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Datasheet for the decision of 15 February 2018

Case Number: T 0648/13 - 3.3.04

Application Number: 02749660.3

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Language of the proceedings: EN

Title of invention:
Antibodies to OPGL

Patent Proprietor:
Amgen Fremont Inc.
Amgen Inc.

Opponent:
Teva Pharmaceutical Industries Ltd.

Headword:
Anti-αOPGL-1 antibody/AMGEN

Relevant legal provisions:
EPC Art. 53(c), 54, 56, 83, 123(2)
EPC R. 115(2)
RPBA Art. 12(4), 15(3)

Keyword:
Main request - requirements of the EPC met (yes)
Late-filed line of argument and evidence - admission into the appeal proceedings (no)

Decisions cited:
T 0561/89, T 1016/93, T 0270/97

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 0648/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 15 February 2018

Appellant I: (Patent Proprietor01)	Amgen Fremont Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 (US)
Appellant I: (Patent Proprietor02)	Amgen Inc. One Amgen Center Drive Thousands Oaks, CA 91320-1799 (US)
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Appellant II: (Opponent)	Teva Pharmaceutical Industries LTD. 5 Basel Street 49131 Petach Tikva (IL)
Representative:	Dehmel, Albrecht Dehmel & Bettenhausen Patentanwälte PartmbB Herzogspitalstraße 11 80331 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 January 2013 concerning maintenance of the European Patent No. 1409016 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	P. de Heij

Summary of Facts and Submissions

I. Appeals were lodged by the patent proprietors (hereinafter "appellant I") and the opponent (hereinafter "appellant II") against the interlocutory decision of the opposition division concerning European patent No. 1 409 016, filed as international application and published as WO 03/002713 (hereinafter the "application as filed"), having the title "*Antibodies to OPGL*".

II. Claims 1 to 9 and 21 of the application as filed read:

"1. An antibody, comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence as set forth in SEQ ID NO:2 or a fragment thereof, and the light chain comprises an amino acid sequence as set forth in SEQ ID NO:4 or a fragment thereof.

2. An antibody, comprising a heavy chain and a light chain, wherein the heavy chain comprises a variable region comprising an amino acid sequence as set forth in SEQ ID NO:13 or a fragment thereof, and wherein the light chain comprises a variable region comprising an amino acid sequence as set forth in SEQ ID NO:14 or a fragment thereof.

3. The antibody of claim 2, wherein the heavy chain and the light chain are connected by a flexible linker to form a single-chain antibody.

4. The antibody of claim 3, which is a single-chain Fv antibody.

5. The antibody of claim 2, which is a Fab antibody.

6. The antibody of claim 2, which is a Fab' antibody.

7. The antibody of claim 2, which is a (Fab')2 antibody.

8. The antibody of claim 2, which is fully human.

9. The antibody of claim 2, wherein the antibody inhibits binding of OPGL to an osteoclast differentiation and activation receptor (ODAR).

[...]

21. A pharmaceutical composition comprising an antibody of any of claims 1 to 9 or 14 to 20."

III. Claims 1, 12 and 13 of the patent as granted read:

"1. An antibody, comprising a heavy chain and a light chain, wherein:

a) the heavy chain comprises:

1) an amino acid sequence as set forth in SEQ ID NO:2; or
2) an amino acid sequence as set forth in SEQ ID NO:13; and

b) the light chain comprises:

1) an amino acid sequence as set forth in SEQ ID NO:4; or
2) an amino acid sequence as set forth in SEQ ID NO:14; and

wherein the antibody binds to an osteoprotegerin ligand (OPGL) and inhibits binding of OPGL to an osteoclast differentiation and activation receptor (ODAR).
[...]

12. An antibody of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO:2 from residue 20 to residue 467, and wherein the light chain comprises an amino acid sequence of SEQ ID NO:4 from residue 21 to residue 235.

13. An antibody of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain consists of an amino acid sequence of SEQ ID NO:2 from residue 20 to residue 467, and wherein the light chain consists of an amino acid sequence of SEQ ID NO:4 from residue 21 to residue 235." (emphasis in both claims added)

IV. In the decision under appeal the opposition division held that claims 1 of the main request and of auxiliary requests 1 to 3 - being identical to claim 1 as granted - and claims 12 and 13 of auxiliary requests 4 and 5 - being identical to claims 12 and 13 as granted - comprised subject-matter extending beyond the content of the application as filed. Claims 2, 7, 15 to 20, 25 and 34 of auxiliary request 4 were held to comply with the requirements of Articles 100(c) or 123(2) EPC, respectively.

Auxiliary request 6 was found to meet the requirements of the EPC in relation to Articles 123(2), 83, 53(c), 54 and 56 EPC. Claim 1 of auxiliary request 6 reads:
"1. An antibody, comprising a heavy chain and a light chain, wherein:
a) the heavy chain comprises:

1) an amino acid sequence as set forth in SEQ ID NO:2;

and the light chain comprises:
2) an amino acid sequence as set forth in SEQ ID NO:4;
or
b) the heavy chain comprises:
(1) an amino acid sequence as set forth in SEQ ID NO: 13;

and the light chain comprises:
(2) an amino acid sequence as set forth in SEQ ID NO: 14;
and

wherein the antibody binds to an osteoprotegerin ligand (OPGL) and inhibits binding of OPGL to an osteoclast differentiation and activation receptor (ODAR)."

V. In the decision under appeal the opposition division summarised a line of argument of appellant I (then the patent proprietors) with regard to the novelty of the subject-matter of claim 1 of auxiliary request 6 as follows:

"In fact, *the skilled person was very aware at the time that antibodies having different heavy and light chain amino acid sequences could be raised against a single antigen, with germline diversity causing sequence distinctions in antibodies from lymphocytes of independent origin, and somatic mutation contributing to sequence diversity and the fine specificity of antibodies expressed by single lymphocyte clones at various stages of development (D41, paragraph bridging pages 697-698, and at page 701, line 43 to page 702, line 11). P also cites D42: WO 03/086289 A2 which discloses six antibodies prepared by immunization that*

bind specifically to OPGL. In comparison to the presently claimed antibodies each of the antibodies disclosed by D42 has different heavy and light chain amino acid sequences" (see decision under appeal, point 10.7).

VI. With their statement of grounds of appeal, appellant I submitted a main request identical to the main request dealt with in the decision under appeal, and 31 auxiliary requests (auxiliary requests 1a to 1c, 2, 3, 4, 5a to 5c, 6, 7, 8, 9a to 9c, 10, 11, 12a to 12c, 13, 14, 15a to 15c, 16, 17, 18a to 18c, and 19).

Further, in reply to appellant II's statement of grounds of appeal, appellant I submitted auxiliary requests 20, 21 and 22.

Lastly with a letter dated 15 December 2017, appellant I submitted auxiliary requests 20 and 20a to 20e, wherein auxiliary request 20d was identical to the previously filed auxiliary request 20.

VII. With its statement of grounds of appeal, appellant II submitted *inter alia* arguments as to why certain claims of requests dealt with in the decision under appeal, i.e. claim 1 of the main request, claims 2, 7, 15 to 20, 25 and 34 of auxiliary request 4 and claims 1, 2, 7, 13 to 18, 23 and 32 of auxiliary request 6, comprised added subject-matter.

Further with regard to auxiliary request 6, appellant II submitted - as in the opposition proceedings - that claims 8, 13 and 32 comprised subject-matter excepted from patentability, that the subject-matter of claims 1, 28 and 29 lacked sufficiency of disclosure and that the subject-matter of claims 1, 3 to 6, 12 and 18 to 21

lacked novelty in view of documents D1 and D7. Lastly, appellant II submitted that the subject-matter of claim 1 was obvious based on documents D47 to D55, including documents D50a and D52a (the documents are identified in section VIII below).

In reply to appellant I's statement of grounds of appeal, appellant II *inter alia* submitted that subject-matter of claims 1 of the main and of several of the auxiliary requests filed with their statement contravened the requirements of Article 123(2) EPC as far as they concerned antibodies having the sequence combinations of SEQ ID NOs: 2 and 14 and 13 and 4, respectively.

Moreover, appellant II submitted arguments as to why the subject-matter of claims 12 and 13 of the main request had no basis in the application as filed.

Appellant II did not submit any observations with regard to auxiliary requests 20, 20a to 20e, 21 and 22.

VIII. The following documents are cited in this decision:

D1: WO 98/46751

D7: WO 01/62932

D22: Stigbrand T., *et al.*, (1993), Acta Oncologica, 32: 841-844

D31: Stryer L., (1981), Biochemistry, second edition, W.H. Freeman and Company, San Francisco, CA, USA, 713-714

D41: Clarke S.H., *et al.*, (1985), J. Exp. Med., 161: 687-704

D42: WO 03/086289

D47: Dolan R., (2001), "Abgenix and the XenoMouse" Harvard Business School Publications, Boston MA, US

D48: Little M., (2009), "Recombinant Antibodies for Immunotherapy", Cambridge Univ. Press, Cambridge, UK

D49: WO 98/50433

D50: Jakobovits A., (1995), Current Opinions Biotechnol., 6: 561-566

D50a: MedLine printout showing that document D50 is a review article

D51: Jakobovits A., (1998), Advanced Drug Delivery Rev., 31: 33-42

D52: Green L. L., (1999), J. Immunol. Methods, 231: 11-23

D52a: MedLine printout showing that document D52 is a review article

D53: Little M., *et al.*, (2000), Immunol. Today, 21: 364-370

D54: Yang X. D., *et al.*, (1999), Cancer Res., 59: 1236-1243

D55: WO 98/24893

IX. Oral proceedings before the board were held on 15 February 2018, in the absence - as announced - of appellant II. At these proceedings the board expressed its preliminary opinion that appellant II's line of argument with regard to inventive step based on documents D47 to D55, including documents D50a and D52a, be excluded pursuant to Article 12(4) RPBA. Appellant I selected auxiliary request 20 filed with its letter dated 15 December 2017 as the main request.

At the end of the oral proceedings the chair announced the board's decision.

Claims 1 to 10 of the main request read:

"1. An antibody, comprising a heavy chain and a light chain, wherein:
the heavy chain comprises:
an amino acid sequence as set forth in SEQ ID NO: 13; and
the light chain comprises:
an amino acid sequence as set forth in SEQ ID NO: 14; and
wherein the antibody binds to an osteoprotegerin ligand (OPGL) and inhibits binding of OPGL to an osteoclast differentiation and activation receptor (ODAR).

2. The antibody of claim 1, wherein the heavy chain and the light chain are connected by a flexible linker to form a single-chain antibody.

3. The antibody of claim 2, which is a single-chain Fv antibody.

4. The antibody of claim 1, which is a Fab antibody.

5. The antibody of claim 1, which is a Fab' antibody.

6. The antibody of claim 1, which is a $(Fab')_2$ antibody.

7. The antibody of claim 1, which is fully human.

8. An antibody of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO:2 from residue 20 to residue 467, and wherein the light chain comprises an amino add sequence of SEQ ID NO:4 from residue 21 to residue 235.

9. An antibody of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain consists of an amino acid sequence of SEQ ID NO:2 from residue 20 to residue 467, and wherein the light chain consists of an amino add sequence of SEQ ID NO:4 from residue 21 to residue 235.

10. A pharmaceutical composition comprising an antibody of any of claims 1 to 9."

X. Appellant I's arguments, as far as they are relevant to the present decision, may be summarised as follows:

Main request

Amendments (Article 123(2) EPC)

The subject-matter of claims 1 to 7 and 10 had a basis in claims 2 to 8 and 21 as filed, respectively.

Furthermore, the subject-matter of claims 8 and 9 had an implicit basis in paragraphs [0086], [201], [204]

and [210] of Example 1 and in paragraphs [212] and [225] of Examples 2 and 3, respectively, in conjunction with the disclosure in Figures 2, 4, 17 and 18 of the application as filed.

Figure 2 in the application as filed disclosed the amino acid sequence of the heavy chain of the anti-α-osteoprotegerin ligand 1 (αOPGL-1) antibody consisting of 467 amino acids, wherein the first 19 amino acids of the signal sequence were underlined. The skilled person would had thus derived from Figure 2, that the "mature" amino acid sequence of the heavy chain, i.e. the sequence without the signal sequence, started at position 20 and terminated at position 467 of SEQ ID NO: 2.

Figure 4 in the application as filed disclosed the amino acid sequence of the light chain of the anti-αOPGL-1 antibody consisting of 235 amino acids, wherein the first 20 amino acids of its signal sequence were likewise underlined. Thus, the skilled person would have derived from Figure 4, that the mature light chain of the antibody consisted of residues 21 to 235 of SEQ ID NO: 4.
The same disclosure was derivable from Example 1 in the application as filed, which reported the cloning of cDNAs encoding the full-length light chain and heavy chain of the anti-αOPGL-1 antibody, i.e. the antibody of the invention (see paragraph [0201]). In this context, paragraph [0204] read that "*a 738 bp fragment encoding the 235 amino acid residues (including the 20 amino acid kappa chain signal sequence) of the αOPGL-1 kappa chain protein (Figure 4, SEQ ID NO: 4)*" was obtained and paragraph [0210] reported that "*a 1433 bp fragment encoding the 467 amino acid residues (including the 19 amino acid IgG signal sequence) of*

the αOPGL-1 IgG2 heavy chain protein (Figure 2, SEQ ID NO: 2)" was obtained.

Example 2 further disclosed that a stable expression of both antibody chains was achieved upon co-transfecting CHO cells and that "*αOPGL-1 expressed in CHO cells is secreted into the extracellular medium*" (see paragraphs [0212] and [0225] in Example 3 of the application as filed).

The skilled person reading the term "*secreted*" in this context on the basis of its common general knowledge (see document D31) would have immediately understood that it necessarily implied that the sequences of the heavy and light chains of the anti-αOPGL-1 antibody in the culture medium lacked their signal sequences, i.e. the region underlined in SEQ ID NOs.: 2 and 4 as disclosed in Figures 2 and 4, since the signal sequence was cleaved off in secreted proteins.

At the filing date of the application, the role of signal sequences in labeling the export of antibodies expressed under *in vivo* conditions was well established (see e.g. document D31, page 713, third paragraph to page 714, third paragraph).

Furthermore, Figures 17 and 18 disclosed the amino acid sequences of the antibody's variable light and heavy chains lacking both a signal sequence.

Novelty (Article 54 EPC)

Neither of documents D1 and D7 disclosed the amino acid sequences SEQ ID NOs: 13 and 14 referred to in claim 1.

Moreover, the skilled person would not have inevitably arrived at these two sequences following the technical instructions provided in the examples of both documents, in view of the considerable number of amino acid residues involved.

Therefore, the subject-matter of claim 1 was not directly and unambiguously derivable from the disclosure of documents D1 and D7 and the antibody according to claim 1 was novel.

Admission of a line of argument with regard to inventive step based on documents D47 to D55, including documents D50a and D52a (Article 12(4) RPBA)

In the first instance proceedings appellant II had merely argued that the antibody of the patent was an arbitrary selection. In its statement of grounds of appeal appellant II had significantly amended its case regarding inventive step, arguing for the first time in the proceedings that the difference between the antibody in document D1 as the closest prior art and the claimed antibody was that the antibody of the patent was a fully human form of the antibody disclosed in document D1.

Appellant II had submitted new documents D47 to D55 relating to methods used in the art for generating fully human antibodies. These documents were submitted in a new attempt to challenge inventive step, by asserting that there would have been a need for fully human antibodies, and alleging that the use of the methods disclosed in these documents would have readily lead to such antibodies possessing the advantageous properties of the claimed antibody as inherent features. However, these new submissions were neither

in direct response to the decision under appeal nor to the submissions of appellant I (then the patent proprietors) during the oral proceedings. The new documents were also not *prima facie* relevant.

Therefore, the new facts, evidence and arguments could and should have been filed in the course of the first instance proceedings and should not be admitted into the appeal proceedings.

Inventive step (Article 56 EPC)

The opposition division was correct to find that the subject-matter of claim 1 of auxiliary request 6 which encompassed the subject-matter of claim 1 of the present main request involved an inventive step.

XI. Appellant II's written arguments, as far as they are relevant to the present decision, may be summarised as follows:

Main request

Amendments (Article 123(2) EPC)

The subject-matter of claims 12 and 13 of the main request (having the identical wording of claims 8 and 9 of the present main request) had no explicit basis in the application as filed, which only disclosed the sequences of the entire SEQ ID NOs: 2 and 4 and not parts of these sequences lacking amino acid residues 1 to 19 and 1 to 20 respectively, i.e. the signal sequences (see e.g. Figures 2 and 4). Moreover, an implicit disclosure of the sequences of SEQ ID NOs: 2 and 4 lacking their signal sequences was likewise not derivable from the application as filed. Paragraph

[086] disclosed the term "*include*" relating to an open-ended meaning which did not exclude the presence of signal sequences.

Furthermore, the wording "*(including the 20 amino acids kappa chain signal sequence)*" in paragraph [204] and the wording "*(including the 19 amino acid IgG signal sequence)*" in paragraph [210] of the application as filed explicitly disclosed the presence of signal sequences in SEQ ID NOs: 2 and 4.

Paragraphs [113], [117] and [118] of the application as filed disclosed in general cloning procedures, transformations and expressions of the antibody in different cell lines. However, none of these paragraphs disclosed a direct or indirect connection with the absence or presence of signal sequences in this antibody. Moreover, the common general knowledge of the skilled person, as for example disclosed in document D31, only demonstrated that N-terminal signal sequences of proteins are present in prokaryotic and eukaryotic cells and that these sequences can be cleaved. However, since the application as filed did neither disclose the possibility or importance of mature antibodies, i.e. of antibodies lacking their signal sequences, the application as filed, when read by the skilled person in the light of his or her common general knowledge, did not disclose the sequences of SEQ ID NOs: 2 and 4 lacking signal sequences.

Novelty (Article 54 EPC)

The antibody according to claim 1 of the upheld claim request (which encompasses the subject-matter of claim 1 of the present main request) lacked novelty in view of the disclosure of documents D1 and D7, since both

documents disclosed antibodies binding to OPGL that inhibited the binding of OPGL to ODAR (see document D1, page 19, lines 8 to 12, page 30, lines 9 to 14, example 13, page 61 to 63; document D7, page 3, lines 28 to 32, page 8, lines 3 to 6).

Although both documents did not disclose the amino acid sequences set forth in SEQ ID NOs: 13 and 14 recited in claim 1, the skilled person performing the experimental steps disclosed in example 11 of document D1 (see pages 53 to 59), or in examples 2 to 4 and 7 in document D7 (see pages 86 to 95, 100 to 104) would have inevitably arrived at antibodies having these sequences.

Inventive step (Article 56 EPC)

Document D1 represented the closest prior art for an antibody according to claim 1 of the upheld claim request. The document disclosed antibodies binding to OPGL, and the inhibition of OPGL's binding to ODAR based on the use of compounds that included antibodies. Thus, it related to the same purpose as the patent, namely the provision of an antibody with the ability to bind to OPGL.

The claimed antibody was distinguished therefrom in that its sequence was fully humanised, i.e. a fully human form of the murine antibody disclosed in document D1.

The objective technical problem was considered as the provision of an alternative antibody capable of binding to OPGL and suitable for human treatment.

The antibody according to claim 1 provided a solution to this problem.

At the priority date the skilled person was motivated to generate a fully human anti-OPGL monoclonal antibody to overcome the drawbacks of murine antibodies or of antibodies which are not of complete human origin (see document D22, page 841, column 1, second paragraph). In the decision under appeal the opposition division had considered that the antibody of the patent had surprising and unexpected properties with regard to high affinity and specificity and rapid and prolonged suppression of bone resorption. The skilled person however would have expected that a fully human antibody inherently possessed such beneficial properties.

The skilled person solving the technical problem identified above would have used the transgenic XenoMouse® technology to generate a fully human antibody binding to a human antigen, since this technology was well-established for this purpose at the priority date of the patent. Beneficial properties of antibodies produced with the XenoMouse® technology included, for example, a high binding specificity and affinity and an extended half-life/bioavailability, i.e. the beneficial properties of the claimed antibodies. Thus, these were inherent properties which were anticipated and not surprising in view of the already existing experience.

Further evidence in support was derivable from the disclosure of documents D47 to D54.
Thus, the skilled person using the XenoMouse® technology had an expectation of success in arriving at the claimed antibody. The patent amounted to no more than following known techniques to achieve known results. Thus, contrary to the finding in the decision under appeal, the claimed antibodies did not involve an inventive step.

Furthermore, documents D50 to D53 were review articles which represented the common general knowledge of the skilled person at the priority date. Documents D47 to D49, and D54 were cited to further substantiate the common general knowledge of the skilled person concerning the existing technology for the production of fully human antibodies at the relevant date. In addition, document D55 was already referred to in the patent and could therefore not be considered as a newly

introduced document. Lastly, also in view of the case law of the boards of appeal, for example, decisions T 1016/93 and T 561/89, documents D47 to D54 should be admitted into the appeal proceedings.

XII. Requests

Appellant I requested that appellant II's appeal be dismissed and that a patent be granted on the basis of the main request. Further it requested that a new line of argument with regard to inventive step based on documents D47 to D55, including documents D50a and D52a, all submitted by appellant II with its statement of grounds of appeal, not be admitted into the appeal proceedings.

Appellant II requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Reasons for the Decision

1. The appeal is admissible.

2. The duly summoned appellant II did not attend the oral proceedings which in accordance with Rule 115(2) EPC

took place in its absence. In accordance with Article 15(3) RPBA, appellant II was treated as relying on its case as presented in writing.

Introduction to the invention

3. The claimed invention concerns a human antibody that binds to an osteoprotegerin ligand (OPGL) and inhibits OPGL's binding to an osteoclast differentiation and activation receptor (ODAR, also called RANK).

4. OPGL is a member of the tumour necrosis factor (TNF) family of cytokines and promotes the formation of osteoclasts through its binding to ODAR (see paragraph [0003] in the patent).

5. Bone tissue includes minerals (e.g. calcium and phosphorous), a matrix of collagenous and non-collagenous proteins, and cells. Living bone tissue exhibits a dynamic equilibrium between the formation of bone, called deposition, and the breakdown of bone, also called resorption. Different cell types are involved in these processes. Osteoblasts, for example, promote the formation of bone tissue, while osteoclasts are associated with bone resorption, i.e. the dissolution of bone matrix and minerals (see paragraph [0002] in the patent).

Main request

Amendments (Article 123(2) EPC)

6. In the following references are to passages and claims in the application as filed.

7. Any amendment to the parts of a European patent application or of a European patent (description, claims and drawings) can only be made within the limits of what a skilled person would derive directly and unambiguously, either explicitly or implicitly, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the document as filed. An implicit disclosure in this context is what the person skilled in the art would consider as necessarily implied by the disclosure of the document as a whole (see Case Law of the Boards of Appeal, 8th edition 2016 (hereinafter "CLBA"), II.E. 1.2.1 and II.E.1.2.2).

8. Compared to the main request in the decision under appeal, claim 1 of the present main request relates to amended subject-matter, as do claims 2 to 10 due to their direct or indirect dependency on claim 1. The wording of claims 2 to 10 is identical to the wording of claims 2 to 7 and 12 to 14 of the main request dealt with in the decision under appeal except for claim 10 having an adapted claim dependency.

9. The board notes that the subject-matter of claims 1 to 7 and 10 has a basis in original claims 2 to 9 and 21, respectively, in conjunction with paragraph [002] of the application, and considering that the binding of the claimed antibody to OPGL, which inhibits OPGL's binding to ODAR, is an inherent property of the antibody. Moreover, none of the subject-matter objected under Article 123(2) EPC by appellant II in any of the requests filed in the appeal proceedings (see section VII above) is present in these claims.

10. The wording of claims 8 and 9 of the present main request is identical to the wording of claims 12 and 13

of the main request dealt with in the decision under appeal. The opposition division and appellant II considered both that these claims contained added subject-matter, because in their view the application did not directly and unambiguously disclose antibody sequences of the light and heavy chain of SEQ ID NOs: 2 and 4 that lacked a signal sequence.

11. Claim 8 is directed to an "antibody of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO:2 from residue 20 to residue 467, and wherein the light chain comprises an amino acid sequence of SEQ ID NO:4 from residue 21 to residue 235". Claim 9 solely differs from claim 8 in that the term "comprises" is replaced by "consists of".

12. The amino acids at positions 1 to 19 in SEQ ID NO: 2 and at positions 1 to 20 in SEQ ID NO: 4 relate to the signal sequences of both immunoglobulin chains (see Figures 2 and 4). The amino acids at positions 20 to 467 of SEQ ID NO: 2 and the amino acids at positions 21 to 235 of SEQ ID NO: 4 are the variable and constant regions of the heavy and light chains, respectively.

13. Therefore, claims 8 and 9 encompass as embodiments immunoglobulin heavy and light chain sequences comprising both variable and constant regions and lacking a signal sequence, since the "comprising" language in claim 8 relates to antibodies containing "at least" the amino acids at positions 20 to 467 of SEQ ID NO: 2 and positions 21 to 235 of SEQ ID NO: 4, while the "consisting" language in claim 9 excludes the signal sequences in both chains.

14. As regards these embodiments at issue, the application explicitly discloses an anti-α-osteoprotegerin ligand 1 (αOPGL-1) antibody comprising amino acid sequences of the variable regions of the heavy and light chains lacking a signal sequence (see SEQ ID NOs: 13 and 14, paragraph [009], Figures 17 and 18) and also, as submitted by appellant II, the full-length sequences represented by SEQ ID NOs: 2 and 4. However, indeed, the application does not explicitly disclose an anti-αOPGL-1 antibody comprising the amino acid sequences of SEQ ID NOs: 2 and 4 lacking the signal sequences, i.e. an anti-αOPGL-1 antibody that contains the variable and constant regions of the heavy and light chains without their signal sequences.

15. Therefore, appellant II submits that the embodiments at issue are not disclosed in the application, whereas appellant I submits that these embodiments are disclosed in the application, yet implicitly.

16. In fact, Figure 2 in the application discloses the amino acid sequence of the heavy chain of the antibody encoded in SEQ ID NO: 2 consisting of 467 amino acids, wherein the residues at positions 1 to 19, i.e. the signal sequence, is underlined. The skilled person would derive from this figure the information that the signal sequence consists of 19 amino acids and that the "mature" sequence, i.e. the sequence without the signal peptide, starts at position 20 and terminates at position 467.

17. Figure 4 in the application discloses the amino acid sequence of the light chain of the antibody encoded in SEQ ID NO: 4 consisting of 235 amino acids including an underlined region located between positions 1 and 20 that represents the signal sequence. Thus, the skilled

person would derive from this figure the information that the signal sequence of the light chain consists of 20 amino acids, and that the "mature" sequence starts at position 21 and terminates at position 235.

18. Paragraph [204] in the application describes the cloning of the αOPGL-1 kappa chain cDNA, i.e. the light chain of SEQ ID NO: 4, reading as follows: "*The PCR reaction generates a 738 bp fragment encoding 235 amino acid residues (including the 20 amino acid kappa chain signal sequence) of the αOPGL-1 kappa chain (Figure 4, SEQ ID NO: 4)*".

This fragment is cloned into an expression vector identified as "*αOPGL-1 kappa/pDSRα19*" (see paragraph [205], Figure 5).

A similar disclosure is found in paragraph [210] in the application for the cloning of the heavy chain cDNA encoded in SEQ ID NO: 2 that reads: "*The PCR generates a 1433 bp fragment encoding the 467 amino acid residues (including the 19 amino acid IgG signal sequence) of the αOPGL-1 IgG2 heavy chain protein (Figure 2, SEQ ID NO: 2)*".

Also this fragment is cloned into an expression vector, however, identified as "*αOPGL-1-IgG2/pDSRα19*" (see paragraph [211], Figure 6).

19. The application further reports that "*Stable expression of αOPGL-1 antibody is achieved by co-transfection of αOPGL-1-kappa/pDSRα19 and αOPGL-1-IgG2/pDSRα19 plasmids*", i.e. the two expression vectors referred to in point 15 above, containing either the heavy chain or the light chain amino acid sequence of SEQ ID NOs: 2

and 4, into a Chinese hamster ovary (CHO) cell line (see paragraph [212]).

20. Lastly, the application describes that "*αOPGL-1 is produced by expression in Cell Line 125Q, a clonal line of CHO cells that expresses αOPGL-1 from plasmids αOPGL-1-kappa/pDSRα19 and αOPGL-1-IgG2/pDSRα19*" (see paragraph [0218]), and that for purification purposes the "*αOPGL-1 expressed in CHO cells is secreted into the extracellular medium*" (see paragraph [0225] including its heading, emphasis added).

21. In other words, the skilled person would derive from the passages in the application cited above that an anti-αOPGL-1 antibody composed of the heavy chain and the light chain amino acid sequences set forth in SEQ ID NOs: 2 and 4 is recombinantly produced in CHO cells and purified after its secretion into the culture medium.

22. Document D31 is a textbook in the field of biochemistry and thus represents the common general knowledge of the skilled person at the filing date of the application reading the term "*secreted*" in the context of an anti-αOPGL-1 antibody in the passage cited in point 17 above.

With regard to a signal sequence, document D31 reports that "*SIGNAL SEQUENCES ENABLE SECRETORY PROTEINS TO CROSS THE ENDOPLASMIC RETICULUM MEMBRANE*" since it "*is the marker on a nascent protein that determines whether its associated ribosome is to be free in the cytosol or bound to the ER membrane? In 1970, David Sabatini and Günter Blobel postulated that the signal for attachment is provided by a sequence of amino acid residues near the amino-terminus of the nascent polypeptide chain.*

This signal hypothesis (Figure 29-42) was soon supported by the finding of Cesar Milstein and George Brownlee that an immunoglobulin chain synthesized in vitro by free ribosomes contained an amino terminal sequence of twenty residues that was absent from the mature protein synthesized in vivo" (see page 713, title and third paragraph, emphasis added).

23. In other words, signal sequences in proteins generated under *in vivo* conditions are responsible for attaching ribosomes to the membrane of the endoplasmic reticulum (ER), and thus label proteins, including antibodies, for export into the ER. They are located at the N-terminus of the respective proteins, while they are absent from the mature protein produced in a cell under *in vivo* conditions, since they have been removed upon crossing the ER membrane.

24. Regarding the mechanism of their removal, document D31 discloses that "*The signal sequence is then cleaved by a peptidase on the luminal side of the ER (see Figure 29-42). Nascent chains destined to become integral membrane proteins probably contain specific sequences that block the transfer of the polypeptide across the ER membrane before the carboxyl-terminal end is reached. In contrast, the entire polypeptide chain is transported across the ER membrane in the case of secretory proteins*" (see page 714, third paragraph, emphasis added).

25. In other words, all secreted proteins, including antibodies, lack their signal sequences. Therefore, since the anti-αOPGL-1 antibody is secreted into the culture medium, the skilled person would derive from the application in the passages cited in points 15 to 17 above, that an antibody having the light chain and

the heavy chain disclosed in Figures 2 and 4, i.e. the sequences set forth in SEQ ID NOs: 2 and 4 referred to in claims 8 and 9, necessarily lack their signal sequences.

26. It follows from this that the board considers the subject-matter of claims 8 and 9 to be implicitly, but clearly and unambiguously disclosed in the application.

Thus, the board arrives at a conclusion different from that of the opposition division in the decision under appeal (see point 7 above), and is also not persuaded by appellant II's arguments.

27. In summary, the main request meets the requirements of Article 123(2) EPC.

Exceptions from patentability (Article 53(c) EPC); Sufficiency of disclosure (Article 83 EPC)

28. None of the claims that were objected by appellant II either under Articles 53(c) or 83 EPC (see section VII above) are contained in the present main request. The objections are therefore moot.

29. Thus, the main request meets the requirements of Articles 53(c) and 83 EPC.

Novelty (Article 54 EPC)

30. It was common ground between the parties that documents D1 and D7 disclose antibodies binding to OPGL that block the interaction between OPGL and its receptor ODAR. Furthermore, the parties agreed that neither document D1 nor D7 disclose the amino acid sequences of

the immunoglobulin heavy and light chains set forth in SEQ ID NOs: 13 and 14 of claim 1.

31. Appellant II argued that the skilled person following the techniques and instructions disclosed in example 11 of document D1 (see page 53 to 59) or in examples 2 to 4 and 7 disclosed in document D7 (see pages 86 to 95 and 100 to 104) would have arrived at antibodies according to claim 1 as an inevitable outcome of the experiments carried out. This was so since the methods for generating the claimed antibodies and the antibodies disclosed in documents D1 and D7 were very similar and the antibodies exhibited the same functional properties. Hence, performing the experiments as reported in documents D1 and D7 would necessarily result in antibodies comprising the sequences recited in claim 1, since they were inherent.

32. According to established case law of the boards of appeal, the disclosure in the prior art only anticipates the claimed subject-matter if the latter is directly and unambiguously derivable from the prior art disclosure, including any features implicit to a person skilled in the art. In this context an implicit disclosure means a disclosure which the person skilled in the art would objectively consider as necessarily implied in the explicit content.

With regard to products obtained by a process, it is well-established by the case law that any product that is the inevitable result from a process properly defined as to its starting substance and reaction conditions is considered to be disclosed, even if it is not cited *expresses verbis* in the prior art document (see CLBA, I.C.4.3. and decision T 270/97 cited therein).

33. Thus, assumed in appellant II's favor that the claimed antibodies and the prior art antibodies are generated by essentially identical methods and share similar functional properties, it has to be assessed whether or not their immunoglobulin heavy and light chains have inevitably identical amino acid sequences.

34. In this context the board refers to the decision under appeal where in point 10.7 the opposition division summarised appellant I's (then the patent proprietors) arguments (see section V above).

35. The board concurs with the arguments that, as a matter of fact, although antibodies are raised by the same method and exhibit identical binding properties, the amino acid sequences of their immunoglobulin heavy chain and light chain will differ. This is the result of a high natural germline diversity of genes encoding the antibodies' light chains and heavy chains and various mutational processes at several stages during the formation of an antibody.

This has not been disputed by appellant II.

36. In these circumstances, the board is not persuaded by appellant II's argument that the antibodies disclosed in documents D1 and D7 inevitably have the same amino acid sequences as those of the claimed antibodies. Thus, the antibodies according to claim 1 are novel in the light of the disclosure of documents D1 and D7.

37. Hence, the main request meets the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

Admission of new facts and documents D47 to D55, including documents D50a and D52a, concerning inventive step (Article 12(4) RPBA)

38. According to Article 12(4) RPBA the boards of appeal have a discretion to hold inadmissible facts and evidence which could have been presented in the first instance proceedings. The case law relied on by appellant II dates from 1991 and 1995 and is thus less relevant as the present Article 12(4) RPBA, applicable to the admission of new facts and evidence in the appeal proceedings, which was introduced in 2003 (see OJ 2003, 61).

39. In the first instance proceedings appellant II argued that, starting from the closest prior art antibodies disclosed in document D1, the technical problem to be solved by the skilled person would be the provision of an alternative antibody for interfering with the OPGL/ODAR interaction (see notice of opposition, page 14, point 2.2; minutes, point 6.1; decision under appeal, point 12). According to appellant II, the claimed antibody did not show any advantage or surprising effect compared to the closest prior art antibodies and was therefore to be considered as an arbitrary selection. Thus, the antibodies according to claim 1 were obvious and did not meet the requirements of Article 56 EPC.

40. The opposition division considered in the communication annexed to the summons (see point 7) that the claimed antibodies exhibited an unexpected and surprisingly high affinity and binding specificity for the OPGL

protein, and that the skilled person would not have arrived at the antibodies in an obvious manner.

41. In reply appellant II solely addressed issues other than inventive step raised in the opposition division's communication. Likewise at the oral proceedings before the opposition division, appellant II argued that the claimed antibodies were an obvious alternative to the antibodies reported in document D1 without discussing their alleged advantageous properties. These arguments did not persuade the opposition division.

42. In view of the above, the board cannot see any reason - and appellant II did not provide such reason - why the present facts and evidence concerning the common general knowledge of the skilled person with regard to the XenoMouse® technology and his or her expectations of the advantageous properties of fully human antibodies obtained by it (hereinafter: the new line of arguments), could not have been introduced in the first instance proceedings as an alternative to or a substitution of its previous entertained view, that the claimed antibodies constituted merely an arbitrary alternative to the antibodies of the closest prior art. Neither the decision of the opposition division nor appellant I's stance in the first instance proceedings occasioned these new submissions.

43. The fact that document D55 is cited in the patent application to illustrate the preparation of the claimed antibodies may be taken into account when assessing the admissibility of this document according to Article 12(4) RPBA, but does not necessarily justify its admission into the appeal proceedings. The same applies to the alleged relevance of documents D47 to D55 and the fact that these documents are introduced at

an early stage of the appeal proceedings. In the present case these circumstances are of insufficient weight to allow a fresh case on inventive step in the appeal proceedings.

44. The board therefore concluded that the new facts and new documents D47 to D55, including documents D50a and D52a, were not to be admitted into the appeal proceedings.

Other lines of argument submitted by appellant II as regards inventive step

45. The opposition division had taken the view in the decision under appeal that the subject-matter of claim 1 of auxiliary request 6 involved an inventive step (see section IV above). Antibodies according to claim 1 of the present main request are encompassed by claim 1 of auxiliary request 6. Therefore the burden of arguing a lack of inventive step of the claimed antibodies has continued to rest with appellant II.

46. However, appellant II's new lines of argument are not substantiated (see point 44 above), and thus not persuasive, whereas no other lines of argument of appellant II have been put forward contesting the opposition division's conclusion with regard to inventive step.

47. Therefore, the board has no reason to deviate from the decision under appeal on this issue as far as it applies to the presently claimed subject-matter.

48. Hence, the main request is found to meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The appeal of appellant II is dismissed.

2. The decision under appeal is set aside.

3. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted thereto:

   Claims 1 to 10 of the main request, filed as auxiliary request 20 with the letter of 15 December 2017.

The Registrar: The Chair:

P. Cremona G. Alt

Decision electronically authenticated