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Datasheet for the decision of 29 November 2016

Case Number: T 0172/13 - 3.3.04

Application Number: 04779660.2

Publication Number: 1648939

IPC: C07K16/00, C12N15/13, A61P35/00

Language of the proceedings: EN

Title of invention:
Anti-VEGF antibodies

Applicant:
Genentech, Inc.

Headword:
Anti-VEGF antibodies/GENENTECH

Relevant legal provisions:
EPC Art. 111(1), 113(1), 115
EPC R. 103(1)(a)

Keyword:

Right to be heard - violation (yes)
Substantial procedural violation - (yes)
Remittal to the department of first instance (yes)
Observations by third parties - not considered in view of remittal
Reimbursement of appeal fee - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

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Case Number: T 0172/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 29 November 2016

Appellant: (Applicant)	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 (US)
Representative:	Denison, Christopher Marcus Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 25 May 2012 refusing European patent application No. 04779660.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	R. Morawetz
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal of the applicant ("appellant") lies against the decision of the examining division refusing European patent application No. 04779660.2. The title of the application is "*Anti-VEGF antibodies*".

II. The examining division informed the applicant in a communication pursuant to Article 94(3) EPC that the subject-matter of the claims then on file was novel. It also stated that claims directed to specific antibodies were considered inventive while claims directed to antibodies in general were considered to lack an inventive step. In support of its findings the examining division referred to the following documents:

D1 Chen Y. *et al.*, J. Mol. Biol. (1999), vol. 293, pages 865-881

D2 Popkov M. *et al.*, J. Mol. Biol (2003), vol. 325, pages 325-335

D3 Klohs W.D. and J.M. Hamby, Current Opinion in Biotechnology (1999), vol. 10, pages 544-549

D4 Sone H. *et al.*, Biochemical and Biophysical Research Communications (2001), vol. 281, pages 562-568

III. In reply the applicant submitted an amended set of claims, together with arguments regarding inventive step for the claimed subject-matter.

IV. Next the examining division issued a summons to oral proceedings and indicated that none of the claimed subject-matter was inventive.

V. The applicant reacted by submitting an amended main request and an auxiliary request and arguments in support of inventive step for the claimed subject-matter.

VI. In a telephone consultation between the first examiner and the representative the first examiner informed the representative that "*None of the amended main request or auxiliary request prima facie overcomes the inventive steps* [sic] *objections raised*."

VII. At the end of the oral proceedings the examining division refused the application on the sole ground of lack of inventive step.

VIII. The appellant appealed against the decision and filed a new main request and four auxiliary requests with its statement of grounds of appeal.

IX. On 20 January 2016 observations by a third party were filed; the appellant requested that they be held inadmissible.

X. On 19 September 2016 further observations by a third party were filed.

XI. The appellant was informed of the board's opinion that a violation of the appellant's right to be heard (Article 113(1) EPC), and thus a substantial procedural

violation, had taken place in the proceedings before the examining division and that therefore the decision under appeal was to be set aside.

XII. With letter dated 28 October 2016 the appellant indicated that it would not attend the oral proceedings and requested that the case be remitted to the examining division on the basis of the claim requests filed with the grounds of appeal.

XIII. Oral proceedings before the board were held on 29 November 2016. The appellant was absent, as announced beforehand. At the end of the oral proceedings the chairwoman pronounced the board's decision.

XIV. The appellant's arguments may be summarised as follows:

Right to be heard (Article 113(1) EPC)

The examining division's decision was based on an objection which was completely new to the proceedings. At no previous point in the written or oral proceedings had the examining division referred to the use of naïve (or synthetic) phage display libraries to avoid the known problems of negative selection. In refusing the application on the basis of an objection on which the appellant had not had an opportunity to comment, the examining division had contravened Article 113(1) EPC.

Remittal

The case should be remitted to the examining division to permit the appellant to argue against the objection before two instances.

XV. The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division for further prosecution on the basis of the claim requests submitted with the statement of grounds of appeal. It also requested that the appeal fee be refunded pursuant to Rule 103(1)(a) EPC.

Reasons for the Decision

Right to be heard (Article 113(1) EPC)

1. Article 113(1) EPC stipulates that the decisions of the European Patent Office may only be based on grounds or evidence on which the parties concerned have had an opportunity to present their comments. According to established case law of the boards of appeal the term "*grounds or evidence*" in Article 113(1) EPC is to be understood as meaning the essential legal and factual reasoning on which the decision is based (see Case Law of the Boards of Appeal, 8th edition 2016, section III.B.2.3.2).

2. In the present case, the appellant submits that the examining division's decision was based on an objection - the use of naïve (or synthetic) phage display libraries to avoid the known problems of negative selection - which was new to the proceedings.

3. It thus needs to be determined (i) whether the objection is part of the essential legal and factual reasoning on which the decision is based, and if so, (ii) whether the appellant has had an opportunity to present its comments on it.

4. As to (i) of point 3, the present application was refused by the examining division for the sole reason that it was found to lack an inventive step.

5. The examining division held (see decision under appeal, reasons, point 7.3) that document D4 or document D2 may be considered to represent the closest prior art. Document D4 is said to disclose a polyclonal antibody (Ab) to VEGF which was obtained from rabbits immunised with human VEGF and which also reacted with and neutralised murine VEGF. Document D2 is said to disclose that a key motivation for the generation of therapeutic monoclonal Abs from rabbits was their potential cross-reactivity with human, non-human primate, and mouse antigens, and in addition "*D2 successfully employed a rabbit immune library to generate a human-mouse cross species specific anti-Tie Ab (p327, rhc, §2 ff.)*". The examining division defined the problem to be solved as "*to provide a neutralizing anti-VEGF mAb showing human/mouse crossreactivity*".

6. The examining division then stated that "*at the time of the present application, phage display technology was a well known alternative to hybridoma technology (e.g. D2 p 325, rhc, l 4 ff; Ref. 12, 30). Therefore, from a technical point of view and being aware of the problem the skilled person would have had no difficulty avoiding immunisation of an animal with high homologous VEGF and negative selection of possibly cross-reacting epitopes (c.f. D2 p 326, lhc, §3) by using suitable phage display technology.*" (*ibid.*, point 7.5).

The examining division concluded that in view of:

"*a) prior art explicitly expressing the need of mVEGF/ hVEGF cross-reactive (m)Ab,*

b) the reported high homology between hVEGF and mVEGF and the, at the relevant date, well characterized VEGF-VEGFR interaction, and
c) the technically mature phage display technology at the filing date,
a skilled person would have been able to arrive at neutralizing human-mouse cross-reactive anti-VEGF Ab without inventive skills just by avoiding technologies known to be susceptible to negative selection (such as hybridoma technology) and by using appropriate selection steps in e.g. phage selection." (*ibid.*, point 7.5).

7. It is thus apparent that the objection at issue, i.e. that the skilled person would have used phage display technology to solve the technical problem, is part of the essential legal and factual reasoning for finding a lack of inventive step for the subject-matter of claim 1 of the claim requests before the examining division (*ibid.*, points 7.5, 7.8 and 7.11).

8. As to (ii) of point 3, i.e. the question of whether the appellant has had an opportunity to present its comments on this objection, the board has taken into account the documentation of the prosecution history before the examining division.

9. In its first (and sole) communication pursuant to Article 94(3) EPC (see section II), the examining division considered document D1 to represent the closest prior art and the problem to be solved as the provision of "*high affinity, mouse-human-crossreactive anti-VEGF Ab suitable for therapeutic and preclinical use*". The examining division acknowledged an inventive step for the specific antibodies characterised by their specific CDRs because "*in view of the reported*

difficulties reported [sic] in D2 & D3, there is no reasonable expectation of success that a skilled person can obtain more Ab having the desired properties using the different techniques known in the field without undue experimentation." For the same reasons though no inventive step was acknowledged for claims relating to antibodies in general. The disclosure of document D2 is summarised briefly (see paragraph bridging pages 5 and 6), but the communication does not mention that document D2 discloses the use of naïve (or synthetic) phage display libraries to avoid the known problems of negative selection.

10. With the response (see section III) the appellant filed an amended set of claims and submitted that nothing in the prior art suggested to the skilled person that antibodies as claimed could be produced.

11. In the next communication, which accompanied the summons to oral proceedings (see section IV), the examining division considered that document D4 represented the closest prior art and that the problem to be solved was the provision of "*an alternative cross-hu/mouse species specific anti-VEGF*". Based on document D4, which showed the production of polyclonal anti-VEGF Ab to human and mouse VEGF which can neutralise mouse VEGF activity, none of the general or specific antibodies were considered inventive, because document D4 "*generates the reasonable expectation that other such antibodies may be produced*". The possibility of using naïve (or synthetic) phage display libraries to avoid the known problems of negative selection is not mentioned in that context or at all in the communication.

12. In response, the appellant limited the claims to monoclonal antibodies and argued that document D4, which disclosed polyclonal antibodies, did not provide the skilled person with any realistic expectation of producing cross-reactive, neutralising monoclonal anti-VEGF Abs due to the high homology of mouse and human VEGF.

13. In a note of a telephone consultation (see section V) held shortly before the oral proceedings the examiner informed the representative that "*none of the amended main request or auxiliary request prima facie overcomes the inventive step objections raised*". It is not reported that any reasoning was provided by the examiner at this point in time.

