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Datasheet for the decision of 28 July 2022

Case Number: T 0509/20 - 3.3.04

Application Number: 11714860.1

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IPC: C07K16/00

Language of the proceedings: EN

Title of invention:
Antibodies with modified affinity to FcRn that promote antigen clearance

Patent Proprietor:
Chugai Seiyaku Kabushiki Kaisha

Opponents:
Ablynx N.V.
Alexion Pharmaceuticals, Inc.
Glaxo Group Limited
Murphy, Colm Damien
Shire Human Genetic Therapies, Inc.
Tillotts Pharma AG

Headword:
Modified antibodies/CHUGAI

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
Amendments - extension beyond the content of the application as filed (yes)

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Beschwerdekammern

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 0509/20 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 28 July 2022

Appellant: (Patent Proprietor)	Chugai Seiyaku Kabushiki Kaisha 5-1, Ukima 5-chome Kita-ku Tokyo 115-8543 (JP)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent I: (Opponent 1)	Ablynx N.V. Technologiepark 21 9052 Ghent-Zwijnaarde (BE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Former Respondent II: (Former Opponent 2)	Alexion Pharmaceuticals, Inc. 100 College Street New Haven, CT 06510 (US)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Respondent III: (Opponent 3)	Glaxo Group Limited 980 Great West Road Brentford Middlesex TW8 9GS (GB)
Representative:	Drury, Elizabeth Anne GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)

Respondent IV: (Opponent 4)	Murphy, Colm Damien Cooley (UK) LLP Dashwood 69 Old Broad Street London EC2M 1QS (GB)
Representative:	Cooley (UK) LLP 22 Bishopsgate London EC2N 4BQ (GB)
Respondent V: (Opponent 5)	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent VI: (Opponent 6)	Tillotts Pharma AG P.O. Box Baslerstrasse 15 4310 Rheinfelden (CH)
Representative:	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 December 2019 revoking European patent No. 2552955 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	B. Rutz
	M. Blasi

Summary of Facts and Submissions

I. The appeal by the patent proprietor (appellant) lies from the opposition division's decision to revoke European patent No. 2 552 955 ("the patent") entitled "*Antibodies with modified affinity to FcRn that promote antigen clearance*", based on international application PCT/JP2011/001888 ("the application"), which was published as WO 2011/122011.

II. Claim 1 of the main request reads as follows:
"1. An antibody comprising an antigen-binding domain and a human FcRn-binding domain, which has a human FcRn-binding activity at pH 5.5 and at pH 7.0 and a lower antigen-binding activity at pH 5.5 than at pH 7.0, wherein the human FcRn-binding activity at pH 7.0 and at 25°C is stronger than KD 3.2 μM, wherein the human FcRn-binding domain is an Fc domain resulting from substituting a different amino acid for at least one amino acid in the Fc domain of a human IgG1, IgG2, IgG3 or IgG4, and wherein said antibody comprises an amino acid mutation of the antigen-binding domain, which comprises a substitution of histidine for at least one amino acid of the antigen-binding domain or the insertion of at least one histidine."

III. The opposition proceedings, initiated by six opponents, were based on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and of Article 100(b) and (c) EPC.

IV. The opposition division decided, *inter alia*, that claim 1 of the main request (filed by letter dated 6 September 2019) extended the subject-matter beyond the content of the application as filed. The same

applied to claim 1 of auxiliary requests 1 to 32, filed by letter dated 6 September 2019.

V. With its statement of grounds of appeal, the appellant filed sets of claims of a main request and of auxiliary requests 1 to 32 (identical to the claim requests on which the decision under appeal was based, except for claim 8 of auxiliary request 26, in which a claim dependency has been changed) and of auxiliary requests 33 to 64 (newly filed in the appeal).

VI. Opponents 1, 2, 4, 5 and 6 (respondents I, II, IV, V and VI) replied to the appeal.

VII. Respondent II later withdrew its opposition and, as no issues other than compliance of the patent as amended with the EPC were within the scope of this appeal, respondent II ceased to be a party to these proceedings.

VIII. Opponent 3 (respondent III) did not reply to the appeal and did not submit any requests.

IX. The board summoned the parties to oral proceedings, as requested, and informed them of its preliminary opinion in a communication under Article 15(1) RPBA 2020.

X. At the end of the oral proceedings, which were held in the absence of duly summoned respondents III and VI in accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020, the Chair announced the board's decision.

XI. The appellant's submissions are summarised as follows.

Main request
Amendments (Article 123(2) EPC) - claim 1

The application as filed disclosed that the invention related to antigen-binding molecules having characteristic FcRn-binding activity at two specific pH values, the early endosomal pH and the plasma pH (see paragraph [0013], lines 7 to 10). The paragraph went on to disclose that the antigen-binding molecules were further characterised by having a certain antigen-binding activity at the same pH values. This teaching was repeated throughout the application.

The skilled person knew that measurements of binding activities could not be taken "in a range", but had to be taken at a specific value. The same pH value for the FcRn-binding activity and the antigen-binding activity could also be derived from the general definitions relating to the characterisation of binding activities, e.g. as set forth in paragraphs [0055], [0056] and [0059], and from the claims as filed and the embodiments spanning pages 6 to 15. Moreover, paragraphs [0055] and [0056] being connected by the word "thus" also indicated that the same pH value should be used.

Paragraph [0055] (and similarly paragraphs [0197] and [0224]) disclosed that the antibody Fc-FcRn interaction could be undetectable and unmeasurable at neutral pH. The application provided a solution, namely characterisation of Fc-FcRn-binding at pH 7.0 (see in particular paragraph [0108] in this respect). This value was therefore preferred and would have been used

by the skilled person because there was a technical reason for doing so. Because the pH range(s) for FcRn-binding and antigen-binding were the same, the skilled person would have directly and unambiguously recognised the limitation for one activity, e.g. FcRn-binding, as also being applicable to the other, e.g. antigen-binding activity. Therefore, limiting the neutral pH range for both activities to the same value, specifically pH 7.0 as claimed, did not violate Article 123(2) EPC.

pH 5.5 was consistently disclosed at the identical "level" as pH 7.0 in the semantic structure of paragraphs [0055], [0197] and [0224] as well as embodiment [42] and claim 42 as filed. Since pH 7.0 was preferred, the skilled person would have combined it with pH 5.5, disclosed at the same level. Moreover, pH 5.5 and pH 7.0 were disclosed as lower end points of preferred ranges for the acidic and the neutral range which applied to both antigen- and FcRn-binding (see e.g. embodiment [42] on page 13, which is dependent on embodiment [35] on page 12; and paragraph [0055]). The combination of those two end points did not amount to added subject-matter.

Auxiliary requests 1 to 64
Amendments (Article 123(2) EPC) - claim 1

The same considerations as for the main request applied to the auxiliary requests.

XII. The respondents' submissions are summarised as follows.

Main request
Amendments (Article 123(2) EPC) - claim 1

Neither pH 5.5 nor pH 7.0 per se, let alone in combination, were identified as the preferred conditions for the claimed pH-dependent antigen-binding. Similarly, neither pH 5.5 nor pH 7.0 per se, let alone in combination, were identified as the preferred conditions for determining the claimed FcRn-binding activities. Each of the selected pHs was merely disclosed in independent lists of equivalent alternative pH values. The subject-matter amounted to a new antibody population based on multiple arbitrary and thus impermissible selections.

The four features of the antibody,
- antigen-binding at pH 5.5,
- antigen-binding at pH 7.0,
- FcRn-binding at pH 5.5 and
- FcRn-binding at pH 7.0,
had to be determined independently and required different experimental setups in different experimental runs.

There was no pointer or unambiguous preference in the application as filed to combine said four specific antibody features.

In contrast, the application as filed consistently disclosed the physiological pH for the endosomal compartment to be pH 5.8 to 6.0 and for plasma to be pH 7.4 (see e.g. paragraphs [0007] and [0055]; Figure 2).

None of the embodiments directed to antigen-binding activity at a specific pH value pointed to preferred antigen-binding at pH 5.5 or pH 7.0. See paragraphs [0057], [0075], [0123], [0124], [0128], [0139] to [0141] and [0150] to [0153] of the application as filed, which exclusively described pH 5.8 (or pH 5.8 to 6.0) in the acidic range and pH 7.4 for antigen-binding in the neutral pH range for antigen-binding.

This was also apparent from the examples in which antigen-binding was determined at pH 5.8 and 7.4 (see paragraph [0277]) while FcRn-binding was determined at pH 6.0 and 7.4 (see paragraph [0289] and Table 5), but also at pH 7.0 (see paragraph [0321] and Table 8).

Neither in paragraph [0013] nor at any other point did the application as filed disclose that both the FcRn-binding activity and antigen-binding activity were to be assessed at the same pH values, let alone at pH 5.5 and pH 7.0.

Auxiliary requests 1 to 64
Amendments (Article 123(2) EPC) - claim 1

The same considerations as for the main request applied to the auxiliary requests.

XIII. Of the parties' requests, the following were relevant for reaching the present decision:

The appellant requested that the decision under appeal be set aside and the patent be maintained in amended form based on the claims of the main request, or, alternatively, of auxiliary requests 1 to 32 dealt with in the decision under appeal, or further alternatively, of auxiliary requests 33 to 64 filed with the statement

of grounds of appeal.

Respondents I, IV, V and VI requested that the appeal be dismissed. In this context, respondent VI requested that auxiliary requests 33 to 64 not be admitted into the appeal proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Main request
Amendments (Article 123(2) EPC) - claim 1

2. For determining whether claim 1 comprises subject-matter extending beyond the content of the application as filed, the answers to the following three main questions are relevant:
1) Does the application as filed disclose that the binding of FcRn and antigen is to be tested at the same pH value?
2) Are the pH values 5.5 and 7.0 disclosed as preferred pH values for measuring the binding of FcRn and antigen?
3) Is there disclosure of the combination of the pH values 5.5 and 7.0 to test the binding of FcRn and antigen?

3. The appellant argued that the antibody as a whole encountered the same physiological conditions for both, the FcRn-binding domain and the antigen-binding domain, in the endosomal compartment and in plasma (see Figure 2 of the application). The skilled person would therefore recognise that the conditions for FcRn-binding and antigen-binding had to be the same. In this

regard the appellant referred to paragraph [0013], which, for both binding activities, referred to the same physiological pH values, namely the "*early endosomal pH*" and the "*plasma pH*".

4. The board agrees that the physiological pH is the same for both binding activities; however, while the skilled person would consider that the antibody should optimally be tested under conditions resembling the physiological conditions, the application as filed does not disclose testing both binding activities at exactly the same pH values. In contrast, the skilled person learns from the application that both binding activities can be tested under different conditions. In Example 2 the antigen-binding activity of Fv4-IgG1 is described at pH 5.8 and pH 7.4 (see paragraph [0274]). In Example 4, however, the FcRn-binding activity of the same antibody was tested at pH 6.0 and pH 7.4 (see paragraph [0289] and Table 5) and in Example 9 the FcRn - binding activity was tested at pH 7.0 (see paragraph [0321] and Table 8). Moreover, the pH values mentioned in the claim ("pH 5.5", "pH 7.0") do not correspond to the physiological pH values in the respective compartments as disclosed in the application (see paragraph [0007]: "*acidic condition (pH 6.0)*", "*neutral condition (pH 7.4)*"; paragraph [0055]: "*pH 5.8 to pH 6.0, which is close to the pH in early endosome in vivo*", "*pH 7.4, which is close to in vivo plasma (blood) pH*"; paragraph [0059]: "*pH 5.8 to pH 6.0, which is comparable to the in vivo early endosomal pH*", "*pH 7.4, which is comparable to the in vivo plasma pH*"; Figure 2: "*pH7.4*", "*pH5~6*").

5. The appellant further pointed out that the application disclosed that the antibody had to be tested in the same "neutral pH range" and "acidic pH range" for both

binding activities (see e.g. embodiments [1] and [5] on page 6; embodiment [13] on page 7; embodiment [35] on page 12 and embodiment [42] on page 13). The skilled person knew that binding activities could not be measured in pH ranges, but had to be determined at individual pH values. The skilled person would therefore take from the disclosure of the same pH ranges for both binding activities, and especially from the single disclosure of pH ranges in embodiment [42], that the pH values for testing both binding activities had to be the same.

6. The board does not agree, because a pH range includes an indefinite number of individual values and the skilled person had no reason to assume that the same value from each range had to be chosen to test both binding activities.

7. The appellant further argued that embodiment [42] on page 13, which referred back to embodiments [30] to [41], disclosed "*the acidic pH range is pH 5.5 to pH 6.5 and the neutral pH range is pH 7.0 to pH 8.0*". These ranges applied to both binding activities because embodiment [42] referred back to several embodiments which referred to "the acidic pH range" and "the neutral pH range" for both binding activities (see e.g. embodiments [30], [31] and [35]). The lower end points of both ranges in embodiment [42] disclosed the combination in claim 1.

8. Again, the board does not agree, because the disclosure of two pH ranges is not a direct and unambiguous disclosure of two specific pH values within those ranges for testing the two binding activities. The fact that both pH values mentioned in the claim represent end points of the disclosed ranges is not relevant in

this regard because the skilled person would not consider those values to be in any way preferred and/or disclosed in combination.

9. The appellant made a further argument based on the semantic structure of paragraph [0055] in the application (also found in paragraphs [0128], [0197] and [0224]). Those paragraphs provided general definitions of the "acidic pH range" and the "neutral pH range". Both pH values mentioned in the claim (pH 5.5 and pH 7.0) appeared in the same position, namely as the lower end point of a range used with the expression "preferably" and as the first value in a list of 11 pH values said to be "preferably selected". Moreover, the passages in these paragraphs relating to the acidic pH range and the neutral pH range were connected by the conjunction "meanwhile". This meant that the conditions were connected and, due to this, the skilled person would have chosen a pH value corresponding to the same position in the semantic structure for testing binding to FcRn and antigen.

10. The board does not agree, because the application as a whole provides no technical reason to combine pH values which are in the same position in the semantic structure of those paragraphs, but instead discloses using pH values which are technically meaningful, e.g. which correspond to the physiological pH values, or pH values which are favourable for other technical reasons. Paragraphs [0055] and [0056] being connected by the word "thus" does not change this finding because those paragraphs disclose preferred ranges, but do not disclose using the same pH value to test both binding activities.

11. In conclusion and in answer to question 1) above, the application as filed does not disclose that the pH values for determining antigen-binding and FcRn-binding of the antibody are the same.

12. The appellant further argued that the pH value of 7.0 was singled out as "an alternative to pH 7.4" in several passages of the application (see e.g. paragraphs [0056], [0128] and [0129]), which also provided a technical reason for this choice. The value pH 7.0 was also the only pH value for which the quantitative feature mentioned in the claim was disclosed ("human FcRn-binding activity at pH 7.0 and at 25°C is stronger than KD 3.2 μM"; see paragraph [0108]).

13. The board agrees, but considers the singling out of pH 7.0 to be limited to FcRn-binding, to which the technical reason whereby "*it is difficult to assess the binding affinity between human FcRn-binding domain and human FcRn due its low affinity at pH 7.4*" is applicable (see paragraphs [0055] and [0128] of the application). This is also apparent from paragraph [0108], which discloses pH 7.0 and is found in a section which is exclusively concerned with FcRn-binding (see paragraphs [0106] to [0109]).

14. The skilled person would have no reason to use the same pH when testing antigen-binding for which the affinity can be measured at the physiological pH of plasma, i.e. pH 7.4. The pH value of 7.0 is thus only disclosed as a particularly preferred value for testing the binding to FcRn.

15. As already set out in points 8. and 10. above, neither representing the lower limit of a disclosed range nor

its specific position in the semantic structure of some paragraphs in the application renders the pH value of 5.5 particularly preferred for testing the binding to FcRn or antigen.

16. In conclusion and in answer to question 2) above, the pH value of 7.0 is only disclosed as being particularly preferred for testing binding to FcRn. The pH value of 5.5 is not particularly preferred.

17. Therefore, at least three selections have to be made to arrive at the subject-matter of claim 1, namely pH 5.5 for testing binding to FcRn and pH 5.5 and 7.0 for testing the binding to antigen. In view of the lists of preferred values in paragraph [0055] this amounts to three selections from three lists of 11 items for which no pointer or unambiguous preference is found in the application as filed.

18. The board thus agrees with the decision under appeal and answers question 3) above such that the combination of pH 5.5 and pH 7.0 for testing binding to FcRn and antigen is not disclosed in the application as filed.

19. Claim 1 extends the subject-matter beyond the content of the application as filed within the meaning of Article 123(2) EPC.

Auxiliary requests 1 to 32
Amendments (Article 123(2) EPC) - claim 1

20. The same considerations as for the main request apply because claim 1 of each of these claim requests also contains the feature "has a human FcRn-binding activity at pH 5.5 and at pH 7.0 and a lower antigen-binding activity at pH 5.5 than at pH 7.0".

21. Claim 1 of all these requests therefore extends the subject-matter beyond the content of the application as filed within the meaning of Article 123(2) EPC.

Auxiliary requests 33 to 64
Admission (Article 12(4) RPBA 2020)

22. While respondent VI had requested that auxiliary requests 33 to 64 not be admitted into the proceedings, the board decided, in the circumstances of the case at hand, to admit them in order to judge them on their merits.

Amendments (Article 123(2) EPC) - claim 1

23. The same considerations as for the main request apply because claim 1 of each of these claim requests also contains the feature "has a human FcRn-binding activity at pH 5.5 and at pH 7.0 and a lower antigen-binding activity at pH 5.5 than at pH 7.0".

24. Claim 1 of all these requests therefore extends the subject-matter beyond the content of the application as filed within the meaning of Article 123(2) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

A. Chavinier Tomsic M. Pregetter

Decision electronically authenticated