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Datasheet for the decision of 18 January 2018

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Language of the proceedings: EN

Title of invention:
Parathyroid hormone antibodies and related methods

Patent Proprietor:
Quest Diagnostics Investments Incorporated

Opponent:
Immundiagnostik AG

Headword:
Anti-PTH antibodies/QUEST

Relevant legal provisions:
EPC Art. 54
RPBA Art. 13(1)

Keyword:
Main and auxiliary requests 1 to 3 - novelty (no)
Late filed auxiliary request 4 - admitted (no)

Decisions cited:

Catchword:

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Case Number: T 1318/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 18 January 2018

Appellant I: (Patent Proprietor)	Quest Diagnostics Investments Incorporated 300 Delaware Avenue Wilmington, DE 19899 (US)
Representative:	Häusler L.C. and Duez S. Viering, Jentschura & Partner mbB Patent- und Rechtsanwälte Kennedydamm 55 / Roßstrasse 40476 Düsseldorf (DE)
Appellant II: (Opponent)	Immundiagnostik AG Stubenwald-Allee 8a 64625 Bensheim (DE)
Representative:	Benedum, U.M. Nebens IP Patente Marken Designs Oberföhringer Strasse 172 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 22 April 2013 concerning maintenance of the European Patent No. 1455821 in amended form.**

Composition of the Board:

Chairman	M. Montrone
Members:	A. Chakravarty
	P. de Heij

Summary of Facts and Submissions

I. Appeals were lodged by the patent proprietor and the opponent (appellants I and II, respectively) against the interlocutory decision of the opposition division to maintain European patent No. EP 1 455 821, entitled "*Parathyroid hormone antibodies and related methods*", in amended form.

II. The opposition division considered a main request and three auxiliary requests. It held that claims 5, 9, 15 and 20 of the main request and claims 1, 6, 11 and 15 of auxiliary request 1 did not meet the requirements of Article 123(2) EPC, that the subject-matter of auxiliary request 2 lacked novelty and that the patent as amended according to auxiliary request 3 and the invention to which it related, met the requirements of the EPC.

III. With the statement of grounds of appeal, appellant I re-filed the main request and auxiliary requests 1 to 2 considered by the opposition division.

IV. With the statement of grounds of appeal, appellant II filed documents D17 to D21.

V. Oral proceedings took place before the board on 18 January 2018. During these proceedings, appellant I filed auxiliary request 4. At the end of the oral proceedings, the chairman announced the decision of the board.

VI. Claim 1 of the main and auxiliary requests 1 to 4 are reproduced below:

Main request and auxiliary request 2

"1. An isolated antibody that recognizes and selectively binds a three-dimensional epitope of parathyroid hormone, wherein the three-dimensional epitope of parathyroid hormone comprises amino acids located between amino acids 1-13 of SEQ ID NO: 1 and includes the first amino terminal amino acid of native PTH along with the intact helix of the amino terminus".

Auxiliary request 1

"1. An isolated antibody that recognizes and selectively binds a three-dimensional epitope of parathyroid hormone, wherein the three-dimensional epitope of parathyroid hormone comprises a first portion that includes amino acids 1-2 of SEQ ID NO: 1 and a second portion that includes amino acids 10 to 13 of SEQ ID NO: 1 along with the intact helix of the amino terminus".

Auxiliary request 3

"1. An isolated antibody that recognizes and selectively binds a three-dimensional epitope of parathyroid hormone, wherein the three-dimensional epitope of parathyroid hormone comprises amino acids 1-13 of SEQ ID NO: 1".

Auxiliary request 4

"1. An isolated antibody that recognizes and selectively binds a three-dimensional epitope of parathyroid hormone, wherein the three-dimensional epitope of parathyroid hormone comprises amino acids 1-13 of SEQ ID NO: 1, wherein the antibody recognizes a

peptide consisting of an amino acid sequence from Ser in the 1 position to Lys in the 13 position of SEQ ID NO: 1".

VII. The following documents are mentioned in this decision:

D1: Magerlein M. *et al.*, 1998, Arzneimittelforschung / Drug Research, 48(7):783-787.

D3: Tampe J. *et al.*, 1992, Journal of Immunoassay, 13(1):1-13.

VIII. Appellant I's arguments presented in writing and at the oral proceedings, as far as relevant to the decision, are summarised as follows:

Claim construction

The claimed subject-matter was an isolated antibody, which could be either mono- or polyclonal. In the case of polyclonal antibodies, the claimed antibody could be a population of antibodies. Regardless of whether it was mono- or polyclonal, the claimed antibody selectively bound to a non-linear, three dimensional epitope of human parathyroid hormone (hPTH) present only when the protein was in its bioactive conformation. The antibody did not recognise inactive hPTH, which lacked said three dimensional epitope. The epitope recognised by the claimed antibodies contained an intact helix which mirrored that found at the amino terminus of bioactive hPTH. Amino acids 1 to 13 of SEQ ID NO: 1 represented the minimum stretch necessary to form said intact helix. Each of said amino acids 1 to 13 did not necessarily interact individually with the CDRs of the claimed antibody, rather the antibody bound to the accessible sections of the three dimensional,

helical, structure formed when the protein was correctly folded. A population of polyclonal antibodies as claimed could contain antibodies with different specificities interacting with different parts of the non-linear, three dimensional epitope of active hPTH.

Novelty - Article 54 EPC

The antibodies disclosed in documents D1 and D3 did not anticipate the claimed subject-matter because they could not distinguish between active and inactive hPTH. Furthermore, document D1 only disclosed antibodies directed to amino acids 1 to 10 of SEQ ID NO: 1 but not to amino acids 1 to 13 of said SEQ ID.

The antibodies disclosed in document D3 also were only directed to amino acids 1 to 10 of SEQ ID NO: 1. Moreover, these antibodies recognised hexapeptides used to carry out epitope mapping (Figure 1) but document D3 did not disclose that they could bind to the intact three-dimensional helical epitope comprising at least amino acids 1 to 13 of hPTH.

In addition the antibodies disclosed in documents D1 and D3 were not isolated.

Example 2 of the patent was an illustrative embodiment of the claimed invention. Here sera containing a population of polyclonal antibodies, raised to $hPTH_{1-84}$, were affinity purified to remove antibodies specific for $hPTH_{38-84}$ and $hPTH_{13-34}$. A final affinity column of bearing $hPTH_{1-13}$ was used to isolate anti-$hPTH_{1-13}$ antibodies which recognised (i) the first amino terminal amino acid of hPTH and (ii) the intact helix of the amino terminus. It was apparent that neither the antibodies disclosed in document D1 or in document D3

had this binding profile. At most, document D1 disclosed antibodies that had only one of these binding specificities. Specifically, document D1 disclosed that the antisera K_1 to K_3 could bind to the first amino terminal amino acid of hPTH but did not disclose that they could bind to the intact amino terminal helix (see document D1, page 786, lines 38-41). The fact that the antisera of document Dl were capable of binding to $hPTH_{1-10}$ was evidence that they had a different binding specificity from the antibodies as claimed.

Example 5, Figure 10 and paragraph [0107] of the patent demonstrated that the claimed antibodies had binding specifity for the first amino terminal amino acid of hPTH and for the intact helix of the amino terminus. It disclosed antibodies that could bind to $hPTH_{1-13}$ but not to either of $hPTH_{1-6}$ or $hPTH_{7-13}$. This demonstrated that the claimed antibodies bound to epitopes from each part of the $hPTH_{1-13}$ fragment. Figure 11 of the patent showed that cleavage of the first amino terminal amino acid resulted in a near complete abolition of antibody binding, demonstrating that the antibodies bound to this first amino terminal amino acid.

Auxiliary request 1 - claim 1

The claim more clearly defined the structural determinants bound by the claimed antibody. In particular, the expression "*selectively binds*" was used to convey the fact that the antibody could distinguish between bioactive and inactive hPTH.

Auxiliary request 3 - claim 1

Claim 1 defined the epitope of hPTH as comprising amino acids 1 to 13 of SEQ ID NO: 1. None of the cited prior

art documents, including documents D1 and D3, disclosed antibodies that recognised this epitope. The opposition division had therefore been right to hold that the subject-matter of auxiliary request 3 was novel for the reasons set out in the decision under appeal.

Auxiliary request 4

Admissibility - Rule 13(1) RPBA

The request, filed at the oral proceedings before the board, should be admitted into the proceedings. It could not have been submitted earlier because the amendments made took into account the board's position on claim construction given at the oral proceedings, which had not been foreseeable from the written procedure.

IX. Appellant II's arguments relevant to the decision are summarised as follows:

Novelty - Article 54 EPC

Main request - claim 1

The opposition division was incorrect to hold that document D3 did not disclose antibodies meeting the specifications of the claim. It disclosed the immunisation of goats with natural $hPTH_{1-84}$. The polyclonal goat antibodies so obtained bound to native parathyroid hormone in the amino terminal region of $hPTH_{1-34}$. These antibodies therefore inherently recognised a "*three-dimensional epitope of parathyroid hormone*", which, being the native epitope at the amino terminus of parathyroid hormone, inherently included amino acids 1 to 13 of SEQ ID NO: 1. The antibodies

disclosed in document D3 were polyclonal and included some binding outside of this region, as was normal for a polyclonal antibody population. However, this did not alter the fact that antibodies meeting the terms of the claim were present in the disclosed sera. Document D3 disclosed epitope mapping of hPTH using hexapeptide probes which showed that the above mentioned antiserum comprised a predominant antibody population that bound to the amino terminal hPTH sequence located at amino acids 1 to 13 (Fig. 1). The fact that the antibody population was not tested for binding ability with a 13mer peptide did not mean that the antibodies could not bind such a 13mer peptide in its three-dimensional conformation.

The disclosure of document D1 also anticipated the claimed subject-matter. It related to antisera K1, K2 and K3, raised to a synthetic MAP (Multiple Antigenic Peptide). The resulting antibodies recognised $hPTH_{1-10}$, $hPTH_{2-10}$ and $hPTH_{4-12}$ (see document D1, section 3.2) and thus recognised and selectively bound an epitope comprising amino acids 1 to 13 of hPTH, i.e. the same three-dimensional epitope present in natural $hPTH_{1-84}$ as recognised by the claimed antibodies.

Auxiliary request 1 - claim 1

The claim related to the same subject-matter as claim 1 of the main request. The epitope recognised by the claimed antibody was still the same region of hPTH and included amino acids 1 to 2 and 10 to 13 of SEQ ID NO: 1. These amino acids were anyway part of the intact helix which was also required by the claim. This interpretation of the claim was confirmed by the wording of dependent claim 3 which specified the presence of the entire region 1 to 13 of SEQ ID NO: 1.

Auxiliary request 3 - claim 1

The claimed subject-matter was also the same as that of claim 1 of the main request. As set out for the main request, this subject-matter lacked novelty.

Auxiliary request 4

This claim request was filed very late in the proceedings and should therefore not be admitted. The amendments caused substantive problems including a broadening of scope compared to the granted claims and a lack of clarity.

X. Appellant I requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or on the basis of the claims of auxiliary requests 1 to 4.

XI. Appellant II requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Main request - claim 1

Claim construction

1. In line with established case law, the board interprets the claims giving the terms used their broadest technically sensible meaning (cf. Case Law of the Boards of Appeal of the European Patent Office, 8th edition, I.C.4.1). Applying these principles, the claimed subject-matter is an antibody, defined by its binding specificity to a particular structure of human parathyroid hormone (hPTH). In agreement with both

parties, the claimed antibody can be a population of polyclonal antibodies. In all cases, the claimed antibody binds to an epitope on native hPTH containing a helix which includes amino acids 1 to 13 of SEQ ID NO: 1, which epitope is identical to that found at the amino terminus of bioactive hPTH (i.e. it binds to the intact helix of the amino terminus). However, the antibody does not necessarily interact (i.e. binds via its CDRs) with each amino acid in the region spanned by amino acids 1 to 13 of SEQ ID NO: 1, individually. Instead, it may bind to exposed segments of the three dimensional, helical structure formed by amino acids 1 to 13 of SEQ ID NO: 1 when correctly folded.

2. In contrast to appellant I, the board can see no wording in the claim that would indicate to the skilled reader that the claimed antibody is able to distinguish bioactive and inactive hPTH. The claimed antibody is defined only by its target antigen and can bind to hPTH in a region which comprises amino acids 1 to 13 of SEQ ID NO: 1, which region forms a tertiary (three-dimensional) structure and inherently includes the intact helix at the amino terminus and the first amino terminal amino acid of native PTH.

Novelty - Article 54 EPC

3. Document D3 discloses an antiserum raised by immunising goats with the amino terminal part of hPTH (see page 3). The polyclonal antibodies contained in this antiserum are specific for $hPTH_{1-34}$. Separately, monoclonal antibodies are raised in mice with synthetic $hPTH_{1-38}$. The specificity of the antibodies in the goat antiserum is tested by epitope mapping using hexapeptides covering the entire $hPTH_{1-34}$ sequence (see page 4). Both the goat and the mouse antisera recognise

correctly folded hPTH in the region of amino acids 7 to 14 (i.e. in a region containing the intact helix of the amino terminus) - "*This was the epitope predominantly recognised by the goat antiserum and also by one of four larger antibody subpopulations of the mouse antiserum*" (see page 11). In three dimensional models of hPTH, this region was said to be exposed on the surface, making it accessible for antibody binding (see paragraph bridging pages 11 and 12).

4. Given that document D3 discloses goat polyclonal antibodies and mouse monoclonal antibodies that bind to a correctly folded three-dimensional epitope at the amino terminal end of parathyroid hormone which epitope comprises amino acids 7 to 14, this epitope must be identical to the epitope defined in the claim, which is also defined as that found at the amino terminal end of the correctly folded hPTH (see point 1, above). It inherently includes the first amino terminal amino acid of native PTH along with the intact helix of the amino terminus. The epitope mapping procedure used, leads to sub-populations of antibodies binding to solid phase "pins". These sub-populations are "isolated" in the sense of the claim in that they have been removed from the antiserum and from other antibody populations.

5. Document D1 discloses ten polyclonal antisera raised by immunising rabbits with synthetic peptides, *inter alia* $hPTH_{1-10}$ MAP (Multiple Antigenic Peptide; see page 784, "Peptide synthesis"). The antisera are characterised by epitope mapping, involving testing for binding to peptides including hPTH 1 to 10, 2 to 10, 4 to 10 and 6 to 15. Sera K1 to K3 raised to MAP 1 to 10 show a predominant binding sequence at hPTH amino acids 1 to 5 (see abstract) - "*Antisera K1-K3 bound to the very first N-terminal amino acids*" (see page 786, right

column). Binding of antibodies in the K1 to K3 antisera is also shown in Fig. 3 (a) on page 785. As was the case for the antibodies disclosed in document D3, the epitope mapping procedure leads to sub-populations of antibodies binding to a solid phase which are "isolated" in the sense that they have been removed from the antiserum and from other antibody populations.

6. Thus, both documents D1 and D3 disclose isolated antibodies that bind to hPTH in a region as defined in the claim, comprising amino acids 1 to 13 of SEQ ID NO: 1, when this region is folded in a tertiary (three-dimensional) structure (i.e. the intact helix at the amino terminus).

7. In view of the above, and of the fact that the claim does not require that the antibodies are able to distinguish between bio-active and inactive hPTH, the board concludes that the subject-matter of claim 1 lacks novelty. It follows that the main request does not meet the requirements of Article 54 EPC.

Auxiliary request 2 - claim 1

8. Since claim 1 of auxiliary request 2 is identical to claim 1 of the main request, the above conclusion applies equally and auxiliary request 2 does not meet the requirements of Article 54 EPC either.

Auxiliary requests 1 and 3 - claim 1

Claim construction

9. Claim 1 of auxiliary request 1 differs from claim 1 of the main request in the definition of the three dimensional epitope of PTH bound by the claimed

antibody. While claim 1 of the main request states that this "*comprises amino acids located between amino acids 1-13 of SEQ ID NO: 1 and includes the first N-terminal amino acid of native PTH along with the intact helix of the amino terminus*", claim 1 of auxiliary request 1 states that it "*comprises a first portion that includes amino acids 1-2 of SEQ ID NO: 1 and a second portion that includes amino acids 10 to 13 of SEQ ID NO: 1 along with the intact helix of the amino terminus*".

10. In both claims the epitope of hPTH comprises the intact helix at the amino terminus, which, in agreement with all parties, comprises at least amino acids 1 to 13. Indeed, it is the board's view that, since the stretch of amino acids 1 to 13 of SEQ ID NO: 1 includes amino acids 1 and 2 and 10 to 13 of SEQ ID NO: 1, the phrase "*comprises a first portion that includes amino acids 1-2 of SEQ ID NO: 1 and a second portion that includes amino acids 10 to 13 of SEQ ID NO: 1*" does not alter the scope of the claim vis-à-vis that of claim 1 of the main request. The claimed subject-matter is therefore identical and lacks novelty for the reasons set out in points 3 to 7, above.

11. Claim 1 of auxiliary request 3 also differs from claim 1 of the main request in the wording used to define the three dimensional epitope of hPTH bound by the claimed antibody. It states that "*the three-dimensional epitope of parathyroid hormone comprises amino acids 1-13 of SEQ ID NO: 1*". By virtue of the use of the non-limiting term "*comprises*", the epitope defined includes but is not limited to amino acids 1 to 13 of SEQ ID NO: 1. The subject-matter of the claim therefore includes the subject-matter of claim 1 of the main request and lacks novelty for the reasons set out in points 3 to 7, above.

12. Thus, auxiliary requests 1 and 3 do not meet the requirements of Article 54 EPC.

Auxiliary request 4

Admissibility - Rule 13(1) RPBA

13. Article 13(1) RPBA provides that any amendment to a party's submissions after it has filed the statement of grounds of appeal or reply thereto, may be admitted and considered at the board's discretion. In case of new claim requests, the discretion is to be exercised in view of, *inter alia,* the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy.

14. The present request was filed at the oral proceedings before the board, i.e. at a very late stage of the appeal proceedings. Appellant I's reason for filing the request at this late stage was that it was a reaction to the board's construction of claim 1 of the preceding requests which only became apparent at the oral proceedings.

15. However, the filing of the request cannot be seen as a response to a new objection or claim construction raised for the first time by the board at the oral proceedings. The objection of lack of novelty with respect to the disclosure of document D1 and document D3 was raised in appellant II's statement of grounds of appeal, which objection already relied on the claim construction adopted by the board in the present decision. Thus, the board's claim construction and the resulting finding of lack of novelty cannot have been a surprise to appellant I and therefore

cannot justify the submission of the request at this very late stage.

16. The board furthermore agrees with appellant II that discussion of the proposed amendment would require assessment of whether the amendments raise new issues at least under Article 123(2) EPC and Article 84 EPC, for which neither the board nor appellant II was able to prepare.

17. In view of the above considerations the board does not admit the claim request into the proceedings.

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:

P. Cremona M. Montrone

Decision electronically authenticated