14. According to the relevant passages in the minutes of the oral proceedings before the examining division, "*the C [chairman] informed the R [representative] that the examining division was of the preliminary opinion that the main request on file did not meet the requirements of Article 56 EPC for lack of inventive step. The C gave a preliminary reasoning based on D1 and D2 p. 331 left-hand column last paragraph. The C referred also to D3 p. 544 right-hand column last paragraph, then invited the R to explain his argumentation in favour of inventive step for the subject-matter of independent claim 1 of the MR*" (see minutes, point 4), and further "*After a break for deliberation, the C indicated that the examining division remained of the preliminary opinion that inventive step for the subject-matter of claim 1 would not be acknowledged and provided further arguments based on D2 and D4 as regards the said objection*" (*ibid.*, point 4.2).

15. Considering that pursuant to Rule 124 EPC minutes of oral proceedings are to contain the essentials of the oral proceedings and the relevant statements made by the parties and in the light of the passages recited in point 14 above, the board cannot come to the conclusion that the use of naïve (or synthetic) phage display libraries to avoid the known problems of negative selection had been discussed during the oral proceedings.

16. Moreover, the sole text passage of document D2 reported as being explicitly referred to by the examining division during the oral proceedings, i.e. page 331, left hand column, last paragraph, differs from the text passages of document D2 relied on in the decision under appeal (see point 6 above). Thus, the passage of document D2 on page 331 relates to antibodies that are cross-reactive with human and mouse antigens and are generated by immunising rabbits but not by using phage display. It reads "*a key motivation for the generation of therapeutic mAbs from rabbits is their potential cross-reactivity with human, non-human primate, and mouse antigens, a highly relevant property facilitating preclinical evaluation. Supporting this claim, we here describe for the first time a rabbit mAb that recognizes both human and mouse antigen with the same affinity.*"

17. Also the sole passage in document D3 referred to explicitly by the examining division during the oral proceedings (see point 14 above) is silent about the possibility of using naïve (or synthetic) phage display libraries to avoid the known problems of negative selection. It relates to cross-reactivity and more particularly to the fact that "*one of the major difficulties in the development of mAb directed*

therapies to VEGF is the lack of cross reactivity of the human anti-VEGHF antibody with murine VEGF and visa versa".

18. On the basis of the available evidence of the prosecution history before the examining division, the board has to conclude that the objection at issue, i.e. that the skilled person would have used phage display technology to solve the technical problem, was not communicated to the appellant before the decision was issued. Accordingly, the appellant did not have an opportunity to comment on it or on relevant passages in the prior art. Therefore, the examining division's decision contravenes the principle of the right to be heard enshrined in Article 113(1) EPC.

19. The sole reason for the refusal of the present application was lack of inventive step. The violation of the appellant's right to be heard was thus decisive for the outcome of the decision under appeal and therefore constitutes a substantial procedural violation.

20. It follows from points 1 to 19 that the decision under appeal can not be upheld by the board and is to be set aside. Accordingly, the appeal is allowable.

Remittal

21. Article 11 RPBA stipulates that the board is to remit the case to the department of first instance if fundamental deficiencies are apparent in the first instance proceedings, unless special reasons present themselves for doing otherwise. The substantial procedural violation is held to be a fundamental deficiency under Article 11 RPBA. The board is not

aware of any special reasons that would speak against remittal and notes that the appellant has requested remittal of the case. Accordingly, the board finds it appropriate to remit the case to the examining division.

Reimbursement of the appeal fee

22. In the present case, the appellant was deprived of its right to be heard with respect to an issue decisive for the outcome of the decision under appeal. It had no choice but to file an appeal which results in a remittal without the substantive issues being dealt with. Therefore, the reimbursement of the appeal fee is equitable (Rule 103(1)(a) EPC).

Observations by a third party

23. Under Article 115 EPC, in proceedings before the European Patent Office, following the publication of the European patent application, any third party may, in accordance with the Implementing Regulations, present observations concerning the patentability of the invention to which the application or patent relates.

24. In the present case, first observations by a third party were filed (see section IX), arguing that the claim requests filed with the statement of grounds of appeal should be held "*inadmissible under Article 12(4) RPBA*". As these observations relate to a procedural issue and not to the patentability of the invention, the board decides to hold them inadmissible.

25. The second observations by a third party (see section X) contained *inter alia* comments relating to the patentability of the claimed invention. Since the case will be remitted to the examining division for further prosecution, the board finds it appropriate to leave the decision as to whether or not to take these observations into account to the examining division.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division for further prosecution on the basis of the claim requests submitted with the statement of grounds of appeal.

3. The appeal fee is to be reimbursed.

The Registrar: The Chairwoman:

L. Malécot-Grob G. Alt

Decision electronically authenticated