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Datasheet for the decision of 31.08.2023

Case Number: T 0273/22 - 3.3.04

Application Number: 14172437.7

Publication Number: 2786657

IPC: A01K67/027

Language of the proceedings: EN

Title of invention:
A method of producing an antibody comprising a human variable region and a rodent constant region

Patent Proprietor:
REGENERON PHARMACEUTICALS, INC.

Opponents:
Kymab Limited (opposition withdrawn)
Ligand Pharmaceuticals Incorporated
James Poole Limited
Novo Nordisk A/S (opposition withdrawn)
Merus N.V., Kymab Limited (opposition withdrawn)
Icely, Dominic

Headword:
Chimeric antibodies/REGENERON

Relevant legal provisions:
EPC Art. 76(1)

Keyword:
Divisional application - subject-matter extends beyond content of earlier application (yes)

Decisions cited:
G 0001/03, G 0002/03, G 0002/10, G 0001/16

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Case Number: T 0273/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 31 August 2023

Appellant: (Patent Proprietor)	REGENERON PHARMACEUTICALS, INC. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707 (US)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Respondent II: (Opponent 2)	Ligand Pharmaceuticals Incorporated 3911 Sorrento Valley Boulevard, Suite 110 San Diego, CA 92121 (US)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Respondent III: (Opponent 3)	James Poole Limited One Southampton Row London WC1B 5HA (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent IV: (Opponent 6)	Icely, Dominic Prama House 267 Banbury Road Oxford Oxfordshire OX2 7HT (GB)
Representative:	Appleyard Lees IP LLP 15 Clare Road Halifax HX1 2HY (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 25 October 2021 revoking European patent No. 2786657 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman M. Pregetter
Members: B. Rutz
L. Bühler

Summary of Facts and Submissions

I. An appeal was lodged by the patent proprietor (appellant) against the decision of the opposition division to revoke European patent No. 2786657. The patent is entitled "*A method of producing an antibody comprising a human variable region and a rodent constant region*" and is based on the second-generation divisional European patent application No. 14172437.7. The parent application is European patent application No. 10010741.6, and the grandparent application is European patent application No. 02709544.7, published as international application WO 02/066630.

II. The patent was opposed 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.

III. The opposition division decided the following.

- The main request and auxiliary request 1 (both filed with the letter of 3 June 2019) and auxiliary requests 2 to 11 (filed with the letter of 19 August 2020) contravened Article 123(2) EPC.

- The amendment to claim 1 of auxiliary request 12 (filed with the letter of 19 August 2020) lacked clarity (Article 84 EPC).

- Auxiliary request 13 (filed during oral proceedings) was admitted and met the requirements of Article 84 EPC but contravened Article 123(2) EPC.

- Auxiliary request 14 (filed as auxiliary request 8 with the letter of 3 June 2019, then renumbered as auxiliary request 13 and later as auxiliary request 14) contravened Article 123(2) EPC.

IV. In its statement of grounds of appeal, the appellant stated that it relied on the sets of claims of the main request and auxiliary requests 1, 2 and 3, all of which had been considered in the decision under appeal. It furthermore filed auxiliary requests 4 to 21.

V. Opponents 1, 2, 3 and 6 (respondents I to IV) replied to the appeal. Opponents 4 and 5 had withdrawn their oppositions prior to the decision under appeal.

VI. Respondent IV stated that it relied on the submissions by respondents I and II.

VII. With its letter dated 28 October 2022, opponent 1 (respondent I) withdrew its opposition and is no longer a party to the proceedings.

VIII. With its letter dated 7 December 2022, the appellant filed new auxiliary requests 5, 11, 17, 20, 21, 24 and 26 to 29, and renumbered the previously filed requests accordingly.

IX. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA. The board furthermore requested that the appellant refile a complete, numbered set of auxiliary requests, together with a filing history for each request.

X. With its letter dated 17 July 2023, the appellant refiled the main request and auxiliary requests 1 to 29

and provided the history for each of the claim requests.

XI. Claim 1 of the main request reads as follows:
"1. A method of producing an antibody comprising a human variable region and a rodent constant region, comprising exposing to antigenic stimulation a rodent comprising a hybrid immunoglobulin heavy chain locus that produces said antibody, wherein said hybrid locus comprises human V, D and J gene segments operably linked to rodent heavy chain constant regions, and wherein said rodent does not produce fully human antibodies."

The wording of auxiliary requests 1 to 29 can be found in the annexes to the appellant's letter dated 17 July 2023.

XII. Oral proceedings before the board took place on 31 August 2023. At the end of the oral proceedings, the chairwoman announced the board's decision.

XIII. The appellant's arguments, where relevant to the decision, may be summarised as follows.

Extension of subject-matter beyond the content of the earlier application as filed (Article 76(1) EPC)
Disclaimer

Main request and auxiliary request 2

The opposition division was correct, in point 4.3.2 of the decision under appeal, that the introduction of the disclaimer did not contravene Article 123(2) EPC, as it did not give rise to new technical information. The opposition division, citing page 42, lines 20 to 32 and

page 43, lines 9 to 11 of the grandparent application as filed in the form of WO 02/066630, pointed out that the entire focus of the original disclosure was on the production of hybrid antibodies in rodents. The production of fully human antibodies was only disclosed in connection with subsequent recombinant manipulation. Thus, there was a clear disclosure that hybrid antibodies and not fully human antibodies were produced in rodents, and there was also an implicit basis for the disclaimer in the technical teaching of the application. The disclaimer was also fully applicable to the subject-matter of random integration and embodiment 30 of the application as filed, which was identical to claim 30 of the grandparent application, as embodiment 30 related to the production of hybrid antibodies with the technical advantages discussed at page 43, line 20 to page 44, line 3. Thus, no information was added by the disclaimer.

The disclaimer was not covered by the exceptions to "undisclosed" disclaimers in decisions G 1/03 and G 1/16, nor did decision G 2/10 apply in respect of "disclosed" disclaimers. Rather, the disclaimer related to an amendment which the skilled person would have directly and unambiguously derived from the teaching of the grandparent application as filed.

It was clear from the disclosure on pages 42 and 43 that the interaction of the endogenous constant region with the host animal's immune system was crucial for a strong and specific immune response, for the proliferation and maturation of B cells, and for the affinity maturation of antibodies. This was applicable to any context, i.e. targeted or random integration, and to any host organism. This crucial interaction thus also applied to embodiment 30 of the application as

filed, which was not limited to *in-situ* replacement of the mouse variable region (VDJ/VJ) genes.

Auxiliary request 18

The claimed method was limited to mice, wherein the hybrid locus was at the mouse endogenous locus, i.e. the disclaimer was in the specific context of a targeted integration. The benefits disclosed on pages 42 and 43 and on page 45, lines 24 to 27 and lines 10 to 14 for such targeted integration applied, and would have indicated to the skilled person that fully human antibodies should be avoided. The disclaimer was an implicit feature of the disclosed method for producing antibodies in a mouse having targeted integration of a human variable region which created hybrid antibodies and not fully human antibodies.

XIV. The respondents' arguments, where relevant to the decision, may be summarised as follows.

Extension of subject-matter beyond the content of the earlier application as filed (Article 76(1) EPC)
Disclaimer

Main request and auxiliary requests 2 and 18

The disclaimer was an unallowable disclaimer, as it presented the skilled person with new information. Furthermore, the disclaimer did have a technical effect on the scope of the claims: each claim now required the essential technical feature that the transgenic animal did not produce any type or any level of fully human antibody. However, the grandparent application as filed did not rule out the possibility that a fully human antibody could be produced as well as the chimeric

antibody. The grandparent application as filed did not include any language that was the same as or came close to that of the disclaimer.

Even if one were to accept that the general disclosure of the application was directed to the expression of hybrid antibodies comprising human variable regions and rodent constant regions and to alleged benefits that this may provide, that was not the same as there being a complete exclusion of fully human antibodies.

The alleged advantages of the hybrid antibodies were achieved through the use of a hybrid locus, but the application as filed did not teach that that was incompatible with the production of fully human antibodies.

The opposition division decided that "*the disclaimer had no technical effect on the claim*" and that, in any event, the grandparent application implicitly disclosed that the mice of the invention did not produce fully human antibodies. However, the negative feature in claim 1 significantly impacted on which rodents may be used in the performance of the claimed method. Thus, for example, with the negative feature present, a mouse that produced fully human antibodies in addition to human-mouse hybrid antibodies could not be used. In contrast, if the negative feature was removed, then a mouse that produced both fully human and human-mouse hybrid antibodies could be utilised. Indeed, the negative feature was inserted into claim 1 to try to distance the claims from the use of prior art mice that produce both fully human and human-mouse hybrid antibodies.

Example 3, specifically on page 43, last two paragraphs, contrasted mice that produced fully human antibodies with the transgenic mouse that had been subjected to *in-situ* replacement of its VDJ gene segments (as described on page 43, lines 14 to 19 of the grandparent application). Therefore, if there was an implicit basis for the negative feature, it was limited to that specific context. However, claim 1 was much broader, and so the presence of the negative feature exacerbated the added subject-matter that resulted from the omission of a feature specifying targeted integration. The opposition division also referred to confirmation being provided by the preceding passage in the grandparent application, specifically on page 42, lines 20 to 32 and page 43, lines 9 to 11. This was also all within the context of example 3, which was entitled "*Use of LTVEC's* [sic] *to produce chimeric and human antibodies*". The skilled person would therefore understand the "applicants technology" on page 43, line 9 to refer to mice that had been subjected to targeting vector-based methods of introducing human VDJ segments. Indeed, this was especially clear when page 43, line 9 was read together with the preceding sentence.

Therefore, to the extent that this passage confirmed that there was a contrast between the mice of the prior art that produced fully human antibodies and the mice of the grandparent application that produced hybrid antibodies, the latter were mice that had been subjected to *in-situ* replacement of their VDJ gene segments (as described in the very next paragraph, page 43, lines 14 to 19 of the grandparent application). This, however, was not the subject-matter of claim 1 of any of the requests. Claim 1 of all the requests contravened Article 76(1) EPC.

XV. The appellant (patent proprietor) requested the following:

- that the decision under appeal be set aside,
- that, should the appealed decision be set aside, the case be remitted to the opposition division for further prosecution,
- that, should the board not agree to remittal, the patent be maintained by the board on the basis of the claims of the main request or any of auxiliary requests 1 to 29.

The respondents (opponents 2, 3, and 6) requested the following:

- that the appeal be dismissed and the decision to revoke the patent be upheld,
- that, if the board was minded to set aside the opposition division's decision, the case be remitted to the opposition division for further prosecution,
- that auxiliary requests 4, 10, 16, 19 and 23 (filed with the statement of grounds of appeal as auxiliary requests 4, 9, 14, 16 and 20 respectively) and auxiliary requests 5, 11, 17, 20, 21, 24 and 26 to 29 (filed with the letter of 7 December 2022) not be admitted into the proceedings, in accordance with Article 12(4) and (6) RPBA and Article 13(1) RPBA respectively.

Reasons for the Decision

Extension of subject-matter beyond the content of the earlier application as filed (Article 76(1) EPC)
Disclaimer

1. Claim 1 of all the requests contains a proviso or negative feature (called "disclaimer" below) which reads: "wherein said rodent/mouse or rat/mouse does not produce fully human antibodies". The term "rodent" appears in the main request and auxiliary requests 1 to 5, 25 and 26; the term "mouse or rat" appears in auxiliary requests 6 to 11 and 27; the term "mouse" appears in auxiliary requests 12 to 24, 28 and 29.

2. It is undisputed that the subject-matter which is disclaimed in claim 1 of all the requests, i.e. a rodent/mouse or rat/mouse which produces fully human antibodies, is not disclosed as a (positive) embodiment of the invention in the earlier ("grandparent") application as filed.

3. Mice producing fully (or "entirely" or "totally") human antibodies are only disclosed in respect of the prior art in the grandparent application as filed (see page 42, lines 20 to 32: "*More recently, endogenous genes have been knocked out of mice, and the genes replaced with their human counterparts to produce entirely human antibodies* [...] *Mice producing fully human antibodies*" and page 43, lines 23 to 25: "*previous methods, e.g.* [...] *the generation of fully human antibodies in HuMAb mice*" and lines 29 to 30: "*previously available HuMAb mice that produce totally human antibodies*").

4. The board therefore concludes that the disclaimer in claim 1 of all the requests is not a "*disclaimer*

disclaiming from [a claim] *subject-matter disclosed in the application as filed*", in the sense of decision G 2/10 of the Enlarged Board of Appeal of the EPO (see Order, point 1a).

5. It is also undisputed that the disclaimer in claim 1 of all the requests does not fall under the criteria allowing so-called "undisclosed" disclaimers as established in decision G 1/03 (see Order, point 2.1) and confirmed by decision G 1/16 (see Order) of the Enlarged Board of Appeal of the EPO.

6. It is further undisputed that the disclaimer is not explicitly disclosed in the grandparent application as filed, since the wording "fully/entirely/totally human antibody" occurs only in relation to the prior art (see page 42, lines 24 to 25 and page 43, lines 23 to 25 and lines 29 to 30) or with regard to recombinant technology envisaged to produce "fully human antibodies" by modification of chimeric antibodies obtained from transgenic mice.

7. The board's view on negative technical features ("disclaimers") is the following. There exists a fundamental difference between (i) an implicit disclosure in an (earlier) application as filed of the absence of certain features derivable from the comparison of the invention with the prior art, in the present case the (alleged) implicit disclosure that the animals employed in the methods should not produce fully human antibodies, and (ii) a claim wording that specifies the mandatory absence of certain features as an explicit negative technical feature from the specific subject-matter defined in the claim under consideration.

8. While the content of the first (i.e. the implicit disclosure) can be at best vaguely understood from the disclosure actually made in the application as filed, the second (i.e. the disclaimer in a claim) should be, and in a granted patent claim must be, of a precise nature.

9. In the present case, one might speculate about the actual content of the implicit disclosure. Several questions arise. Does the absence of the feature under consideration have to be absolute, i.e. absence of any fully human antibody production whatsoever? Or does it concern only antibodies having the same target specificity as the chimeric (also called "hybrid") ones? Does the method by which the mouse has been generated and induced to produce the antibodies matter? These speculations must be contrasted with the wording of the disclaimer, which states that "*said rodent/mouse or rat/mouse does not produce fully human antibodies*".

10. In view of the uncertainties caused by the absence of any explicit disclosure of the (alleged) preferable absence of fully human antibodies, the board considers that the disclaimer concerned is in fact an undisclosed disclaimer. The findings of decisions G 1/03, G 2/03 (see Order 2.1) and G 1/16 (points 44 and 47 of the Reasons) thus apply, and the fact that the disclaimer does not fall into any of the categories established in those decisions means that, for this reason alone, it is not allowable.

11. In contrast, the appellant argued that a disclaimer not falling within the definitions provided in decisions G 1/03, G 2/03, G 2/10 and G 1/16 could still lead to an allowable claim, relying solely on the "gold" standard for amendments. The board understands this

line of argument to be equivalent to arguing that the subject-matter of claim 1, including the negative technical feature in it which has been labelled "disclaimer", see point 1. above, is derivable from the earlier application as filed in line with the so-called "gold" standard of disclosure, namely "*what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of* [the] *documents* [of the application] *as filed*" (see decision G 2/10, point 4.3 of the Reasons and decision G 1/16, point 17. of the Reasons).

12. Even taking this approach, the board considers that the subject-matter of claim 1 extends beyond the content of the earlier application as filed, for the following reasons.

Auxiliary request 18

13. The board considers it useful to examine the subject-matter of claim 1 of auxiliary request 18 first, because it is the most restricted request for which the appellant provided specific arguments. In particular, claim 1 is limited to methods in mice, defines the human variable regions as V, D and J segments and requires that the hybrid locus is at the mouse chromosomal immunoglobulin heavy chain locus.

14. Claim 1 of auxiliary request 18 reads as follows.
"1. A method of producing an antibody comprising a human variable region and a mouse constant region, comprising exposing to antigenic stimulation a mouse comprising a hybrid immunoglobulin heavy chain locus that produces said antibody, wherein said hybrid locus comprises human V, D and J gene segments operably

linked to endogenous mouse heavy chain constant regions at the mouse chromosomal immunoglobulin heavy chain locus, and wherein said mouse does not produce fully human antibodies."

15. As an introductory remark, the board does not share the opposition division's view that "*in view of the application as a whole, it is only with a mind unwilling to understand claim 1, that one would interpret the claim -when disregarding the disclaimer- as also embracing 'fully human' antibodies. In other words, since even when disregarding the disclaimer, fully-human antibodies are not embraced by the claim, the disclaimer has no technical effect on the claim*" (see decision under appeal, point 4.3.2.3). Rather, the board considers that subject-matter "comprising" certain features is not limited to having only those features. In the present case, therefore, the wording of claim 1 without the disclaimer does not exclude the possibility that the mouse contains further genetic modifications such that the mouse produces fully human antibodies by some other mechanism. This means that the addition of the disclaimer changes the subject-matter of the claim, by excluding all methods in which mice also produce fully human antibodies.

16. The appellant considers claim 30 of the grandparent application as filed to be a relevant basis for the disclosure of the subject-matter of claim 1 in combination with passages on page 42 and 43 of the grandparent application as filed.

17. The board will therefore start its analysis by comparing claim 30 of the grandparent application as filed with claim 1 of auxiliary request 18.

Claim 30 of the grandparent application as filed reads: "30. A transgenic mouse having a genome comprising human heavy and/or light chain variable region loci operably linked to endogenous mouse constant region loci such that the mouse produces a serum containing an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation."

18. Despite the numerous differences, the board recognises that both claim 1 of auxiliary request 18 and claim 30 of the grandparent application as filed concern a mouse comprising a human variable region operably linked to an endogenous mouse constant region.

19. What claim 30 of the grandparent application does not disclose, however, is that "said mouse does not produce fully human antibodies". On the contrary, because the term "comprising" is used, the claim includes mice having further modifications in their genome, e.g. such that the mice also produce fully human antibodies. This, moreover, is a technically reasonable reading of claim 30 because, as also acknowledged by the appellant, mice expressing both chimeric and fully human antibodies were known in the prior art (see point 9.7 of the statement of grounds of appeal, referring to documents D4 (WO 99/45962) and D301 (WO 98/24893)).

20. As the basis for the disclaimer, the appellant referred to example 3 in the grandparent application as filed, which in its view "implicitly" disclosed that the generated mice did not produce fully human antibodies. In view of the application as a whole, the skilled person would apply this teaching to the subject-matter of claim 30 of the grandparent application as filed and thus, in combination, the claimed subject-matter was disclosed.

21. The appellant further referred to disadvantages of the prior art technology and advantages of the invention highlighted in the application. In particular, it referred to page 42, lines 20 to 32, which discussed the disadvantages of the prior art technology of fully human antibodies (HuMAb), and page 42, line 34 to page 43, line 11, which disclosed the advantages of chimeric antibodies generated utilising the applicant's technology. Further advantages were disclosed in the passages on page 43, lines 21 to page 45, line 32. By comparing the invention with the prior art technology in these passages, the skilled person would know that mice producing fully human antibodies were not an aspect of the invention.

22. The board does not agree, for several reasons. First, the passage on page 42, lines 20 to 32 relates to prior art methods without indicating that those methods had to be completely avoided or were not compatible with the invention as disclosed. Rather, the application states that the prior art method "*has not resulted in optimal antibodies*", which indicates only that the method was not optimal but not that it failed completely. Thus, the passage does not exclude from the disclosed invention mice which also produce fully human antibodies.

23. Secondly, example 3 relates to a specific method and its outcome, a mouse having certain genetic modifications. Most of the features of this exemplified method are not reflected in claim 1. In particular, the passage on page 43, lines 6 to 11 refers to "*large scale replacement of the entire variable gene encoding segments with human genes, thereby producing chimeras in both the heavy and light chains*" (emphasis added by

the board), i.e. a method resulting in a mouse in which all of the endogenous variable gene segments are replaced *in situ*. This, however, is not required in the method of claim 1, which only specifies that the "*human V, D and J gene segments* [are] *operably linked to endogenous mouse heavy chain constant regions at the mouse chromosomal immunoglobulin heavy chain locus*", but not that there is replacement of all the variable gene encoding segments of the mouse. Moreover, the large-scale replacement in example 3 is achieved with special vectors (LTVEC) which are not mentioned in claim 1 (see "Material and methods" section, page 46 ff.).

24. Thirdly, claim 30 of the grandparent application as filed, which is considered a relevant basis for the subject-matter of claim 1, relates to a mouse comprising "*heavy and/or light chain variable region loci operably linked to endogenous mouse constant region loci*", i.e. a mouse which can retain its original variable region or in which only a part of the variable region is replaced. The mouse of claim 30 is thus defined much more broadly than the mouse resulting from example 3.

25. Thus, even if example 3 was interpreted as implicitly disclosing mice which do not produce fully human antibodies and claim 30 was considered to provide a basis for the subject-matter of claim 1 without the disclaimer, the skilled person had no reason to read any implicit restrictions on the specific method of example 3 into the wording of the much more broadly defined mouse of claim 30 of the grandparent application as filed, and thus to arrive at the subject-matter represented by the method of claim 1.

26. Introducing the disclaimer "wherein the mouse does not produce fully human antibodies" adds subject-matter.

27. Claim 1 of auxiliary request 18 extends the subject-matter beyond the content of the earlier (grandparent) application as filed (Article 76(1) EPC).

Main request and auxiliary requests 1 to 17 and 19 to 29

28. The appellant did not provide any further reasons, beyond what is discussed in points 1. to 26. above, why these requests comply with the requirements of Article 76(1) EPC.

29. The fact that claim 1 of auxiliary requests 26 to 29 relates to a rodent/mouse or rat/mouse and not to a method of producing an antibody cannot be seen to change the situation with regard to Article 76(1) EPC, because this difference was not decisive for the question of added subject-matter (see reasoning in points 1. to 26. above).

30. The reasoning with regard to claim 1 of auxiliary request 18 above applies accordingly to claim 1 of each of these requests.

31. Claim 1 of the main request and of auxiliary requests 1 to 17 and 19 to 29 extends the subject-matter beyond the content of the earlier (grandparent) application as filed (Article 76(1) EPC).

Auxiliary requests 4, 5, 10, 11, 16, 17, 19 to 21, 23, 24 and 26 to 29
Admission (Article 12(4) and (6) RPBA and Article 13(1) RPBA)

32. In view of the finding that there is an extension of subject-matter as defined in Article 76(1) EPC (see points 1. to 31. above), the board sees no need to provide reasons for the admission of these requests.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated