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Datasheet for the decision of 7 June 2018

Case Number: T 0605/14 - 3.3.04

Application Number: 05854387.7

Publication Number: 1838733

IPC: C07K16/22, C07K16/28, C12N15/13, C12N15/85

Language of the proceedings: EN

Title of invention:
Antibodies directed to angiopoietin-2 and uses thereof

Patent Proprietor:
Medimmune Limited

Opponent:
F.Hoffmann-La Roche AG

Headword:
Anti-angiopoietin-2 antibodies/MEDIMMUNE

Relevant legal provisions:
EPC Art. 56

Keyword:
Main request, auxiliary requests 1 to 6 - inventive step (no)

Decisions cited:
T 0735/00

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 0605/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 7 June 2018

Appellant I: (Patent Proprietor)	Medimmune Limited Milstein Building Granta Park Cambridge, Cambridgeshire CB21 6GH (GB)
Representative:	MacLean, Martin Robert Mathys & Squire LLP The Shard 32 London Bridge Street London SE1 9SG (GB)
Appellant II: (Opponent)	F.Hoffmann-La Roche AG 124 Grenzacherstrasse 4070 Basel (CH)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 January 2014 concerning maintenance of the European Patent No. 1838733 in amended form.**

Composition of the Board:

Chair	G. Alt
Members:	R. Morawetz
	L. Bühler

Summary of Facts and Submissions

I. The appeals of the patent proprietor ("appellant I") and of the opponent ("appellant II") lie against the interlocutory decision of the opposition division that European patent No. 1 838 733 could be maintained in amended form.

II. The patent is entitled "*Antibodies directed to angiopoietin-2 and uses thereof*".

Claim 1 as granted reads:

"1. An antibody or antigen binding fragment thereof comprising a variable light chain having a sequence defined by SEQ ID NO:81 and a variable heavy chain having a sequence defined by SEQ ID NO:79."

III. An opposition was filed against the patent. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) and 100(c) EPC.

IV. The opposition division decided that the main request and auxiliary request 2 before it failed to meet the requirements of Article 123(2) EPC, that auxiliary requests 1 and 3 failed to meet the requirements of Article 83 EPC, that auxiliary request 4 failed to meet the requirements of Article 56 EPC and that auxiliary request 5 failed to meet the requirements of Article 84 EPC.

It held that the subject-matter of the set of claims of auxiliary request 6 before it fulfilled the requirements of the EPC and maintained the patent on

the basis of this claim request. Claim 1 of this request is identical to claim 1 as granted.

V. With its statement of grounds of appeal, appellant I filed a main request and auxiliary requests 1 to 6, with auxiliary request 6 corresponding to auxiliary request 6 considered allowable by the opposition division. Claim 1 of each of these claim requests is identical to claim 1 as granted. Appellant I submitted arguments regarding the patentability of the subject-matter of the main request and of auxiliary requests 1 to 5.

In reply to appellant II's statement of grounds of appeal, appellant I provided arguments as regards the inventive step of the subject-matter of claim 1 of auxiliary request 6 maintained by the opposition division. A declaration by Dr Buchanan was submitted.

VI. In its statement of grounds of appeal, appellant II raised objections as regards lack of inventive step of the subject-matter of claim 1 of auxiliary request 6 maintained by the opposition division.

In reply to appellant I's statement of grounds of appeal, appellant II submitted a declaration by Dr Regula.

VII. The board issued a summons to oral proceedings and gave its preliminary opinion in respect of some issues in a communication pursuant to Article 15(1) RPBA.

VIII. Oral proceedings were held on 7 June 2018. At the end of the oral proceedings, the chair announced the board's decision.

IX. The following documents are referred to in this decision:

D1 WO 03/030833 (17 April 2003)

D10 Declaration by Dr. J. Moelleken, 23 May 2012

D16 Leow C.C. et al., International Journal of Oncology (2012), vol. 40, pages 1321 to 1330

D20 Brown J.L. et al., Mol Cancer Ther. (2010), Vol. 9, pages 145 to 156

D22 WO 2011/014469 (3 February 2011)

D29 Declaration by Dr A. Buchanan, 10 October 2014

D30 Declaration of Dr J.T. Regula, 13 October 2014

X. The arguments of appellant I submitted in writing and during the oral proceedings may be summarised as follows:

Main request

Inventive step (Article 56 EPC) - claim 1

Closest prior art

Document D1 was the closest prior art. Table 8 of document D1 provided EC50 (potency) data for antibody Ab 536.

Technical problem and its solution

The opposition division acknowledged the coexistence of both (i) a high affinity for angiopoietin-2 (Ang-2) and (ii) a preferential binding for Ang-2 versus angiopoietin-1 (Ang-1) as a difference between monoclonal antibody (mAb) 3.19.3, an embodiment of claim 1 disclosed in the application, and antibody (Ab) 536.

A preferential affinity of mAb 3.19.3 to Ang-2 versus Ang-1 was disclosed in the patent. Thus, Example 9 reported the side-by-side results of an Ang-1 and Ang-2 high-resolution Biacore study with mAb 3.19.3. Two independent experiments were run with each antigen and the data were reproducible. The estimated k_{off} value was on the low side so that the K_D value was somewhat overestimated, and the actual affinity for Ang-2 might be even higher. The results in Table 8 of the patent showed that the K_D value for Ang-1 (30.4 or 30.2 pM) was higher than for Ang-2 (5.3 or 5.6 pM), i.e. that mAb 3.19.3 had a higher affinity for Ang-2 than for Ang-1 and thus a preferential binding affinity for Ang-2 over Ang-1.

Document D10 was only relied on for a comparison with Ab 536. It was possible to rely on later evidence for a comparison with the closest prior art.

In addition, mAb 3.19.3 had a lower absolute potency for inhibiting Ang-1 binding to Tie-2 (EC_{50} 218.5 nM for mAb 3.19.3 versus 30 nM for Ab 356) whilst retaining good potency for inhibiting Ang-2 binding to Tie-2 (sub 1 nM for both mAb 3.19.3 and Ab 536).

Thus, mAb 3.19.3 had the following unexpected advantages over Ab 536: the coexistence of both a high affinity for Ang-2 and a preferential binding for Ang-2 versus Ang-1 and a lower absolute potency for inhibiting Ang-1 binding to Tie-2 whilst retaining a good potency for inhibiting Ang-2 binding to Tie-2.

All these properties of mAb 3.19.3 were advantageous for the therapeutic usefulness of the antibody.

Secondly, in any event, claim 1 was a product claim and there was no requirement for the advantageous properties of the antibody to be therapeutically relevant. In addition to therapeutic uses, the patent discussed diagnostic uses (see paragraphs [0001], [0118] and Example 24). The coexistence of both a high affinity for Ang-2 and a preferential binding for Ang-2 versus Ang-1 was advantageous for diagnostic uses (see document D29).

In view of the various differences between mAb 3.19.3 and antibody 536, the technical problem to be solved was the provision of an improved anti-Ang-2 antibody.

Obviousness of the solution

The claimed solution had the unexpected advantageous properties of mAb 3.19.3. The case law acknowledged inventive step when there was evidence that a claimed monoclonal antibody showed unexpected properties.

XI. The arguments of appellant II submitted in writing and during the oral proceedings may be summarised as follows:

Main request

Inventive step (Article 56 EPC) - claim 1

Closest prior art

In the experimental section of the patent, affinity determination of mAb 3.19.3 was followed by potency studies. MAb 3.19.3 inhibited Ang-2 binding to Tie-2 299 times better than Ang-1 binding to Tie-2 (see Table 10 of the patent) and was chosen for further studies because of its preferential potency for inhibiting Ang-2 binding versus Ang-1 binding to Tie-2 and not because of its affinity to Ang-2.

Document D1 related to the same purpose as the patent, the provision of anti-Ang-2 antibodies that recognise and specifically bind Ang-2 for diagnostic and therapeutic use and was the closest prior art. It disclosed anti-Ang-2 antibodies for use in treating diseases associated with undesired angiogenesis, such as cancer (see page 4, line 30 to page 6, line 9 and page 7, penultimate paragraph). One of these antibodies was Ab 536. In Table 8 of document D1, IC50 values reflected data from a neutralisation assay while EC50 values reflected affinities. This could be seen from the last row of the table, which reported "*no inhibition*" and "*no binding*", respectively. Ab 536 showed a 1433 higher potency (IC50) to neutralise Ang-2 than Ang-1, while Ab 545 showed only a 8 fold higher potency (see Table 8).

Technical problem and its solution

The skilled person reading the patent would have understood that Ang-2 affinity could not be determined reliably. The different Biacore affinity measurements regarding binding of mAb 3.19.3 to Ang-2 reported in the patent gave different K_D values (see Tables 6 and 8). The patent, in paragraphs [0159] and [0180], explained that the off-rate was an estimate and that "*to more precisely measure the binding affinity of mAb 3.19.3 for Ang-1 and Ang-2, a further experiment (see example 10) was run*". Example 10, which was the only reliable experiment in the patent as regards Ang-2 affinity, reported a K_D value for affinity of mAb 3.19.3 to Ang-2 of 86.4 pM. This value was higher than the K_D value for Ang-1 reported in Table 8 of the patent, thus actually showing that the affinity of mAb 3.19.3 to Ang-1 was higher than to Ang-2. The K_D values from different assays for Ang-1 and Ang-2 with the same antibody could be compared, (see document D20, page 148, left hand column, last paragraph).

The preferential affinity of mAb 3.19.3 for Ang-2 versus Ang-1 could thus not be deduced from the patent, to the contrary, the opposite was derivable from Examples 6, 9 and 10.

The opposition division had correctly held that K_D values for mAb 3.19.3 and Ab 536, i.e. different antibodies, could only be compared if they were obtained in side-by-side measurements and also that the binding affinity for Ang-2 could not be considered a truly distinguishing feature between mAb 3.19.3 and Ab 536 (see decision under appeal, point 8.1).

The opposition division did not take into account the potency of the antibodies to neutralise Ang-2 binding to Tie-2 but formulated the problem on the basis of a K_D which was not reliably determined and after having considered post-published document D16. Thus, the formulation of the problem involved hindsight.

The technical problem had to be based on what the art conveyed and what the application as filed disclosed. It could not be based on data that were not in the patent (see document D10) or on document D16 as it was post-published.

The technical effect to be considered in the assessment of inventive step should have been viewed in light of the purpose of providing anti-Ang-2 antibodies with improved therapeutic properties for treating pathological angiogenesis, in particular, cancer.

From the patent it was derivable that for the therapeutic efficacy of an anti-Ang-2 antibody, the selective capacity to block Ang-2 binding to Tie-2 (compared with the blocking activity of Ang-1 binding to Tie-2) was essential (see paragraphs [0044],[0047] and [0148]).

Document D22 provided an experiment in Example 6 in which antibodies 3.19.3 and 536 were directly compared for their capacity to block binding of Ang-1 and Ang-2, respectively, to Tie-2. The results in Table 19 showed a clear advantage of Ab 536 over mAb 3.19.3 regarding the therapeutically relevant parameter of selective Ang-2 blocking activity. The only objective conclusion was that mAb 3.19.3 did not present an improvement over Ab 536.

The technical problem to be solved was the provision of an alternative anti-Ang-2 antibody with preferential potency for Ang-2 versus Ang-1 for use in the therapy of pathological angiogenesis.

Obviousness of the solution

Once an antibody was known, it was a routine matter to identify and/or otherwise develop alternative antibodies having the same specificity and/or similar characteristics, such as binding affinities and cross-reactivities (see decision T 877/03, Reasons, point 23). Document D1 disclosed how antibodies that were even better than mAb 3.19.3 in the relevant function could be isolated. Only routine experimentation was required to get more antibodies. Thus, the provision of the antibody defined in claim 1 was obvious in view of the teaching of document D1.

If the board accepted the technical problem as formulated by the opposition division, then the claimed subject-matter was obvious in view of another antibody, Ab 545 of document D1, and prior art techniques to increase antibody affinity.

XII. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims of the main request, or, alternatively, of one of auxiliary requests 1 to 6.

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

Reasons for the Decision

1. In the oral proceedings, the board heard the parties on appellant II's appeal first and came to a decision. Therefore, the sole issue dealt with in this decision is inventive step.

Main request

Inventive step (Article 56 EPC) - claim 1

Closest prior art

2. Claim 1 is directed to an antibody comprising a variable light chain having a sequence defined by SEQ ID NO:81 and a variable heavy chain having a sequence defined by SEQ ID NO:79. These sequences are the full variable heavy and light chain amino acid sequences for monoclonal antibody (mAb) 3.19.3 (see Table 1 of the patent). One embodiment of the invention as claimed is therefore mAb 3.19.3. It is this embodiment which will be considered in the following.

3. The invention relates to monoclonal antibodies against human angiopoietin-2 (hAng-2 or Ang-2) and uses of such antibodies. The described antibodies are said to be useful as diagnostics and for the treatment of diseases associated with the activity and/or overproduction of Ang-2 (see paragraph [0001] of the patent). In the background section, the patent describes that Ang-2, as well as human angiopoietin-1 (hAng-1 or Ang-1), binds to the receptor Tie-2 (see paragraph [0003]). Ang-1, Ang-2 and Tie-2 are described to be involved in angiogenesis and, hence, considered as possible targets for anti-cancer therapy (see paragraphs [0002] to

[0010]). As regards anti-Ang-2 antibodies of the invention that are therapeutically useful, the patent discloses that such anti-Ang-2 antibodies "*preferably have desirable therapeutic properties including strong binding affinity for Ang-2, the ability to neutralize Ang-2 in vitro, and the ability to inhibit Ang-2 induced angiogenesis in vivo*" (see paragraphs [0022] and [0044]). As regards the underlying mechanism, the patent discloses that anti-Ang-2 antibodies are useful for preventing Ang-2 mediated Tie-2 signal transduction, thereby inhibiting angiogenesis (see paragraph [0047]).

4. In the experimental part of the patent, Examples 1 to 3 describe the generation of monoclonal antibodies against Ang-2.

In Example 4, the inhibitory activities of 27 mAbs on Ang-2 binding to Tie-2 were determined using a competitive binding assay, and ten antibodies that exhibited both relative high efficacy and potency, including mAb 3.19.3, were selected for further investigation. The efficacy (maximal inhibition, expressed as the ratio of bound Ang-2 with mAbs versus without mAbs) and potency (EC50) of these ten antibodies are listed in Table 4 of the patent.

Cross-reactivity of these antibodies to Ang-1 was determined in Example 8.

In Example 12, mAb 3.19.3 was tested for inhibition of Ang-1 and Ang-2 binding to Tie-2, and it was found that the potency of mAb 3.19.3 to inhibit binding to Tie-2 was significantly higher (by a factor of 299) for Ang-2 than for Ang-1 (see Table 10).

Subsequently, in Examples 20 to 22, the anti-tumour activity of mAb 3.19.3 was tested in mouse xenograft models, and it was concluded that the therapeutic efficacy seen in these models was predominantly due to Ang-2 antagonism because the potency of mAb 3.19.3 to inhibit the Ang-1/Tie-2 association was far lower than that on the Ang-2/Tie-2 association.

5. In the board's opinion, although the skilled person would derive from the patent that anti-Ang-2 antibodies can in principle have a diagnostic use as well, they would conclude - in particular from the examples - that the purpose of mAb 3.19.3 is a therapeutic use for treating pathological angiogenesis. The skilled person would also derive from the patent that, in this context, the potency of mAb 3.19.3, i.e. its selective capacity to inhibit the binding of Ang-2 to its receptor, Tie-2, is essential and that mAb 3.19.3 has a 299-fold selectivity (potency) for Ang-2 over Ang-1 as regards the ability to inhibit binding of these ligands to Tie-2 (see paragraphs [0044], [0047] and [0148] and Examples 12 and 20 to 22).

6. It is undisputed between the parties that document D1 is the closest prior art document, and the board sees no reason to differ.

7. This document discloses antibodies which specifically bind to Ang-2 and modulate its activity and their therapeutic and diagnostic use (see page 1, lines 6 to 10 and page 5, lines 4 to 9). Fully human antibodies against Ang-2 were produced (see Example 4). The sequences of the heavy and light chain variable regions are reported in Tables 3 to 5.

In Examples 3 and 4, the antibodies were tested for binding to Ang-2 and Ang-1 and for their effect on the Ang-1/Tie-2 and Ang-2/Tie-2 interactions. The results are set forth in Table 8 in terms of IC50 and EC50 values.

The parties disagreed on whether the EC50 data reported in Table 8 related to potency, as submitted by appellant I, or to affinity, as submitted by appellant II. There was, however, no dispute that the IC50 data reported in Table 8 related to potency (i.e. the capacity of the antibodies to inhibit binding of Ang-2 or Ang-1 to Tie-2).

8. As set out above, the purpose derivable from the patent for mAb 3.19.3 is a therapeutic use. Thus, the relevant property is the blocking of the interaction of Ang-2 with Tie-2.

Ab 536 of document D1 shows a 1433-fold higher potency, i.e. capacity to neutralise Ang-2 binding than Ang-1 binding to Tie-2 while, e.g. Ab 545, shows only a 8-fold higher potency (see Table 8).

Therefore, the board considers that Ab 536 of document D1 qualifies as the closest prior art antibody for the claimed subject-matter.

Objective technical problem and its solution

9. In the light of the features set out in claim 1 and considering that mAb 3.19.3 is an embodiment of this claim, mAb 3.19.3 differs from Ab 536 in the amino acid sequence of its variable heavy and light chain, i.e. in its structure.

10. The opposition division considered that the technical effect of this difference in structure is "*a higher preferential binding affinity for Ang-2 versus Ang-1*", that "*this effect is demonstrated in document D10*" and that document D22 confirms it. The opposition division further considered that "*this preferential binding affinity is therapeutically relevant due to the fact that Ang-1 and Ang-2 seem to have opposite functions and low Ang-1/Ang-2 ratios correlate with advanced tumor stages, as explained by P* [patent proprietor] *by reference to D16*".

The opposition division therefore formulated the problem to be solved as "*the provision of an improved antibody with preferential high-affinity binding for Ang-2 versus Ang-1*".

It considered that, although this problem was not formulated as such in the patent, the reformulation of the problem was possible since "*the effect of preferential binding as such was disclosed in the original application and its functional and therapeutic relevance is directly related to the technical problem explained in the originally application, for examples on paragraphs 37-40*" (see the decision under appeal, Reasons, points 7.2, 7.4 and 7.5).

11. In accordance with established jurisprudence, any effect provided by the invention may be used as a basis for reformulating the technical problem, as long as that effect is derivable from the application as filed. Only if this has been established can evidence produced after the effective date of the application be used in

support of such an effect (see Case Law of the Boards of Appeal, 8th edition 2016, sections I.D.4.4.1 and

I.D.4.6).

11.1 Appellant II disputes that the preferential binding affinity of mAb 3.19.3 for Ang-2 versus Ang-1 can be derived from the application as filed.

11.2 As regards the disclosure in the application as filed, in Example 9 (which is identical in the application and in the patent), the affinity of mAb 3.19.3 for Ang-1 and Ang-2 was determined using high-resolution Biacore analysis. Two independent experiments were run with each antigen.

For Ang-1, the K_D (in pM) was determined to be 30.4 and 30.2, while the K_D for Ang-2 was 5.3 and 5.6. Thus, the measurements are reproducible, as submitted by appellant I.

However, the application also discloses (see paragraph [0180] of the patent) that "*there was no significant dissociation signal recorded for the Ang-2 experiments, so the best off-rate estimate was to hold* k_d *constant at* 1×10^{-6} sec^{-1}" and further that "*to more precisely measure the binding affinity of mAb 3.19.3 for Ang-1 and Ang-2, a further experiment (see example 10) was run to determine the Kd of mAb 3.19.3 towards these antigens*".

Thus, while, according to the application as filed, the high-resolution Biacore measurements are reproducible, the values themselves are not considered reliable in the application.

11.3 Example 10 (which is identical in the application and in the patent) discloses that, "*with the goal of obtaining a more reliable Kd value*", mAb 3.19.3-binding

to Ang-2 was determined using a Kinetic Exclusion Assay (KinExA)(see paragraph [0182] of the patent). It was found that the "*value of KD that fit the data optimally was 86.4 pM with low and high 95% confidence limits at 64.3 pM and 98.7 pM, respectively*" (see paragraph [0183] of the patent).

11.4 In the board's opinion, considering that the application itself indicates that the affinity measurement results of mAb 3.19.3-binding to Ang-2 using high-resolution Biacore analysis are not reliable (see points 11.2 and 11.3), the skilled person would not take the affinity data reported in Table 8 for Ang-2 binding at face value and would therefore also not conclude from the data in Table 8 of the application as filed that mAb 3.19.3 shows a higher preferential binding for Ang-2 versus Ang-1. Indeed, when taking the - according to the application - more reliable affinity data determined in Example 10 for Ang-2 binding into account (86.4 pM), the skilled person would rather derive a preferential binding for Ang-1 (K_D of 30.4 and 30.2 pM).

11.5 The board concludes that the technical effect of a higher preferential binding affinity of mAb 3.19.3 for Ang-2 versus Ang-1 is not derivable from the application as filed. Under these circumstances, appellant I cannot rely on the data in documents D10 and D22, which were generated only after the filing date of the application.

12. Accordingly, a higher preferential binding affinity for Ang-2 versus Ang-1 is also not a technical effect that can be taken into account for the formulation of the technical problem.

13. Thus, there is also no need to consider appellant II's second line of argument, which is based on Ab 545.

14. Appellant I submitted that mAb 3.19.3 had further advantages over Ab 536, namely, (i) the coexistence of both a high affinity for Ang-2 and a preferential binding for Ang-2 versus Ang-1 and (ii) a lower absolute potency for inhibiting Ang-1 binding to Tie-2 whilst retaining good potency for inhibiting Ang-2 binding to Tie-2.

15. However, as a consequence of the above finding (see point 11.5) "coexistence of both a high affinity for Ang-2 and a preferential binding for Ang-2 versus Ang-1" is not a technical effect that can be relied on either. As regards the technical effect of high affinity for Ang-2, the board agrees with appellant II that K_D values for Ang-2 affinity of antibodies 3.19.3 and 536 can only be compared if they are obtained in side-by-side measurements. Document D10 (see table on page 10 and lines 12 to 14 on page 10) and document D22 (see Table 11a) provide such side-by-side comparisons, and the data indicate that Ab 536 has a higher affinity for Ang-2 than does mAb 3.19.3 (see also the decision under appeal, Reasons, point 6 and the table on page 6).

16. As regards potency, the board notes that the application as filed reports that mAb 3.19.3 showed concentration dependent inhibition of both Ang-1 and Ang-2 binding to Tie-2, with EC50=218.5 nM for Ang-1 and EC50=0.7310 nM for Ang-2 (see Table 10). Appellant I compared these data with the data reported in Table 8 of document D1 for Ab 536 (EC50=30 nM for Ang-1 and EC50=0.005 nM for Ang-2) and concluded that mAb 3.19.3 had a further unexpected advantage over

Ab 536, namely, a lower absolute potency for inhibiting Ang-1 binding to Tie-2 (EC50=218.5 nM for mAb 3.19.3 versus EC50=30 nM for Ab 356) whilst retaining good potency for inhibiting Ang-2 binding to Tie-2 (sub 1 nM for both mAb 3.19.3 and Ab 536).

17. However, the parties disagreed on whether the EC50 data in Table 8 of document D1 related to affinity or potency measurements. In the board's judgement, this issue does not need to be decided because it is undisputed that document D22 provides potency data from a side-by-side comparison of Ab 536 (Control I(Ab), see paragraph [0106]) and mAb 3.19.3 (Control IV(Ab), see paragraph [0106]). In Example 6 of document D22, the antibodies are compared as regards the capacity to block the binding of Ang-1 and Ang-2, respectively, to Tie-2. The results are expressed in terms of Inhibitory Concentration (IC50) values, generated by calculating the amount of antibody required to block 50% of the signal from the binding of Ang-2 or Ang-1 to Tie-2. From the results reported in Table 19 it can be concluded that Ab 536 has a higher potency for blocking Ang-2 binding to Tie-2 than mAb 3.19.3 (IC50=93.72 pM versus IC_{50}=147.6 pM) and a lower potency for blocking Ang-1 binding to Tie-2 than mAb 3.19.3 (IC50=61.71 nM versus IC50=4.25 nM).

18. Accordingly, appellant I's argument as regards further advantages of mAb 3.19.3 over Ab 536 fails, because a preferential binding of mAb 3.19.3 for Ang-2 versus Ang-1 is not derivable from the application as filed. Also, in side-by-side comparisons, Ab 536 has i) a higher affinity for Ang-2 than 3.19.3 (see document D10 and point 15 above), and ii) a higher potency for inhibiting Ang-2 binding to Tie-2 than mAb 3.19.3 and a lower potency for inhibiting Ang-1 binding to Tie-2

than mAb 3.19.3 (see document D22 and point 17 above).

19. As a secondary argument, appellant II submitted that the coexistence of both a high affinity for Ang-2 and a preferential binding for Ang-2 versus Ang-1 was also an advantage in the context of diagnostic uses of mAb 3.19.3. However, since preferential binding for Ang-2 versus Ang-1 cannot be derived from the application as filed (see point 11.5 above), this argument cannot succeed either.

20. In the board's judgement, considering that no advantageous properties can be recognised for mAb 3.19.3 and further that in side-by-side comparison Ab 536 shows a clear advantage over mAb 3.19.3 in the therapeutically relevant parameter of selective Ang-2 blocking activity, mAb 3.19.3, and thus one embodiment falling within the scope of claim 1, cannot be considered an improvement over the prior art antibody 536.

21. Starting from document D1, the technical problem to be solved can thus be formulated as the provision of an alternative anti-Ang2 antibody for use in the therapy of pathological angiogenesis.

Obviousness of the solution

22. Document D1 discloses a method to produce fully human anti-Ang-2 antibodies and assays to screen for antibodies having a greater selective capacity ("potency") to block Ang-2/Tie-2 interaction than Ang-1/Tie-2 interaction, a property useful in the therapy of pathological angiogenesis (see point 7 above). It also discloses several antibodies produced by this method having this property (see Table 8).

23. In the board's view, the skilled person, faced with the problem of providing an alternative anti-Ang2 antibody for use in the therapy of pathological angiogenesis, would produce and screen antibodies according to the methods disclosed in document D1 and would thus obtain further antibodies having the desired property by applying routine methods. The provision of these antibodies is thus obvious.

24. That the structure of the thus obtained antibodies, i.e. their amino acid sequences, is not predictable, is not a reason for considering these antibodies as not obvious. The skilled person, aiming at providing an antibody with a particular functional property, knows that such a functional property is the result of the antibody's amino acid sequence, but knows also that such a functional property may be embodied by various different amino acid sequences.

25. Moreover, in the present case, the specific structure of the variable heavy and light chain amino acid sequences of mAb 3.19.3 does not impart an additional property to the antibody which differs from the property screened for and which could be regarded as surprising (see above, points 11.2 to 18). In line with established jurisprudence in the field of antibodies (see decision T 735/00, Reasons, point 26), the mAb 3.19.3 has to be considered as obvious.

26. Thus, one embodiment falling within the scope of claim 1 lacks an inventive step. Therefore, the subject-matter of claim 1 as a whole must be considered

to fail to meet the requirements of Article 56 EPC.

Auxiliary requests 1 to 6

Article 56 EPC - claim 1

27. Claim 1 of these requests is identical to claim 1 of the main request and the same reasoning as set out above for the subject-matter of claim 1 of the main request applies. This was not disputed by appellant I.

Conclusion

28. In the absence of an allowable claim request, the patent is to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

G. Nachtigall G. Alt

Decision electronically authenticated