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**D E C I S I O N**  
**of 10 November 2004**

**Case Number:** T 0716/01 - 3.3.8

**Application Number:** 91900109.9

**Publication Number:** 0502928

**IPC:** G01N 33/68

**Language of the proceedings:** EN

**Title of invention:**

Methods of detecting bone resorption in vivo

**Patentee:**

Washington Research Foundation

**Opponents:**

Osteometer BioTech A/S  
Metra Biosystems Inc.  
Roche Diagnostics GmbH

**Headword:**

Bone resorption/WASHINGTON RESEARCH FOUNDATION

**Relevant legal provisions:**

EPC Art. 83

**Keyword:**

"Sufficiency of disclosure (main request and auxiliary requests 1 to 3) (no) "

**Decisions cited:**

T 0226/85, T 0158/91, T 0409/91, T 0435/91, T 0639/95

**Catchword:**

-



Case Number: T 0716/01 - 3.3.8

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.8  
of 10 November 2004

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**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
26 March 2001 concerning maintenance of  
European patent No. 0502928 in amended form.

**Composition of the Board:**

**Chairman:** L. Galligani  
**Members:** M. R. Vega Laso  
C. Rennie-Smith

## Summary of Facts and Submissions

- I. The appeal lies from the interlocutory decision of the opposition division posted on 26 March 2001, whereby the European patent No. 0 502 928 (based on European patent application No. 91 900 109.9, published as WO 91/08478) with the title "Methods of detecting bone resorption in vivo" was maintained in amended form. The patent had been opposed by three parties on the grounds of Article 100(a), in particular lack of novelty and lack of inventive step, Article 100(b) and 100(c) EPC.
  
- II. In its decision, the opposition division found the main request then on file not to be allowable due to lack of inventive step (Article 56 EPC) of the subject-matter of claims 6, 10 and 11. On the other hand, amended claims 1 to 10 of the first auxiliary request filed during oral proceedings were considered to fulfil the requirements of Articles 123(2), 84, 83, 54 and 56 EPC. The patent was thus maintained on the basis of the first auxiliary request and a description amended accordingly.
  
- III. Opponent 01 (appellant I) and opponent 03 (appellant II) each lodged an appeal against the interlocutory decision of the opposition division and submitted a written statement setting out their grounds of appeal. With its reply thereto, the patent proprietor (respondent) submitted three auxiliary requests, its main request being claims 1 to 10 on the basis of which the patent had been maintained by the opposition division. All parties requested oral proceedings in the event that the board did not intend to grant their respective requests.

IV. The parties were summoned to oral proceedings. In a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal sent with the summons, the board expressed its provisional opinion on both procedural and substantive matters arising from the submissions of the parties, in particular in connection with Articles 123(2), 84, 83 and 54 EPC.

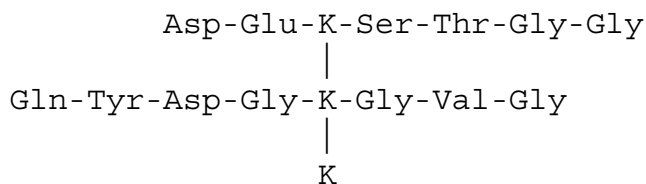
V. In response to the board's communication, the respondent submitted a new main request and two auxiliary requests replacing the requests previously on file.

VI. Oral proceedings took place on 10 November 2004 in the presence of both appellants and the respondent. Opponent 02, a party as of right in the appeal proceedings, had informed the board that it would not attend the oral proceedings. After discussion of the main request and the first auxiliary request then on file, the respondent withdrew all its previous requests and submitted a new main request and three auxiliary requests.

VII. Claims 1 and 8 of the **main request** filed on 10 November 2004 read as follows:

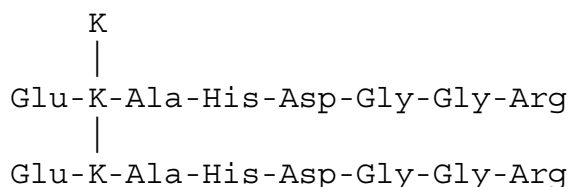
"1. A method of determining the rate of bone resorption, the method comprising quantitating in a sample of body fluid the concentration of both:

(i) a first peptide fragment derived from telopeptide domain of bone type I collagen and which has the structure of general formula III

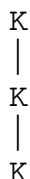


wherein Gln is glutamine or pyrrolidine carboxylic acid;

or general formula VI



wherein



is hydroxylysyl pyridinoline or lysyl pyridinoline;  
and

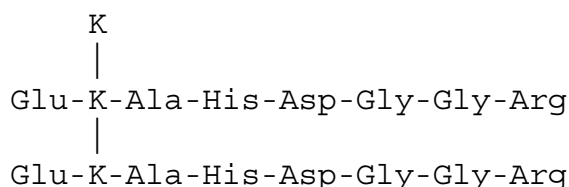
- (ii) a second peptide fragment identical to the first peptide fragment except that the pyridinium ring of the cross-linking amino acid has been cleaved;

said quantitating comprising contacting the body fluid with at least one monoclonal antibody or antigen-binding fragment thereof to the first and second peptide."

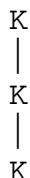
"8. An assay for measuring bone resorption, comprising determining in a sample of body fluid, using at least

one monoclonal antibody or antigen-binding fragment thereof, the presence or concentration of both:

- i) a first carboxy-terminal type I collagen telopeptide comprising



wherein



is lysyl pyridinoline or hydroxylysyl pyridinoline; and

- ii) a second collagen telopeptide identical to the first telopeptide except that the pyridinium ring of the cross-linking amino acid has been cleaved."

Claims 2 to 4 of the main request concerned various embodiments of the method according to claim 1. Independent claim 5 was directed to a cell line which produces a monoclonal antibody that binds to first and second peptides consisting essentially of the structure of formula III as quoted above, the pyridinium ring of the first and second peptides being closed and open, respectively. Dependent claim 6 concerned a cell line with the identifying characteristics of the cell line HB 10611 (1H11) deposited with the ATCC. Claim 7 was directed to a monoclonal antibody produced by any

of the claimed cell lines, and claim 9 to a kit for measuring bone resorption which comprises at least one monoclonal antibody or antigen-binding fragment thereof that binds to the open-ring and closed-ring forms of a telopeptide comprising the structure of formula VI as quoted above.

The **first auxiliary request** consisted of only two claims, these claims being identical to claims 8 and 9 of the main request. In the set of claims of the **second auxiliary request**, claim 1 was identical to the corresponding claim of the main request, except for the phrase "at least one monoclonal antibody or antigen-binding fragment thereof to the first and second peptide" being replaced by "a monoclonal antibody or antigen-binding fragment thereof which recognizes both the first and second peptide". Claims 2 to 7 were identical to claims 2 to 7 of the main request. Claim 8 read as follows:

"8. An assay for measuring bone resorption, comprising determining in a sample of body fluid the presence or concentration of both:

- i) a first carboxy-terminal type I collagen telopeptide [...]; and
- ii) a second collagen telopeptide [...];

said assay using a monoclonal antibody or antigen-binding fragment thereof which recognizes both the first and second peptide."



[the telopeptides in i) and ii) being defined as in claim 8 of the main request; explanatory note by the board]. The kit of claim 9 differed from that of the corresponding claim of the main request in that the expression "at least a monoclonal antibody or antigen-binding fragment thereof" was replaced by "a monoclonal antibody or antigen-binding fragment thereof".

The **third auxiliary request** consisted of two claims which were identical to claims 8 and 9 of the second auxiliary request.

VIII. The following document is referred to in the present decision:

(D23): Declaration of Dr. Simon Robins dated  
22 October 2004 (filed by the respondent on  
25 October 2004).

IX. The submissions made by appellant I, as far as they are relevant to this decision, may be summarized as follows:

The opposition division wrongly dismissed the objection that there was no enabling disclosure in the application of the measurement of a single specific peptide in two forms (open and closed ring). There was ample evidence that producing a monoclonal antibody that recognises only a specific pair of fragments would not be within the abilities of the skilled person. The patentee had never demonstrated an ability to do it, and no antibody had been published by any one else that had the ability to recognise a single pair of pyridinium peptides related by having a closed and an open ring, but being otherwise identical. Neither was

there any screening protocol disclosed or suggested in the patent to achieve this.

The patent specification described the isolation of a fraction enriched in telopeptide fragment of Formula III and a single monoclonal antibody that recognised both forms, open and closed ring, of the fragment. There was no disclosure whatsoever in the patent specification as to how to obtain a telopeptide fragment of Formula VI, let alone monoclonal antibodies that bind to this telopeptide fragment.

X. Appellant II endorsed the arguments of appellant I. It argued further that, with regard to a telopeptide fragment of Formula VI, the disclosure of the patent was meagre. There was no proof whatsoever that this telopeptide fragment would be useful to determine bone resorption.

XI. The respondent's submissions were as follows:

The specification of the patent contained a clear and unequivocal disclosure of the possibility of producing antibodies which had dual specificity for both closed ring and open ring forms. Moreover, the patentee had provided a deposit of an appropriate such antibody, antibody 1H11. Accordingly, the specification not only (by the way of deposit) provided a specific example of an appropriate antibody, but also taught that useful antibodies are in principle obtainable to a hitherto unappreciated epitope. With the technical information provided by the patent on this epitope, the skilled person could search, using conventional techniques, for antibodies similar to 1H11.

In the context of sufficiency of disclosure, two questions had to be answered, namely, whether one could determine bone resorption with the method disclosed in the patent, and whether the means were available. The telopeptide fragment of Formula VI was very similar to that of Formula IV labelled on the chromatogram and disclosed in the patent. Although a telopeptide fragment of Formula VI was not labelled on the chromatogram of Figure 7B, the skilled person could easily find out which of the peaks corresponded to this fragment and isolate therefrom an enriched fraction for immunization. Alternatively, the skilled person could chemically synthesise the peptide of Formula VI.

It had not been proved by the appellants that two antibodies of single specificity to a selected telopeptide fragment cannot be prepared.

- XII. The appellants requested that the decision under appeal be set aside and that the patent be revoked.
- XIII. The respondent requested that the decision under appeal be set aside and that the patent be maintained on the basis of either the main request or one of the first, second or third auxiliary requests filed during the oral proceedings.
- XIV. At the end of the oral proceedings, after the board's decision had been announced but before the oral proceedings had been closed, the respondent announced that it withdrew all its requests on file. This was recorded in the minutes.

## **Reasons for the Decision**

### *Main and auxiliary requests*

#### *Articles 123(2)(3) and 84 EPC*

1. In view of the findings on Article 83 EPC (see points 2 to 17 below), the board does not deem it necessary to discuss the objections raised under Articles 123(2) and 84 EPC. No objections were raised under Article 123(3) EPC.

#### *Article 83 EPC*

2. The decisive issue in the present appeal is whether or not the ground of opposition mentioned in Article 100(b) EPC prejudices the maintenance of the contested patent. In this regard, the question to be judged is whether, having regard to the guidance provided by the patent and using the common general knowledge at the time this guidance was made available to the public, the person skilled in the art would be able to carry out the invention as claimed, without the burden of an undue amount of experimentation or the application of inventive ingenuity (see eg decision T 435/91, OJ EPO 1995, 188).
3. The question of sufficiency of disclosure is a question of fact which has to be answered on the basis of the available evidence in each individual case (see decision T 409/91, OJ EPO 1994, 653). An examination as to the sufficiency of a disclosure in a patent application depends on the correlation of the facts of

the case to certain general parameters, among others, the amount of reliable technical details disclosed in the patent, the character of the technical field and the average amount of effort necessary to put into practice a certain written disclosure in that technical field (see decisions T 158/91 of 30 July 1991, point 2.3 of the reasons; and T 639/95 of 21 January 1998).

4. In the present case, the method for determining the rate of bone resorption according to claim 1 involves the quantification of peptide fragments derived from the telopeptide domain of bone type I collagen and having the structure of either Formula III or Formula VI (see paragraph VII above), by contacting a sample of body fluid with at least one monoclonal antibody or antigen-binding fragment thereof. The antibody or antibodies used in the claimed method are directed against a first and second peptide which are identical, except that the pyridinium ring of the cross-linking amino acid is closed and open, respectively. According to claims 1 and 8 of the main request as well as claim 1 of auxiliary request 1, the monoclonal antibodies can be either of single or dual specificity, ie antibodies which are able to discriminate between the open and closed ring forms of the telopeptide fragments, or antibodies which recognise both forms. Only monoclonal antibodies of dual specificity are used in the methods of claims 1 and 8 of auxiliary request 2 and claim 1 of auxiliary request 3.
  
5. In order to perform the claimed invention without undue burden the person skilled in the art would have needed

monoclonal antibodies or antigen-binding fragments thereof with the required - single or dual - specificity to be readily available. The respondent admitted that monoclonal antibodies with these characteristics are an essential feature of the invention and that such antibodies had not been disclosed before the priority date. Thus, the patent in suit must provide a sufficient teaching for the skilled person to be able to prepare the monoclonal antibodies required to put the invention into practice.

6. The contested patent teaches in very general terms how to obtain immunological binding partners, in particular monoclonal antibodies capable of binding to telopeptide fragments derived from bone collagen (see page 10, line 56 to page 11, line 48). It also provides an example of the preparation of a monoclonal antibody against a peptide of Formula III, using as immunogen a fraction enriched in this peptide (see example starting on page 12, line 33 of the patent). The antibody prepared according to this example (monoclonal antibody 1H11, ATCC HB10611) is said to recognise both the open and the closed ring forms of the telopeptide fragment of Formula III. The enriched fraction used as immunogen is isolated from urine from patients with active Paget's disease by a method described in the section headed "Isolation of Type I Collagen Telopeptides" starting on page 8, line 55 of the patent. Thus, in principle the patent specification offers the skilled person one way to obtain a monoclonal antibody which recognises both the open and close-ring forms of a bone type I collagen telopeptide of Formula III.

7. In its decision, the opposition division held that, on the basis of the example provided in the patent, the skilled person would then be able to prepare any other monoclonal antibody having the properties required in order to perform any assay falling within the scope of the claims, merely on the basis of the information provided in the specification in combination with his/her own common general knowledge (see point 8, paragraph 1) of the decision).
  
8. Having regard to the arguments put forward by the appellants (see paragraphs IX and X above), the issue to be decided is whether in the present case the disclosure of one example allows the claimed invention to be performed across the whole range claimed (see decision T 435/91, *supra*), ie whether or not the technical details provided in the patent specification and the general knowledge available at the priority date allow the person skilled in the art to obtain further monoclonal antibodies having the features specified in claim 1, in particular monoclonal antibodies recognising both the open and closed-ring forms of the telopeptide fragment of Formula VI, or monoclonal antibodies capable of discriminating between both forms of this peptide fragment.
  
9. The board notes that the patent in suit discloses scarcely any technical details related to a telopeptide fragment of Formula VI, apart from its amino acid sequence. Allegedly, this fragment is present in body fluids and - as the structurally related telopeptide fragment of Formula IV also disclosed in the patent - appears to be derived from the carboxy-terminal (C-terminal) telopeptide domain of bone type I collagen.

However, in Figure 7B of the patent, which shows a typical elution profile for C-terminal telopeptide fragments, a peak corresponding to a telopeptide fragment of Formula VI is **not** identified. The patent specification only indicates that smaller peptide fragments of the molecule represented by Formula IV are found in the minor peaks of the C-terminal telopeptide fraction seen in Figure 7B, and can be identified by amino acid composition and sequence analysis (see page 10, lines 47 to 50 of the patent in suit).

10. Thus, a skilled person trying to obtain an immunogenic preparation based on a fraction enriched in the telopeptide fragment of Formula VI is confronted with the initial hurdle of having to identify which of the minor peaks in the elution profile of Figure 7B corresponds to the desired telopeptide fragment. Although the experiments required to do this might be considered routine for a person skilled in the art, a considerable amount of time and effort would be needed.
  
11. The respondent argued that, in order to avoid any possible difficulties in the isolation of a telopeptide fragment of Formula VI from urine, the skilled person could synthesise the peptide on the basis of the amino acid sequence disclosed in the patent. In the board's view, it is questionable whether the skilled person would contemplate chemical synthesis if one considers that the contested patent does not give any hint in that respect, but only discloses the isolation of telopeptide fragments from urine. Nevertheless, as explained below, even if the skilled person could overcome the first hurdle of preparing a suitable immunogen, the preparation of monoclonal antibodies of



- the desired (single or dual) specificity to peptide fragments of Formula VI on the basis of the scarce technical details provided in the patent is still fraught with further uncertainties.
12. Although it is theoretically possible to elicit antibodies against peptides of low molecular weight (eg the telopeptide fragment of Formula VI) in isolated form, conjugation of the peptides to a carrier protein, for instance thyroglobulin or keyhole limpet hemocyanin, is not only the method preferred in the art, but also the method applied in the patent for the preparation of monoclonal antibodies to the telopeptide fragment of Formula III. However, as indicated in the patent (see page 11, lines 9 to 12), the orientation of the peptide, as it is bound to the carrier protein, is of critical importance to the specificity of the elicited antibodies. Therefore, the selection of a protocol for binding a particular telopeptide fragment to the carrier protein depends on the amino acid sequence of the fragment selected.
13. The patent provides neither directions nor a suitable protocol for the binding of a telopeptide fragment of Formula VI to a carrier protein. Thus, in order to select both a carrier protein and a binding agent that are suitable to obtain antibodies of the desired specificity to this telopeptide fragment, the skilled person would have to embark on further painstaking experimentation. Even though a reasonable amount of trial and error could be accepted, the board has serious doubts as to whether such experimentation would lead necessarily and directly towards success through the evaluation of initial failures (see decision

T 226/85, OJ EPO 1998, 336). These doubts arise from the evidence put forward by the respondent itself, in particular in document (D23).

14. In point 8 of the declaration of Dr. Robins (document (D23)), it is stated *inter alia*:

*"It is well known, and has long been appreciated, that a polyclonal antibody response is idiosyncratic to the individual animal used and can vary with the immunisation procedure and other conditions. In addition, the nature of the polyclonal antibody response to an antigen depends also on the relative immunogenicity of different epitopes within the antigen. In view of the enormous variability, it is not possible to predict in advance that any particular polyclonal antibody will include representative antibody molecules reactive with each and every available epitope within the antigen."*

In point 10 of his declaration Dr. Robins further stated:

***"The same is of course true for monoclonal antibodies.*** *Indeed, with monoclonal antibodies where there is only a single species of antibody molecule in the response, and where that antibody binds just one epitope, it is even less likely that any particular antibody chosen at random would recognise both the open and closed-form ring structures."* (emphasis added by the board)

15. In this regard, the board notes that, admittedly, no screening protocol for monoclonal antibodies of dual specificity is disclosed in the patent, either as a protocol generally applicable to monoclonal antibodies against a selected telopeptide fragment or in connection with the isolation of monoclonal antibody 1H11 in the example of the patent. Consequently, the person skilled in the art trying to isolate a monoclonal antibody of dual specificity to the telopeptide fragment of Formula VI would have to rely on pure chance.
  
16. After appraising the technical details contained in the contested patent and the evidence provided by the respondent itself, the board comes to the conclusion that both the lack of predictability and the amount of experimentation required for isolating monoclonal antibodies of dual specificity to the telopeptide fragment of Formula VI amounts to an undue burden. Since these antibodies are essential in order to put into practice embodiments claimed in claims 1 and 8 of the main request, the disclosure of the patent must be considered insufficient.
  
17. The same considerations apply with regard to claim 1 of each of the auxiliary requests 1 to 3. Thus, none of the requests on file fulfil the requirements of Article 83 EPC.

*Withdrawal of all requests by the respondent*

18. The respondent's withdrawal of all its requests, made after the Board's decision was announced, came too late to affect the proceedings. It became apparent from

discussion following the respondent's announcement that it withdrew all its requests in the hope of avoiding a written decision which might affect its pending divisional application. Of course it waited to do so until it was clear that none of those requests would be allowed but, by so waiting, it took the risk that this would only be clear when the Board's decision was announced. Since the decision ends the dispute between the parties, the withdrawal of requests thereafter can have no effect on the proceedings. Thus the decision is unaffected, the Board must produce its written reasons for the decision and the decision can (like all other decisions) be referred to in proceedings relating to the divisional application; though the Board observes that its decision in this case is not binding on any first instance department of the EPO in that or any other case (see Article 111(2) EPC).

## **Order**

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

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani