the relevant consideration is whether or not the skilled person, starting from the "Note Added in Proof" in document (D2), would have rationally predicted the successful conclusion of the identification process of the sequence of the mentioned human URP peptide. This question is to be answered in the affirmative if the skilled person would have had an incentive to embark on the process and would have had a reasonable expectation of achieving the identification.

10. In accordance with established case law of the boards of appeal, a "person skilled in the art" as referred to in Article 56 EPC means an experienced practitioner who is an expert in the relevant technical field, possibly being part of a team with different areas of expertise (see Case Law Book of the Boards of Appeal of the EPO, 7th Edition 2013, section I.D.8.1.1 and 8.1.2). Accordingly, the person skilled in the art for the the present case is therefore not just "any" biologist, but rather one with specialised knowledge in bioinformatics and knowledge of the structure of neuropeptides. This skilled person would have ordinary knowledge of and access to state of the art sequencing technologies, a variety of known search algorithms, biological search strategies and all public gene libraries and databases.

11. The board considers that the publication of the "Note Added in Proof" in document (D2) (see point 4, above) provided the skilled person referred to above with ample incentive to embark on the identification process

of the new peptide mentioned therein in view of such a person's general interest in identifying further neuropeptides.

12. The board in this context does not accept the appellant's argument that, because the "Note Added in Proof" in document (D2) merely referred to the "putative" existence of a peptide and failed to disclose the activity of the peptide or a teaching of the strategy how the peptide had been identified, the skilled person would not have embarked on the identification process.

13. Something which is "putative" means something which is "generally considered" or "reputed" to be. In the field of biotechnology and in the context of a scientific publication (such as document (D2)), the skilled person would normally understand the term "putative" in relation to something as meaning "requiring confirmation", rather than meaning merely "possible" or even "doubtful", interpretations in effect favoured by the appellant. Accordingly, the board considers that the skilled person would have understood the reference to the "putative" 38 amino acid mature peptide as meaning "requiring confirmation", but not as meaning that it was "doubtful" that the 38 amino acids peptide existed at all.

14. The board can accept that, as argued by the appellant, the search for new neuropeptides was known in the relevant technical field to be complex and time-consuming. This fact may support a finding that in such a situation, the skilled person might adopt a particularly cautious and meticulous attitude towards the route to be followed for the identification. In the board's view, however, this would not change the

skilled person's perception of the meaning of the term "putative" and would not lead, therefore, to a sceptical attitude such as to discourage embarking on the identification project altogether. The board notes furthermore in this context that the appellant did not submit any documentary evidence to support the view that the project of the identification of the subject-matter of claim 1 would have involved difficulties going beyond the complexity which is inherent in this particular technical field.

15. The board is furthermore of the opinion that the fact that the "Note Added in Proof" in document (D2) does not provide the skilled person with a particular search strategy on how the putative 38 amino acids peptide referred to was identified, does not constitute a ground for the skilled person to doubt the existence of such a peptide. In fact, the board considers that devising a strategy for the purpose of solving the formulated technical problem merely corresponds to the normal practice of the skilled person in the relevant technical field whereby any technical gaps encountered are filled by applying available knowledge and techniques. The board notes in this context that the appellant has not referred to any concrete technical difficulties involved in the search protocol which was actually followed by the inventors such as would have dampened a skilled person's expectation before embarking on the project. It is also to be noted that the identification process could in fact be successfully concluded and that also the application as filed fails to point out any such hurdles or difficulties. On the contrary, it refers to "*conventional molecular biology techniques*" (see page 9, line 25) and "*standard software available in software data banks*" (see page 18, line 27).

16. In view of the above considerations, the board concludes that the skilled person, when contemplating the disclosure in the "Note Added in Proof" in document (D2), would find there an incentive to embark on the process of identifying the mature peptide reported on and, in the absence of any foreseeable, let alone documented, difficulties or obstacles, would expect that by applying the available knowledge and techniques such an identification process would be successful.

17. The appellant submitted that the skilled person, even if the identification process were embarked upon, would encounter practical difficulties such as would lead him to abandon his efforts in the course of the process.

18. The board considers that, in line with standard practice in the art at the relevant date, the first step in the skilled person's strategy would be to run a bioinformatic search in a number of, if not in all, commonly available databases, including publicly available human EST databases, simultaneously using the pufferfish URP amino acid sequence (shown in Figure 1B of document (D2)) as a query, i.e the sequence which is indicated in the "Note Added in Proof" in document (D2) as having the highest percentage of identity (77%) with the peptide sought to be identified.

19. The board is thus not convinced by the appellant's argument that the skilled person would have started from publicly available human genome databases, considering that this was the strategy followed in the identification of Urocortin II described in document (D2). The board considers furthermore that even if the skilled person were to have initially concentrated his

efforts on human genome databases and, as described in the declaration of Ms Lewis, were to have failed to identify a sequence, it is not conceivable that the skilled person would not then have repeated the search in other commonly available databases.

20. The board notes furthermore in this context that the appellant did not contest that the relevant skilled person was familiar with the abundant information on EST databases as disclosed in document (D8). EST databases are described therein as "*the most abundant source of new coding sequences available today*" and which had been "*used intensively as a source of information for the discovery of new genes whose function can be tentatively deduced from their sequence, and experimentally verified*" (see document (D8), abstract and first paragraph of the right-hand column on page 76). The board is therefore satisfied that EST databases were a standard tool in the art of bioinformatics in the year 2000 and would therefore be included by the skilled person in the database repertoire to be searched with the pufferfish URP query.

21. The appellant has nevertheless argued that the skilled person would have dismissed the use of available EST databases as an appropriate starting point for its search project in view of the drawbacks disclosed in the review article (D8) with respect to such databases.

22. Although document (D8) may mention a number of drawbacks particular as regards the EST databases available at the time (see, *e.g.* page 78, left-hand column), the board considers that the description of certain limitations of data contained in EST databases constitutes part of an objective technical review in a

scientific publication. They are however not of such a severity or magnitude that a skilled person would have summarily dismissed their usefulness in bioinforatics projects. Indeed, the fact that a publication discloses certain drawbacks does not mean that other databases, such as human genome databases, had fewer limitations or were better alternatives. In fact, EST databases are mentioned in prior art document (D1) (see page 467, left-hand column, first paragraph) and throughout document (D2), hence reflecting their common use in identification methods in this very technical field. In the board's view therefore the appellant's argument in this respect must fail.

23. In the context of the selection of an appropriate search algorithm for a search in EST databases in respect of the identification process, the board notes that the simplest and most appropriate algorithm for searching EST databases with an amino acid query was the so-called TBLASTN algorithm (see document (D8), page 84, right-hand column, lines 3 to 5 and page 86, right-hand column, second paragraph). In fact, it was confirmed by the appellant that, when searching available human EST databases with the known amino acid sequence of the pufferfish URP using this algorithm, the skilled person would have identified the sequence of EST clone AW293249 (see point 6 in the declaration of Kathy Lewis dated 3 March 2009). The appellant's argument that the choice of the appropriate search algorithm for a search in EST databases required a higher level of expertise than could be expected from the skilled person must therefore also fail.

24. Accordingly, in view of the above considerations, the board is satisfied that the skilled person, without

further ado and by routine use of databases and algorithms would have identified EST AW293249.

25. After having identified EST AW293249, the board considers, contrary to the appellant's view, that, based on the known structure of the mature pufferfish peptide (see point 18, above), the skilled person would straightforwardly have recognised that the identified EST clone included, in the distal part of the EST, amino acid sequences of a precursor form of a human urocortin peptide, consisting of a truncated form having the first 29 amino acids of the mature peptide region. Indeed, the "Note Added in Proof" in document (D2) refers to a mature peptide which is 38 amino acids long. Nevertheless, the 29 amino acids contained in the distal part of EST AW293249 have 24 amino acids identical with this pufferfish URP sequence. Of the 5 non-matching amino acids in the 29 amino acid sequence identified, only one is non-conservative. In view of these facts and having regard to the intellectual capability of the person skilled in the field of bioinformatics, the board concludes that this person would have realised that there was a more than fair chance of having identified an EST clone containing the sequence of the mature peptide searched for, be it only partial, *i.e.* containing information for merely 29 out of the 38 amino acids in the distal part of the clone. By the same token therefore, the appellant's argument that the identification of the cleavage site within the primary translation product of the identified sequence went beyond the expertise of the skilled person also fails. Accordingly, the skilled person would have had no difficulties in determining the mature peptide's start point and have realised that further sequences were missing in EST AW293249 and that extension of EST sequences at the distal end of the protein was

required. The skilled person would find therein the incentive for attempting "extension" of the sequence. The board considers that this could be routinely achieved with methods customary in biotechnology at the relevant time.

26. The appellant nevertheless argued that the final step of "extending" the partial amino acid sequence of the EST clone in order to identify the complete sequence of the peptide sought to be identified entailed insurmountable technical and intellectual hurdles for the skilled person. In this context, the appellant referred to the "numerous PCR experiments" carried out by the inventors and the difficulty of finding the proper cleavage sites for formation of the mature urocortin III peptide.

27. The board notes in the context of this argument, however, that the appellant has not argued that the skilled person could only achieve the "extension" step by PCR. Indeed, other techniques were equally available to the skilled person for identifying full length sequences, such as *e.g.* cDNA library screening. Furthermore, the board notes that the primers used to extend the sequence information at the C-terminus in the PCR experiments were based on the partial human EST sequence identified and thus available to the skilled person, *i.e.* the actual identified EST clone. Furthermore, the nested PCR strategy employed by the appellant as described in the inventor's declarations was part of the customary practice at the relevant date of the present invention, and the board considers that the number of experiments or the time they take do not render such a strategy inventive.

28. The board can agree with the appellant that it has been established in the case law of the boards of appeal that for the assessment of inventive step by means of the problem and solution approach to be properly and correctly carried out, an *ex post facto* analysis which draws on knowledge of the invention is to be avoided. Neither the board in this decision, nor the examining division in its decision, has based its assessment of inventive step on an *ex post facto* analysis which relies on the knowledge of the invention, as alleged by the appellant. In fact, the only circumstances where a reference is made to the invention and its description in the application is in the context of the evaluation of appellant's arguments which deal with such knowledge. The references merely serve at demonstrating flaws in these arguments and not in the assessment of the course of activities which the skilled person would have conducted when attempting to identify the sequence of the human URP mentioned in the "Note Added in Proof" in document (D2). The board therefore cannot agree with the appellant that the board's assessment of inventive step is based on an *ex post facto* analysis.

29. Summing up the above considerations of the board, the skilled person not only had a incentive to identify the amino acid sequence of the human peptide as announced in the "Note Added in Proof" in document (D2), but would also have had reasons to expect that, by applying standard bioinformatic technology and knowledge, a successful identification was likely. The board therefore concludes, as did the examining division, that the identification of the human urocortin III protein as subject-matter of claim 1 of all the requests was obvious to a skilled person and thus does not involve an inventive step. None of the requests is therefore allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated