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Case Number: T 1856/16 - 3.3.04

Application Number: 04701279.4

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Language of the proceedings: EN

Title of invention:
Identification and engineering antibodies with variant Fc regions and methods of using same

Applicant:
MacroGenics, Inc.

Headword:
Antibodies with variant Fc regions/MACROGENICS

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)

Keyword:
Amendments - allowable (yes)
Claims - clarity (yes)
Sufficiency of disclosure - (yes)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:
T 1599/06, T 0609/02, T 1060/11

Catchword:

Europäisches Patentamt
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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1856/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 24 August 2020

Appellant: (Applicant)	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 (US)
Representative:	Patent Boutique LLP 10A Printing House Yard Hackney Road London E2 7PR (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 4 March 2016 refusing European patent application No. 04701279.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chair	G. Alt
Members:	B. Rutz
	A. Jimenez

Summary of Facts and Submissions

I. The appeal of the applicant ("appellant") lies from the decision of the examining division refusing European patent application No. 04 701 279.4 entitled "*Identification and engineering antibodies with variant Fc regions and methods of using same*".

II. In the decision under appeal, the examining division found that claim 1 of the main request infringed the requirements of Article 123(2) EPC. The claims of auxiliary request 1 fulfilled the requirements of Article 123(2) EPC, but infringed the requirements of Article 84 EPC. The claims of auxiliary request 2 fulfilled the requirements of Article 123(2) EPC, and the subject-matter of claims 1 and "*3* [sic] *to 16*" was novel (Article 54 EPC). The subject-matter of claim 1 of each of auxiliary requests 2 and 3 lacked inventive step (Article 56 EPC) in relation to document D4 as closest prior art.

III. In point 14.2.3 of the decision under appeal, it is furthermore stated: "*Therefore, although the ED agrees with the applicant in that the identification of the P396L substitution* per se *is not obvious in view of the available prior art, ...*".

IV. With the statement of grounds of appeal, the appellant filed a set of 18 claims as a main request which corresponds to auxiliary request 1 dealt with in the decision under appeal, except for minor changes in the wording of claims 1 and 11 to 15.

V. Furthermore, the appellant filed sets of claims of new auxiliary requests I to VI which (i) limit the variant

Fc region to one of human IgG1 (auxiliary request I), (ii) no longer refer to fragments of antibodies (auxiliary request II), (iii) contain the amendments of both auxiliary requests I and II (auxiliary request III; similar to auxiliary request 2 in the decision under appeal), (iv) contain additional functional limitations (auxiliary requests IV and V), or (v) correspond to the main request considered by the examining division, except for minor changes in wording of claims 1 and 11 to 15 (auxiliary request VI).

VI. The board issued a communication setting out its preliminary opinion on the case. The board stated, *inter alia*, that claim 1 of the main request and auxiliary request I infringed Article 123(2) EPC, while the claims of auxiliary request II appeared unclear and unsupported by the description (Article 84 EPC). The claims of auxiliary request III were considered to comply with the requirements of Articles 123(2), 84 and 54 EPC and their subject-matter was considered to involve an inventive step (Article 56 EPC).

VII. In reply the appellant promoted their auxiliary request III filed with the statement of grounds of appeal to their new main request, and renumbered the remaining requests accordingly.

VIII. Claims 1, 9 and 11 of the new main request read as follows:

"1. An antibody comprising a human IgGl variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said antibody specifically binds FcγRIIIA with a greater affinity than a comparable antibody comprising the wild-type Fc region;

and wherein said at least one amino acid modification comprises a substitution at position 396 with leucine, wherein said numbering is according to the EU index as in Kabat.

9. The therapeutic antibody of any of claims 1-8, wherein said antibody additionally comprises an antigen-binding region that is capable of specifically binding to a cancer antigen.

11. The therapeutic antibody of any of claims 9 or 10 for use in the treatment, in a subject, of a cancer characterized by said cancer antigen."

IX. The following documents are cited in this decision:

D1 WO 99/51642 (1999)

D2 WO 00/42072 (2000)

D4 R. L. Shields et al., "High Resolution Mapping of the Binding Site on Human IgG1 for FcγRI, FcγRII, FcγRIII and FcRn and Design of IgG1 Variants with Improved Binding to the FcγR", Journal of Biological Chemistry 276(9), 2001, 6591-6604

D7 J. B. Stavenhagen et al., "Fc Optimization of Therapeutic Antibodies Enhances Their Ability to Kill Tumor Cells In vitro and Controls Tumor Expansion In vivo via Low-Affinity Activating Fcγ Receptors", Cancer Research 67(18), 2007, 8882-8890

D8 B. K. Flesch and J. Neppert, "Functions of the Fc Receptors for Immunoglobulin G",

Journal of Clinical Laboratory Analysis 14, 2000, 141-156

X. The appellant's arguments submitted in writing may be summarised as follows.

Main request

Inventive step (Article 56 EPC)

The examining division erroneously identified the technical problem to be solved as requiring enhanced antibody-dependent cellular cytotoxicity (ADCC), thereby ignoring that achieving enhanced ADCC was not an essential feature of the invention, but only one of the optional and desirable effector functions that might be enhanced in molecules of the invention. In fact, the application contemplated a range of different altered effector functions as alternatives to enhanced ADCC. Indeed, it was known before the priority date that binding to FcγRIIIA could result in a range of different effector functions (see document D8).

The examining division considered "*the provision of further Fc variants that bind FcγRIIIA with increased affinity compared to the wild-type*" to be an alternative (second) problem. This problem was also wrongly formulated, as it was no more than a restatement of the claims, i.e. a statement of the solution rather than the problem.

Moreover, the examining division was wrong to find that the claimed subject-matter failed to solve this second problem over the whole scope. They also applied too strict a standard when requiring multiple repeat

experiments and the presentation of standard deviation or other statistical analysis.

Despite being of the view that P396L was an inventive substitution, the examining division had thus wrongly concluded that the claimed subject-matter lacked inventive step.

In fact, a more appropriate formulation of the technical problem to be solved was "*the provision of alternative antibodies with improved effector function*".

The claimed solution to this problem, i.e. the substitution of proline by leucine at position 396 (P396L) in the Fc region, was not obvious.

XI. The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division for further prosecution based on the new main request filed with a letter dated 27 December 2019 (i.e. auxiliary request III as filed with the statement of grounds of appeal).

Reasons for the Decision

Introduction

1. The present invention relates to antibodies comprising a variant Fc region. The Fc region of antibodies interacts with cells of the immune system through Fc receptors on the cell surface. The interaction of antibody-antigen complexes with cells of the immune system results in a wide array of responses, ranging from so-called "effector" functions, such as antibody-

dependent cellular cytotoxicity (ADCC), mast cell degranulation, and phagocytosis, to immunomodulatory signals such as regulating lymphocyte proliferation and antibody secretion. All these interactions are initiated through the binding of the Fc domain of antibodies, or immune complexes, to specialised cell surface receptors on haematopoietic cells. By modifying the affinity of the Fc region to its receptor, cellular responses to the antibody can be modulated.

Main request

2. Claim 1 of the present main request is identical to claim 1 of auxiliary request 2 dealt with in the decision under appeal, i.e. the variant Fc region is defined as one of human IgG1 and the claim no longer refers to fragments of antibodies. Claims 2 and 3 differ from claims 2 and 3 of auxiliary request 2 by the deletion of a second reference to "said wild-type Fc region". Claims 4 and 5 contain the expression "relative to said comparable antibody" instead of "than a comparable antibody" or "than an antibody". The other claims are identical.

Amendments (Article 123(2) EPC)

3. The expression "or a fragment of said antibody that comprises said Fc region", which was considered as adding subject-matter in the decision under appeal, has been deleted, thus rendering the corresponding objection moot.

4. The board, not having objections of its own, finds that the requirements of Article 123(2) EPC are fulfilled.

Clarity and support (Article 84 EPC)

5. In the decision under appeal, the terms or expressions "a fragment of said antibody" and "variant Fc regions" were objected to for not complying with Article 84 EPC. In the present main request, the first feature has been deleted, while the second now reads "human IgG 1 variant Fc region". The format of the medical use claims 11 to 15 has been corrected.

6. The board, not having objections of its own, finds that the requirements of Article 84 EPC are fulfilled.

Novelty (Article 54 EPC)

7. The board, seeing no substantial difference in the subject-matter of the claims of present main request compared to the claims of auxiliary request 2 dealt with in the decision under appeal, concurs with the examining division that the requirements of Article 54 EPC are fulfilled.

Inventive step (Article 56 EPC)

Closest prior art

8. In accordance with established jurisprudence, the closest prior art for assessing inventive step is normally a prior-art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (see Case Law of the Boards of Appeal of the EPO, 9th edition 2019, section I.D.3.1).

9. The purpose of the invention as claimed in claim 1 is the provision of antibodies with improved effector functions, in particular increased affinity, see paragraph [0002].

10. Like the examining division, the board considers document D4 to represent the closest prior art. D4 discloses, as relevant subject-matter, antibodies comprising a variant Fc region which binds the Fcγ receptor IIIA (FcγRIIIA) with greater affinity than a comparable unmodified antibody (page 6591, Abstract; Table I). The document also discloses that the "*engineered antibodies may have important implications for improving antibody therapeutic efficacy*" (page 6591, Abstract).

Technical problem and its solution

11. It is undisputed that the difference between the subject-matter of present claim 1 and the relevant subject-matter of document D4 resides in the specific position and nature of the mutation in the Fc region, i.e. the "substitution at position 396 with leucine".

12. The examining division, based on the reasoning that "*from the overall teaching of the application (e.g. pg. 1, §2; pg. 7, lines 8-1 0; pg. 21, §58; pg. 23, §62; pg. 53, lines 20-24) it is clear that the goal of increasing Fc binding to FcγRIIIA is to increase ADCC*", defined the problem as "*the provision of alternative human lgG1 Fc variants that bind FcγRIIIA with greater affinity than the wild-type and are, therefore, able to induce a stronger ADCC response*" (point 14.2.1 of the decision under appeal).

13. The examining division, without agreeing to the formulation of the technical problem proposed by the applicant, defined a second problem "*for the sake of argument*" as "*the provision of further Fc variants that bind FcγRIIIA with increased affinity compared to the wild-type*".

14. According to established case law of the boards of appeal, an objective definition of the problem to be solved by the invention should normally start from the problem described in the contested patent. Only if examination shows that the problem disclosed was not solved, or if inappropriate prior art was used to define the problem, is it necessary to investigate which other problem objectively exists (see decision T 1060/11, point 7.2 of the Reasons). Also, the definition of artificial and technically unrealistic problems is to be avoided (see Case Law of the Boards of Appeal of the EPO, 9th edition 2019, section I.D. 4.3.2 and decisions cited there).

15. As regards the first problem (see point 12 above), the board is persuaded by the appellant's view that the application does not disclose ADCC enhancement as the desired goal of the invention, but that it only characterises it as one optional and desirable effector function that may be enhanced in molecules of the invention.

16. As regards the second problem (see point 13 above), the board is persuaded by the appellant's argument that this is merely a restatement of the claims and therefore a statement of the solution rather than the problem.

17. In the board's view, the application discloses in Table 5 on pages 65 ff and Table 10 on pages 182 ff that Fc regions comprising the P396L variant, alone or in combination, exhibit between 0.5- and 5-fold increased affinity for FcγRIIIA. As evidenced by document D8 (see page 141, first paragraph), it is common general knowledge that binding to an Fc receptor is linked to effector functions of the antibody.

18. Hence, the effect of the difference between the claimed subject-matter and the relevant subject-matter disclosed in document D4 that is made plausible by the evidence in the application and the common general knowledge is an improved effector function through increased binding for FcγRIIIA of the claimed antibody compared to an antibody lacking this mutation.

19. Consequently, the board, in agreement with the appellant, formulates the problem as the provision of alternative antibodies with improved effector function.

20. A further effect of the claimed antibodies compared to the antibodies disclosed in document D4 has not been shown in the application as filed or argued by the appellant.

Obviousness

21. It remains to be analysed whether the solution to the above-formulated problem was obvious to the skilled person having regard to the state of the art.

22. The appellant referred to the finding of the examining division in the decision under appeal that it was not obvious to identify the P396L substitution (see sections III and X above).

23. The board agrees with this finding of the examining division and, furthermore, refers to the analysis of the examining division in the annex to the summons to oral proceedings (point 5.2, last paragraph): "... *as explained in the post-published article by the inventors (D7, pg. 8882, final §; pg. 8888, lhc), P396 is neither surface-exposed nor directly involved in the interaction with FcγR and therefore, it would not have been possible to identify it as an important residue for FcγR binding using the approaches described in D4 (alanine-scanning of surface exposed residues)*".

24. In the board's view, a further aspect supports the non-obviousness of the solution provided by the subject-matter of claim 1.

25. Document D4 focuses on alanine substitutions (see Table I) and discloses only some substitutions with other amino acids (see Table II), none of which involves leucine. A substitution of position 396 is not disclosed in document D4, apparently because this position was considered not to be surface-exposed, as predicted from its crystal structure. Close-by positions Lys392 and Leu398 were substituted by alanine, but these substitutions were found to have no effect on binding (see footnotes to Table I).

26. The present application chose an approach different to the structure-guided mutation strategy disclosed in document D4, namely an empirical testing of random variants in a yeast display system. No indication can be found in document D4 or any other prior-art document that a different strategy could or should be used and would identify further mutations.

27. Faced with the problem defined in point 19 above, the skilled person, considering document D4 alone, would not have arrived in an obvious manner at the solution as claimed, because it was not apparent from document D4 that position 396 was a relevant position to be modified by substitution with leucine.

28. The skilled person could have turned to document D1 or D2, both cited during the examination proceedings (see communications of 6 October 2008, 18 July 2011 and 3 January 2014) to reason a lack of inventive step. However, neither of these documents provides the skilled person with an indication to substitute position 396 with leucine or, alternatively, with a method to randomly mutate and screen positions in the Fc region so as to obtain antibody variants which bind FcγRIIIA with greater affinity.

29. In conclusion, the identification of position 396 in the IgG1 Fc region of a human antibody and its substitution with leucine to obtain antibodies with improved effector function is not obvious.

30. Thus, the subject-matter of claim 1 and of its dependent claims involves an inventive step.

Sufficiency of disclosure (Article 83 EPC)

31. The decision under appeal did not raise the issue of sufficiency of disclosure.

32. Claim 1 is directed to an antibody defined by structural and functional features. In particular, the antibody comprises a human IgG1 variant Fc region in which position 396 is substituted with leucine such that the antibody specifically binds the FcγRIIIA with

greater affinity than a comparable antibody comprising the wild-type Fc region, i.e. which does not comprise this mutation. Claim 9 is directed to "[t]he therapeutic antibody of claims 1-8 [...] capable of specifically binding to a cancer antigen".

33. The application discloses how to produce antibodies as claimed (see pages 75 to 78). Furthermore, the application provides experimental evidence of increased binding of Fc regions carrying the P396L substitution to the FcγRIIIA receptor. This includes single substitutions and combinations with other substitutions (see Table 5 on pages 65 ff). The application also discloses a number of known cancer antigens and therapeutic antibodies targeted to those (see paragraph [0017] and Table 6 on pages 119 ff).

34. The board therefore finds that the disclosure in the application not only teaches the skilled person how to produce antibodies as claimed, but also discloses tests by which the functional characteristics as required by the claim can be ascertained.

35. Claim 11, upon which claims 12 to 15 depend, is directed to "[t]he therapeutic antibody of any of claims 9 or 10 for use in the treatment, in a subject, of a cancer characterized by said cancer antigen".

36. It is established case law of the boards of appeal for a claim to a medical use that, in order to fulfil the requirements of Article 83 EPC, unless this is already known to the skilled person at the priority date, the patent has to disclose the suitability of the product to be used for the claimed therapeutic application (see decision T 1599/06 citing decision T 609/02). The board adheres to this case law.

37. The medical use claimed in claims 11 to 15 is limited to a therapeutic antibody against a cancer antigen (see claim 9), a number of which are listed in claim 10.

38. The treatment of cancer via cancer antigens is common general knowledge (see paragraph [0017] of the application). In fact, a number of therapeutic antibodies recognising cancer antigens have been approved for the treatment of cancer and are commercially available (see Table 6 on pages 119 ff of the application).

39. Moreover, the application discloses in Table 5 (see pages 65 ff) evidence of increased binding of Fc regions carrying the P396L substitution to the FcγRIIIA receptor.

40. Thus, the common general knowledge at the time of filing and the experiments in the patent application make the suitability of the compounds referred to in claims 11 to 15 for the treatment of "a cancer characterized by said cancer antigen" plausible.

41. The board concludes that the subject-matter of the claims is disclosed in a manner in conformity with Article 83 EPC.

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 with the order to grant a patent on the basis of the set of claims of the main request filed with the letter dated 27 December 2019 and a description to be adapted accordingly.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated