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Datasheet for the decision of 8 November 2011

Case Number: T 1803/09 - 3.3.08

Application Number: 02759956.2

Publication Number: 1423705

IPC: G01N 33/74

Language of the proceedings: EN

Title of invention:
Conjunctive analysis of biological marker expression for diagnosing organ failure

Applicant:
Syn.X. Pharma, Inc.

Opponent:
-

Headword:
Markers congestive heart failure/SYN.X PHARMA

Relevant legal provisions:
EPC Art. 123(2), 111(1)

Keyword:
"Main Request and Auxiliary Requests 1 to 3 - added subject-matter (yes)"
"Auxiliary Request 4 - added subject-matter (no)"
"Remittal to the department of first instance (yes)"

Decisions cited:
T 0187/91, T 0296/96, T 0040/97, T 1091/00

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1803/09 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 8 November 2011

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted on 27 March 2009 refusing European application No. 02759956.2 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: M. Wieser
Members: P. Julià
J. Geschwind

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division, whereby the European patent application No. 02 759 956.2, published as International patent application WO 03/020123 (hereinafter "*the application as filed*"), was refused.

II. The decision was based on a Main Request and Auxiliary Requests 1 to 3 all filed on 12 December 2008. None of these requests was considered to meet the requirements of Article 123(2) EPC.

III. On 6 August 2009, the appellant filed a statement setting out its grounds of appeal together with a Main Request and Auxiliary Requests 1 to 5. Oral proceedings were requested as a subsidiary measure.

IV. On 27 May 2011, the appellant was summoned to oral proceedings and, in a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached thereto, it was also informed of the board's preliminary, non-binding opinion on some of the substantive issues of the appeal.

V. On 10 October 2011, the appellant replied to the board's communication and filed a Main Request and Auxiliary Requests 1 to 4.

VI. Oral proceedings were held on 8 November 2011. At oral proceedings, the appellant replaced Auxiliary Request 4 by a new Auxiliary Request 4.

VII. The **Main Request** consisted of 8 claims. Claim 1 read as follows:

"1. A method for predicting cardiac mortality in a chronic congestive heart failure patient, said method comprising the steps of:

(A) assaying for the presence of a cardiac marker of cell injury in a body fluid sample drawn from said patient using:

a first antibody that specifically binds to a cardiac marker of cell injury, wherein said cardiac marker of cell injury is cardiac Troponin-I; and

(B) assaying for the presence of a marker of organ adaptation in a body fluid sample drawn from said patient using:

a second antibody that specifically binds to said marker of organ adaptation, wherein said marker of organ adaptation is selected from the group consisting of ANP, N-terminal ANP, BNP, N-terminal BNP and CNP,

wherein when both said marker of cell injury and said marker of organ adaptation are present in said sample at significantly increased levels as compared to control samples from normal individuals, said patient is predicted to have an increased prognosis of cardiac mortality."

Claims 2 to 8 were directed to various embodiments of the method of claim 1. Claim 2 defined the body fluid as being selected from the group consisting of blood, a

blood product, plasma, serum, or urine and, in claim 3, said body fluid was defined as being serum or plasma. In claim 4, the second antibody was defined as specifically binding to a marker of organ adaptation selected from the group consisting of BNP and N-terminal BNP. Claim 5 recited several steps of the method of any one of claims 1 to 4. Claim 6 required the markers to be present in the sample at levels that were two-fold greater than in the control samples. Claim 7 required steps (A) and (B) of the method of any one of claims 1 to 6 to be carried out simultaneously. Claim 8 defined the second antibody as specifically binding to N-terminal ANP.

VIII. **Auxiliary Request 1** read as the Main Request except for the deletion of CNP and ANP as markers of organ adaptation in claim 1. Claim 1 of Auxiliary Requests 2, 3 and 4 read as claim 1 of Auxiliary Request 1 except for the fact that the marker of organ adaptation was selected from N-terminal ANP or N-terminal BNP in **Auxiliary Request 2**, BNP or N-terminal BNP in **Auxiliary Request 3** and, the said marker of organ adaptation was the N-terminal ANP in **Auxiliary Request 4**. This latter Auxiliary Request consisted of six claims, wherein claims 2 to 6 read as claims 2, 3 and 5 to 7 of the Main Request, respectively, except for the fact that in claim 2 of Auxiliary Request 4 the term "urine" was deleted.

IX. The submissions made by the appellant, insofar as they are relevant to the present decision, may be summarized as follows:

Main Request and Auxiliary Request 1 to 3
Article 123(2) EPC

Claim 14 of the application as filed - directed to a method for predicting cardiac mortality rate in a patient - was a basis for the claimed subject-matter. Claim 1 of the Main Request and of Auxiliary Requests 1 to 3 differed from claim 14 as filed by characterizing the patient as having chronic congestive heart failure (CHF) and by the particular combination of markers used. The group of markers of cell injury in claim 1 of the Main Request and of Auxiliary Requests 1 to 3 was limited to cardiac Troponin-I (cTnI) and the group of markers of organ adaptation in claim 1 of the Main Request was identical to that of claim 14 as filed.

From the application as filed when taken as a whole, it was derivable that the heart was the organ at the core of the invention. The term "heart failure" was identified as, and used interchangeable with, CHF throughout the entire application. CHF was further known in the prior art documents either as acute or chronic CHF, whereupon these definitions were not specific but only relative because various and different causes were at the origin of a similar set of symptoms. Whereas acute CHF was a brief life threatening condition, chronic CHF was a condition of a persistent and chronic nature. Therefore, the tests and methods of diagnosis, prognosis, long-term management and prediction mentioned in the application were appropriate only for chronic CHF but not for acute CHF. Accordingly, there was no reference to acute CHF in the application as filed which explicitly referred to, only and exclusively, chronic CHF. There was a clear thread

throughout the application as filed going from the general, broad disclosure of an organ (failure) to the specific heart (failure) and CHF and to the more specific chronic CHF. In the context of the application, the terms "*heart failure*" and "*CHF*" would be read as meaning "*chronic CHF*". The skilled person would have understood the patient of the method of claim 14 to be a chronic CHF patient. This was in line with the case law which stated that the skilled person would interpret a general disclosure in the text of the application (heart failure, CHF) in the light of an exemplified detailed disclosure (chronic CHF) (cf. T 40/97 of 1 December 1998, not published in the OJ EPO).

Likewise, CHF (implicitly including chronic CHF) was always and constantly linked throughout the application as filed to cTnI as marker of cell injury and to natriuretic peptides as markers of organ adaptation. Although the N-terminal ANP was the sole peptide exemplified, it was clearly derivable from the application as filed that this peptide could be replaced by other related natriuretic peptides. In the light of the application as filed when taken as a whole, the combination of claim 14 as filed with the Example was thus a basis for claim 1 of the Main Request and of Auxiliary Requests 1 to 3.

As regards the methods of diagnosis, prognosis and/or monitoring referred to in the application as filed, all of them were interrelated and not entirely separate. For all of them, the focus was laid on the severity of the disease and the prediction of mortality. Moreover,

all of them were cited in relationship to CHF as the disease or condition to be diagnosed and/or monitored.

The Example of the application as filed showed the use of cTnI and N-terminal ANP as markers in a method for predicting the cardiac mortality rate in a chronic CHF patient. These markers were selected because their levels were elevated in CHF patients. It was known in the art and stated in the application, that similar elevated levels of BNP and N-terminal BNP were found in CHF patients. Since these natriuretic peptides were known to be structurally related, to have a similar role in CHF and to be present at elevated levels in CHF patients, the skilled person, following the same rationale as for the selection of N-terminal ANP, would have been prompted to select and to use them in the method of the Example. The results shown in the Example allowed to interpret the disclosure of the application as filed, in particular claim 14 as filed, and provided a rationale to be applied to other natriuretic peptides explicitly mentioned therein. There was nothing to prevent the skilled person to do so and there was no reason why these other peptides should not be an alternative to the exemplified N-terminal ANP. The skilled person would have viewed the teaching of the Example (combination of markers) as being representative of the embodiments of the invention and would have understood that this teaching was also applicable to other embodiments (combinations of markers) disclosed in the application as filed. The skilled person would have seriously contemplated other possible combinations indicated in the application as filed. These combinations were thus directly and

unambiguously (albeit implicitly) derivable from the application as filed when taken as a whole.

This was in line with the case law of the Boards of Appeal which stated that, when the application disclosed features of the invention using terms that encompassed several distinct embodiments, it was appropriate to consider what the skilled person would seriously contemplate as practical embodiments of the invention. Accordingly, the disclosure of a document had to be interpreted in the light of its content as a whole. When considering what was disclosed in the application as filed, the separate sections were not to be considered in isolation from each other. Instead, each aspect of the application had to be read in the context of its content as a whole and it had to be considered whether the skilled person would have seriously contemplated the various implicit combinations that were disclosed therein as embodiments of the invention (T 296/96 of 12 January 2000, not published in the OJ EPO and T 187/91 of 11 March 1993, OJ EPO 1994, page 572).

The skilled person would not have read the application as a reservoir of separate features but would have viewed it as a whole and considered each disclosure in this context. The separation of three groups of interrelated subject-matter at different levels of generalisation was artificial and inappropriate because the teaching of the application taken as a whole assisted to interpret each one of these three groups. Each of these groups had to be interpreted in the context of each other and it had to be considered whether the skilled person would have seriously

contemplated the combination of the different features cited in the application as filed.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the Main Request or, in the alternative, on the basis of one of the first to third Auxiliary Requests, all of them filed with letter of 10 October 2011, or the new Auxiliary Request four filed during the oral proceedings.

Reasons for the Decision

Article 123(2) EPC

1. Article 123(2) EPC states that the European patent application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

According to the established case law, the relevant question to be decided in assessing whether the application as filed provides a basis for an amendment is whether or not the amendment is directly and unambiguously derivable from the application as filed, including information which for the skilled person is implicit in what is explicitly disclosed, i.e. it is a clear and unambiguous consequence of what is explicitly mentioned in the application as filed. An "*implicit disclosure*" should not be construed to mean matter that does not belong to the content of the technical information provided by the application as filed but may be rendered obvious on the basis of that content. The content of the application as filed is not to be

considered as a reservoir from which individual features pertaining to separate sections can be combined in order to artificially create a particular combination (cf. "Case Law of the Boards of Appeal of the EPO", 6th edition 2010, III.A.1 and III.A.7.1, pages 315 and 347, respectively).

The disclosure of the application as filed

2. The application as filed concerns three groups of interrelated subject-matter, namely A) tissue or organ failures, damages or diseases, B) biological markers for these organ failures, damages or diseases and C) uses, applications or purposes of these markers as regards these organ failures, damages or diseases. These groups of interrelated subject-matter are disclosed at different levels of generalization. For each of them, the following levels of generalization can be identified:

2.1 For the first group of subject-matter A), the broadest generalization is represented by the references to "*organ damage*" or "*tissue damage*", such as found in claims 1, 4, 7 and 9 as filed. In an intermediate level of generalization, the tissue or organ is defined as being the heart with references to "*heart damage*", "*heart failure*", etc., such as those in claims 2 and 5 as filed. A narrower definition is represented by the references to "*congestive heart failure*" (CHF) in general, such as those present under the headings "*Field of the Invention*", "*Background of the Invention*" and "D*escription of the Prior Art*" as well as on page 6, lines 19, 24 and 27 under the heading "*Summary of the Invention*". The references to "***chronic*** *heart failure*"

and "***acute*** *myocardial infarction*" (cf. page 6, line 6, page 11, lines 12, 15 and 23) are the most specific disclosures for this first group of subject-matter A).

2.2 For the second group of subject-matter B), the broadest generalization is represented by the references to "*markers of cell injury*" and "*markers of organ adaptation*". Whilst for the former subgroup the references to "*fibrosis markers*" represent an intermediate generalization (cf. page 1, line 6, page 5, line 23), the references to "*natriuretic peptides*" represent an intermediate generalization for the latter subgroup. The list of specific cell injury/necrosis markers given in Table 1 (cf. pages 10 and 11) and the list of specific natriuretic peptides on page 1, lines 12 and 13 correspond, respectively, to the most specific disclosures of the first and second subgroups comprised in the second group of subject-matter B) (cf. *inter alia* claims 2 and 5 as filed).

2.3 For the third group of subject-matter C), the following indications for the conjunctive utilization of the disclosed markers is derivable from the application as filed: i) prediction, distinction and/or diagnosis of a certain condition, ii) monitoring the progression of a certain condition (long-term management), which might as well include monitoring the efficacy of therapeutic agents on said condition (prognostic efficacy of said therapies), and iii) prediction of mortality (relative risk of mortality).

3. The sole Example of the application shows the levels of cTnI (cell injury marker), when used in conjunction with the levels of pro-ANP (organ adaptation marker)

(group B), to be more predictive of survival (mortality prediction) (group C) in patients with chronic heart failure (group A) than the levels of each marker alone or individually (cf. page 11, Example).

Main Request and Auxiliary Requests 1 to 3

4. Claim 1 of the Main Request is directed to a method for predicting cardiac mortality in a chronic CHF patient, wherein the presence of a cardiac marker of cell injury and a marker of organ adaption are assayed. Cardiac Troponin-I (cTnI) is used as cardiac marker of cell injury and the marker of organ adaptation is selected from the group consisting of ANP, N-terminal ANP, BNP, N-terminal BNP and CNP. In claim 1 of Auxiliary Requests 1 to 3, the marker of organ adaptation is selected from the group consisting of N-terminal ANP, BNP or N-terminal BNP (Auxiliary Request 1), N-terminal ANP or N-terminal BNP (Auxiliary Request 2) and BNP or N-terminal BNP (Auxiliary Request 3) (cf. Sections VII and VIII *supra*).

5. In the application as filed, there are only three explicit references to "*chronic heart failure* " (not to "*chronic congestive heart failure*"), namely on page 6, line 6 and on page 11 in the Example of the application as filed.

5.1 First, the first full paragraph on page 6 contemplates the development of an immunological test for two different conditions, namely after arrival of the patient into the emergency room ("*acute heart failure*") and for "*chronic heart failure*". However, it is not clearly and unambiguously derivable that each and every

possible combination of markers indicated in the preceding paragraphs on page 5, namely cTnI with BNP, pro-BNP or pro-ANP, may also be appropriate for both conditions, acute and chronic heart failure, because these paragraphs refer only to "*ailing organ*" or "*ailing heart*" in general.

5.2 Second, the cited paragraphs on pages 5 and 6 refer only to the diagnosis of the conditions described but do not refer to the prediction of "*cardiac mortality*", which is mentioned only in the second paragraph of page 7, after further general references to the diagnosis of these conditions as well as to their long-term management and monitoring. Thus, from these general disclosures, it is not clearly and unambiguously derivable that each and every possible combination of markers indicated on page 5 may also be appropriate for all possible purposes indicated in the other paragraphs.

5.3 Third, the Example of the application describes the conjunctive use of cTnI and pro-ANP, only and exclusively, in chronic heart failure patients (cf. point 3 *supra*). Although the claims as filed disclose the combination of cTnI with ANP and pro-ANP, both for diagnostic purposes (cf. claims 3, 6, 8 and 11 as filed) and for predicting cardiac mortality rate in a patient (cf. claim 13 as filed), these claims are directed to organ or heart damage in general but not to the specific condition "*chronic CHF*". Indeed, claim 14 as filed, relied by the appellant and directed to a method for predicting cardiac mortality rate in a patient, is not restricted to "*chronic CHF*" and contains a large

list of different markers of cell injury and of organ adaptation.

6. Thus, there is no explicit disclosure in the application as filed of the subject-matter of claim 1 of the Main Request or of the Auxiliary Requests 1 to 3.

7. The appellant does not contest the absence of an explicit disclosure of the subject-matter of claim 1 of the Main Request and of Auxiliary Requests 1 to 3 in the application as filed, but its argumentation relies on an implicit disclosure of this subject-matter which, in the appellant's view, is directly and unambiguously derivable from the application as filed when taken as a whole, the specific teachings of the Example assisting the skilled person to understand the general disclosure (T 40/97, *supra*), and from the fact that said disclosure and teachings would prompt the skilled person to seriously contemplate the use of the claimed combinations of markers in the method of the Main Request or of Auxiliary Requests 1 to 3 in chronic CHF patients (T 187/91 and T 296/96, *supra*) (cf. Section IX *supra*).

7.1 The board agrees with the appellant that the entire disclosure of the application as filed is focused on the heart as the organ of study and, in particular, on CHF. However, as stated in the application as filed when acknowledging prior art concerned with CHF (cf. page 1, line 24 to page 2, line 26), various and different causes may be at the origin of CHF and, although some of them may be shared by both acute and chronic CHF, these two conditions are differentiable and distinguished - albeit, admittedly, broadly defined.

Thus, contrary to the appellant's view, the term "*CHF*" as used in the application as filed can not always be, only and exclusively, equated to "*chronic CHF*". Although the former term includes the latter, it is much broader and includes other conditions, such as "*acute CHF*".

7.2 The board does not share the appellant's view that the tests and methods disclosed in the application as filed for use in CHF patients are appropriate only for "*chronic CHF*" and not for "*acute CHF*". Early, preliminary diagnosis methods may distinguish and differentiate patients with one of these conditions. Likewise, methods may be developed for monitoring the long-term management (efficacy of therapeutic agents) of each of these two CHF conditions. Indeed, the references in the application as filed to "*methods for distinguishing CHF*" may be interpreted as referring to methods for distinguishing CHF from other heart failures as well as methods for distinguishing - at an early, preliminary stage - different CHF conditions. If at all, these references are **ambiguous**. It is worth noting here that not all tests and methods referred to in the application as filed are necessarily concerned with the prediction of CHF mortality. A test for early, preliminary diagnosis for CHF may well inform about the specific type of CHF condition but may be of limited value, or of no value at all, for the prediction of the severity or mortality of this condition.

7.3 Although the sole method exemplified in the application as filed refers to criteria for selecting markers of cell injury and organ adaptation having elevated levels in CHF patients, it is also explicitly stated that

"*(h)owever in patients with* ***chronic*** *heart failure, it is* ***unclear*** *whether there is a relationship between either elevated levels of cTnI alone, or in conjunction with elevated levels of pro-ANP, and survival*" (emphasis added by the board) (cf. page 11, lines 11 to 14). Although this uncertainty is set aside for the specific marker combination disclosed in the Example, the board does not see the results reported in the Example for cTnI and pro-ANP to be directly and unambiguously transferable to all other possible combinations of markers fulfilling said criteria. Indeed and contrary to the appellant's view, the same uncertainty remains for other markers, their possible combination does not necessarily have to provide similar or identical results to those obtained with cTnI and pro-ANP. If at all, the sentence referred to above is **ambiguous**. The results shown in the Example may well render the combination of other markers obvious or, in other words, they may be for the skilled person obvious to try but this is not a criteria to apply under Article 123(2) EPC (cf. point 1 *supra*). These combinations are not a direct and unambiguous consequence of the results shown in the Example nor a consequence directly and unambiguously derivable from the application as filed when taken as a whole.

7.4 Thus, not all tissue or organ failures, damages or diseases within the above identified group A) can be directly and unambiguously equated to "*chronic CHF*" (cf. point 7.1 *supra*). Likewise, not all subject-matter within the above identified group C) can be directly and unambiguously understood as relating to mortality prediction for chronic CHF patients (cf. point 7.2 *supra*). Moreover, on the basis of the results shown in

the Example of the application as filed, not all possible marker combinations within the above identified group B) can be seen as being directly and unambiguously interchangeable in the method of that Example (cf. Section 7.3 *supra*). The identification of three groups of interrelated subject-matter and the different levels of generalization for each of them is not artificial and inappropriate but it is clearly derivable from the application as filed taken as a whole. When reading the application as filed, the skilled person would not recognize that the feature "***chronic*** *CHF*" is equally applicable to "***all*** *marker combinations*" disclosed in the application, let alone that all marker combinations might be useful "*for predicting cardiac* ***mortality***" in a patient with this specific CHF condition. This reading can only arise when using the disclosure of the application as filed as a large reservoir from which parts are arbitrarily taken and combined. Such a reading, however, is not allowable under Article 123(2) EPC (cf. point 1 *supra*).

8. Thus, there is no implicit disclosure in the application as filed of the subject-matter of claim 1 of the Main Request and of Auxiliary Requests 1 to 3.

9. It follows from all the above that claim 1 of the Main request and of Auxiliary Requests 1 to 3 does not fulfil the requirements of Article 123(2) EPC.

Auxiliary Request 4
Article 123(2) EPC

10. Claim 1 of Auxiliary Request 4 is directed to a method for predicting cardiac mortality in a chronic CHF

patient based on the conjuctive analysis of cTnI as a marker of cardiac cell injury and N-terminal ANP as a marker of organ adaptation (cf. Section VIII *supra*). The Example given in the application as filed illustrates this method and provides a basis for this subject-matter.

11. The board does not see any reason to raise any other objection under Article 123(2) EPC, the subject-matter of the dependent claims being clearly derivable from the application as filed.

12. Thus, the requirements of Article 123(2) EPC are considered to be fulfilled.

Remittal to the first instance

13. According to Article 111(1) EPC the Board of Appeal may exercise any power within the competence of the department which was responsible for the decision appealed or remit the case to the department for further prosecution. Remittal to the department of first instance is at the discretion of the board (cf. T 1091/00 of 2 July 2002, not published in the OJ EPO).

14. In the decision under appeal, the examining division has only dealt with the question of added subject-matter without considering or touching any other substantial requirements of the EPC. Since essential questions regarding the patentability of the claimed subject-matter have not been discussed in the decision under appeal and not decided by the examining division, the board considers it justified and

appropriate to allow the set of claims of appellant's auxiliary request 4 to be examined by the first instance and therefore, exercises its discretion under Article 111(1) EPC to remit the case to the department of first instance for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution on the basis of claims 1 to 6 of the new fourth Auxiliary Request filed at the oral proceedings.

The Registrar: The Chairman:

A. Wolinski M. Wieser