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Datasheet for the decision of 5 November 2021

Case Number: T 1990/18 - 3.3.04

Application Number: 12171793.8

Publication Number: 2517557

IPC: A01K67/027, C07K16/00, C07K16/46, C12N15/85

Language of the proceedings: EN

Title of invention:
Animal models and therapeutic molecules

Patent Proprietor:
Kymab Limited

Opponent:
Regeneron Pharmaceuticals, Inc.

Headword:
Animal models/KYMAB

Relevant legal provisions:
EPC Art. 54(3), 123(2)
RPBA Art. 12(4)
RPBA 2020 Art. 13(1), 13(2)

Keyword:
Amendments - added subject-matter (no)
Novelty - (yes)

Decisions cited:
T 1439/16

Catchword:

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Beschwerdekammern

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Case Number: T 1990/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 5 November 2021

Appellant: (Opponent)	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown NY 10591 (US)
Representative:	J A Kemp LLP 14 South Square Gray's Inn London WC1R 5JJ (GB)
Respondent: (Patent Proprietor)	Kymab Limited The Bennet Building (B930) Babraham Research Campus Cambridge CB22 3AT (GB)
Representative:	CMS Cameron McKenna Nabarro Olswang LLP Cannon Place 78 Cannon Street London EC4N 6AF (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 August 2018 concerning maintenance of the European Patent No. 2517557 in amended form**

Composition of the Board:

Chairman	B. Claes
Members:	A. Chakravarty
	M. Blasi

Summary of Facts and Submissions

I. European patent 2 517 557, entitled "*Animal models and therapeutic molecules*" was granted for European patent application No. 12 171 793.8.

II. An appeal was filed by the opponent (appellant) against the opposition division's interlocutory decision that the patent as amended in the form of the main request met the requirements of the EPC. The patent proprietor is the respondent to this appeal.

III. Claim 1 of the main request considered allowable by the opposition division reads:

"1. A mouse or mouse cell whose genome comprises:
(a) a plurality of human IgH V regions, one or more human D regions and one or more human J regions upstream of the mouse constant region;
wherein at least one mouse enhancer is maintained in functional arrangement with the mouse constant region and wherein the insertion of the human DNA is targeted to the region between the J4 exon and the Cmu locus in the mouse genome IgH locus
and
(b) human lambda region variable DNA inserted in functional arrangement with a mouse kappa constant region, upstream of said kappa constant region; wherein at least one mouse enhancer is maintained in functional arrangement with the mouse constant region;
wherein the mouse is able to produce a repertoire of chimaeric antibodies, or chimaeric heavy or light chains having a mouse constant region and a human variable region

and wherein the genome is homozygous at one, or both, or all three immunoglobulin loci".

IV. The respondent replied to the statement of grounds of appeal and with this reply submitted sets of claims of a new main request and new auxiliary requests 1 to 3. Furthermore, the respondent re-filed the sets of claims of auxiliary requests 4 to 7 (identical to auxiliary requests 1 to 5 filed during the opposition proceedings) and of auxiliary requests 8 and 9 (identical to the main request considered by the opposition division and auxiliary request 3 filed during opposition proceedings, respectively).

V. The board issued a communication pursuant to Article 15(1) RPBA which set out the board's preliminary view that claim 1 of the main request met the requirements of Articles 123(2) EPC and 54 EPC and also that objections under Articles 56 and 83 EPC, briefly mentioned in the statement of grounds of appeal without any indication of reasons, did not meet the requirements under Article 12(2) RPBA 2007 and were considered as not substantiated and would not to be taken account in these appeal proceedings in accordance with Article 12(4) RPBA 2007.

VI. With a letter dated 3 November 2021, the respondent withdrew the main request and auxiliary request 2. Auxiliary request 1 filed with the statement of grounds of appeal became the main request. Auxiliary requests 3 to 9 filed with the reply to the statement of grounds of appeal were renumbered as auxiliary requests 1 to 7, respectively.

VII. The set of claims of the main request consists of fourteen claims. Claim 1 being directed to a mouse or

mouse cell, claims 2 to 7, 9 and 11 to 13 being dependent on claim 1, claim 8 relating to an immortalised cell or cell line and claims 10 and 14 being for a method for producing an antibody. Since objections in the appeal were directed only against claim 1, it is not necessary to reproduce the wording of claims 2 to 14 here.

VIII. Claim 1 of the main request differs from claim 1 of the claim request held allowable by the opposition division (see section III) in that, in the final line of the claim "or all three" is deleted and the feature "wherein the constant region is the endogenous host wild-type constant region located at the wild type locus" is inserted after the feature (b).

IX. Oral proceedings were held by videoconference, as requested by the parties. At the end of the proceedings the Chair announced the decision of the board.

X. The following documents are referred to in this decision.

D1: WO 2001/163314

D4: US 6 596 541

D27: Declaration of Professor Anthony DeFranco

XI. The arguments of the appellant are summarised as follows:

Main request

Admittance of allegations of fact and related lines of argument (Article 13(1) and (2) RPBA)

The submissions made at the oral proceedings under the headings of Articles 54, 84 and 123(2) EPC in relation to the main request should be taken into account by the board.

The submissions made at the oral proceedings relating to the feature added to claim 1 as compared to claim 1 of the main request underlying the decision under appeal, could not have been raised in the statement of grounds of appeal since the relevant claim request had only been filed with the reply thereto and had been promoted the main request at the very last moment before the oral proceedings.

In relation to the objections under Article 123(2) EPC, the arguments relating to (i) the combination of the "LoK" feature with the "heavy chain" feature in part (a) of the claim and (ii) the combination of the "LoK" feature with the "homozygous" feature had been made in writing - at least in outline - since a fundamental argument in the statement of grounds of appeal had been that the "*overall combination of features of claim 1 as upheld does not find basis in the application as filed*".

It was permissible to present the objections under Article 84 EPC at the oral proceedings since the request containing the claim with the unclear feature had only been filed with the respondent's reply to the appeal. There was no fixed time limit for an appellant to submit objections to such a claim request.

Furthermore, explanations from the respondent for this request were only provided with letter dated 3 November 2021, in which was it stated for the first time what the feature was supposed to mean. The submissions made at the oral proceedings were therefore a prompt reaction. Finally, the objections to novelty made at the oral proceedings were merely an extension of those already made in the statement of grounds of appeal.

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

The homozygosity feature

It was not disputed that the objection previously raised against claim 1 of main request held allowable by the opposition division had been overcome by amendment.

The location of the light chain lambda into kappa (LoK) feature in the mouse genome

The arguments under Article 123(2) EPC not rendered moot by the amendments made in the present main request were as follows:

If the LoK arrangement in feature (b) were at the endogenous position of kappa in the host genome, this was not only a selection of a specific position from an unlimited list of positions but also a further selection of a particular sub-type of LoK arrangement. That is, an arrangement in which the mouse kappa sequences of the LoK are not part of the DNA that is to be inserted, but are kappa sequences that are already present in the host genome. Thus, the feature resulted from an impermissible selection from (at least) two

lists in the combination of features represented by the light chain modification of feature (b).

In addition, claim 1 as considered allowable by the opposition division in feature (b) required the insertion of "human lambda region variable DNA". By contrast, the alleged basis, i.e. feature (b) at the bottom of page 14 explicitly specified the insertion of "one or more human Ig light chain lambda V regions and one or more human Ig light chain lambda J regions" (or corresponding kappa V or J regions). There was no disclosure of any alternative amount of human light chain sequence. The exclusion of this limitation from claim 1 as considered allowable therefore added subject-matter.

Novelty (Article 54 EPC)

Contrary to the finding in the decision under appeal, the homozygosity feature could not render the claimed mouse/mouse cell novel as it was implicit that the mice disclosed in document D1 had this feature. Homozygosity was the inevitable result of following the breeding scheme disclosed in paragraph [00267] of document D1.

The skilled person would have understood that a "suitable breeding schedule", referred to in that paragraph, at the very least required breeding to homozygosity in at least one of the immunoglobulin loci and included further routine steps to introduce homozygosity also at the third locus (see document D27). Mice homozygous for at least one or two immunoglobulin loci would have been obtained with only a single, additional (and routine) breeding step - specifically a cross between F1 offspring (themselves disclosed in document D1). Such a step (interbreeding

between the F1 mice) would happen by default if the F1 mice were simply left unattended.
In short document D27 demonstrated that:
(i) the nature of a suitable breeding schedule is one which leads to homozygosity at all three immunoglobulin loci;
(ii) this would have been immediately apparent to the skilled person reading document D1;
(iii) such a schedule required only the application of highly routine principles of mouse breeding; and
(iv) as a consequence of the above, homozygous mice would have been the inevitable result.

Thus, the disclosure in document D1 anticipated the subject-matter of claim 1.

Article 56 and Article 83 EPC

The claimed subject-matter lacked inventive step and/or the claimed invention was insufficiently disclosed in the patent or application, respectively, for essentially the reasons as set out during the opposition proceedings. The opposition division was incorrect to hold that the requirements of Article 56 EPC and Article 83 EPC were met.

XII. The arguments of the respondent are summarised as follows:

Main request

Admission of allegations of fact and related lines of argument (Article 13(1) and (2) RPBA)

The appellant had not submitted any objections against the main request prior to the oral proceedings. The appellant's submissions under Articles 54, 84 and 123(2) EPC were made for the first time at oral proceedings constituted an amendment to appellant's appeal case and should not be admitted pursuant to Article 13(2) RPBA.

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

The homozygosity feature

The claims had been limited to refer to "one or both" of the immunoglobulin loci. This amendment dealt with the objections raised to the homozygous at "all three loci" feature.

The location of the light chain lambda into kappa feature in the mouse genome

Claim 1 of the main request considered by the opposition division had also been amended to specify the location of the DNA encoding the human lambda region variable DNA inserted in functional arrangement with a mouse kappa constant region, upstream of said kappa constant region, i.e the DNA feature (b) of the claim.

The LoK limitation in part (b) of the claim did not constitute added subject-matter. Basis for this feature was to be found on page 11, third full paragraph of the application as filed: "*Alternatively human lambda region variable DNA might be inserted in functional arrangement with a kappa constant region, for example inserted upstream of a kappa constant region.*"

The amount of human lambda variable region to be inserted was not an undisclosed selection or choice either. The last paragraph of page 14 of the application as filed had a functional requirement to express "*a repertoire of chimaeric antibodies, or chimaeric heavy or light chains having a mouse constant region and a human variable region*". Thus, at a minimum, the "*human lambda region variable DNA*" to be inserted as defined in claim 1(b) had to be sufficient to produce a chimaeric antibody chain and it had to comprise at least one V-lambda gene segment and at least one J-lambda gene segment, as per the disclosure of page 14.

Finally, the limitation to a targeted insertion of the light chain at the endogenous light chain locus was based on page 6, penultimate paragraph of the application as filed.

XIII. The appellant requested that the decision under appeal be set aside and the patent be revoked in its entirety.

The respondent requested that the appeal be dismissed and the patent be maintained in amended form on the basis of the set of claims of the main request, filed as auxiliary request 1 with the reply to the statement of grounds of appeal, or alternatively, the set of claims of one of auxiliary requests 1 to 7, filed as

auxiliary requests 3 to 9, respectively, with the reply to the statement of grounds of appeal.

Reasons for the Decision

1. The appeal is admissible.

Main request - claim 1

2. In this decision reference to "mouse" should be understood to include "mouse cell", as mentioned in the claim.

Admission of new allegations of fact and related lines of argument (Article 13(1) and (2) RPBA)

3. At the oral proceedings, the appellant made submissions under Articles 54, 84 and 123(2) EPC in relation to the main request which had not been made in the written appeal procedure. The submissions on Article 123(2) EPC and Article 84 EPC relating to the part of the claim which differs from claim 1 of the previous main request (see section VIII.) relate to allegations of fact and associated lines of arguments made for the first time at the oral proceedings. All the submissions on Article 54 EPC were also made for the first time in the oral proceedings, as the appellant made reference to different passages in document D1 than when setting out the objection in the statement of grounds of appeal.

4. At oral proceedings the board, applying Article 13(1) and (2) RPBA, decided not to admit any of the above mentioned submissions under the headings of Articles 54, 84 and 123(2) EPC into the appeal proceedings.

5. Under Article 13(1) RPBA any amendment to a party's appeal case after it has filed its grounds of appeal or reply is subject to the party's justification for its amendment and may be admitted only at the discretion of the board which considers, *inter alia*, the current state of the proceedings, the suitability of the amendment to resolve the issues which were admissibly raised by another party in the appeal proceedings or which were raised by the board, whether the amendment is detrimental to procedural economy and in the case of an amendment to a patent application or patent, whether the party has demonstrated that any such amendment, *prima facie*, overcomes the issues raised by another party in the appeal proceedings or by the board and does not give rise to new objections.

6. Under Article 13(2) RPBA any amendment to a party's appeal case made after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

7. The designation of former auxiliary request 1 as the main request was the consequence of the withdrawal of the main request by letter dated 3 November 2021 and does not constitute an exceptional circumstance pursuant to Article 13(2) RPBA. The claim request had been filed with the respondent's reply to the statement of grounds of appeal and the appellant could and should have made any submissions on this claim request as soon as possible after this date. The appellant provided no justification for not having presented the submissions in written proceedings. The appellant's reference to the absence of a time limit for presenting such submissions is of no assistance to its case. While it

is true that there is no time limit for making further submissions after the statement of grounds of appeal and the reply have been filed, it is clear that under Article 13 RPBA, the later any such submissions are made, the higher the hurdle for their admission.

8. The appellant's submission of new allegations of fact and arguments concerning Articles 54, 84 and 123(2) EPC in relation to the claim request at oral proceedings confronted both the respondent and the board with new issues which had not been addressed before during the appeal proceedings. Neither the respondent nor the board could reasonably be expected to deal with these new issues in the absence of sufficient time for their proper consideration.

9. It was the appellant's own request that the former main claim request not be allowed and the foreseeable consequence of this request being successful was that auxiliary request 1 would be considered next. The appellant's decision to wait until the date of oral proceedings to present its objections led to a situation which, for reasons of procedural fairness and to ensure that the respondent's right to be heard was respected, would have necessitated giving the respondent an opportunity to react to the new objections possibly necessitating an adjournment of the oral proceedings. Such a course of action would not have been in the interest of procedural economy (Article 13(1) RPBA).

10. The appellant argued that objections under Article 123(2) EPC relating to (i) the combination of the "LoK" feature with the "heavy chain" feature in part (a) of the claim and (ii) the combination of the "LoK" feature with the "homozygous" feature had been

made in writing, at least in outline, since it had been the fundamental argument presented in paragraph 4.26 of the statement of grounds of appeal which reads "*...there are further issues of added matter when the light chain features are combined with the other features of claim 1 as upheld, such as the heavy chain of part (a). The overall combination of features of claim 1 as upheld does not find basis in the application as filed. The claims as upheld do not comply with Article 123(2) EPC or Article 76(1) EPC*".

11. However, this paragraph does not explain which combination of features in particular is supposed to add subject-matter or why. Instead, it merely makes a general assertion, which is not equivalent to the detailed explanation given at the oral proceedings. The board therefore considered that the objections under Article 123(2) EPC submitted at the oral proceedings had not already been made in writing.

12. In relation to the objections under Article 84 EPC, the appellant submitted that no explanation for this claim request had been provided by the respondent when it was filed with the statement of grounds of appeal. In the appellant's view, explanations were only provided with letter dated 3 November 2021 in which it was stated for the first time what the feature was supposed to mean. The submissions made at the oral proceedings were therefore a prompt reaction to the respondent's late submissions.

13. This allegation is factually incorrect. An explanation (albeit a short one) of auxiliary request 1 was provided in the reply to the statement of grounds of appeal. Specifically, in paragraph 1.2 it was explained that the amendment to the claim further limited to a

targeted insertion of the light chain at the endogenous light chain locus. Thus, the objection could and should have been raised earlier in the appeal proceedings. Accordingly, the board, exercising its discretion pursuant to Article 13(1) and (2) RPBA did not admit into the appeal proceedings those objections under the headings of Articles 84, 123(2) EPC and Article 54 EPC which were submitted for the first time at the oral proceedings. Only objections which were presented with the statement of grounds of appeal in relation to the main request and which clearly apply to auxiliary request 1 were taken into account.

Admission of document D27 (Article 12(4) RPBA 2007)

14. The board did not exclude document D27 from the proceedings as had been requested by the respondent during oral proceedings. However, given the board's decision on the appeal (see point 32.), the reasons for this are moot.

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

15. The descriptions of the application underlying the patent and of the parent application as filed (published as WO 2011/004192) are identical except that the former incorporates the claims of the latter as 'statements of the invention'. In the decision under appeal and in the parties' submissions on Article 123(2) EPC, reference is made only to passages in the parent application as published, with the understanding that the identical text is present in the parent application as filed and in the application as filed. For the sake of consistency with these submissions, the board continues this practice in this decision.

16. The appellant argued that the claim request considered allowable by the opposition division (see section III.), contravened the requirements of Article 123(2) EPC and that this also applied to the subject-matter claim 1 of the main request.

The homozygosity feature

17. Due to the deletion of the option homozygous at "all three loci", as compared to claim 1 of the request considered allowable by the opposition division, the appellant's objections in relation to this feature, have been rendered moot. The appellant did not dispute this view.

The location of the light chain lambda into kappa feature in the mouse genome

18. The objection relating to "*where in the endogenous genome the LoK arrangement should be placed*" is likewise rendered moot by the newly introduced feature "wherein the constant region is the endogenous host wild-type constant region located at the wild type locus" which now requires that the mouse kappa constant region mentioned in claim 1(b) is the endogenous host wild-type constant region.

19. The LoK arrangement for the human lambda variable region is disclosed on page 11, third full paragraph of the application as follows: "*The human kappa variable region DNA might be inserted into the genome in functional arrangement with a lambda constant region, for example inserted upstream of a lambda constant region* [kappa on lambda or KoL]*. Alternatively human lambda region variable DNA might be inserted in functional arrangement with a kappa constant region,*

for example inserted upstream of a kappa constant region [lambda on kappa or LoK]". KoL and LoK are read as alternatives to "*kappa on kappa*" or "*lambda on lambda*", disclosed e.g. on page 2, paragraph 1.

20. The choice of the LoK arrangement is therefore a selection from a single list, each element of which is individually disclosed. The claimed subject-matter including the LoK feature is therefore directly and unambiguously disclosed in the application as filed.

21. The appellant also argued that if the LoK feature were at the endogenous position of kappa in the host genome, this would represent a further selection of a particular sub-type of LoK arrangement, i.e. one in which the mouse kappa sequences of the LoK are not part of the DNA that is to be inserted, but are kappa sequences that are already present in the host genome.

22. However, the board considers that basis for the limitation that the constant region is the endogenous host wild-type constant region located at the wild type locus is to be found on page 6, penultimate paragraph of the application which reads "*The host non-human mammal constant region herein is preferably the endogenous host wild-type constant region located at the wild type locus, as appropriate for the heavy or light chain*". Furthermore, by indicating this as a preferred option, there is also a pointer to the combination of this feature with the remaining claimed features.

23. In summary, the objections pursuant to Article 123(2) EPC set out in the statement of grounds of appeal have either been overcome by amendment or are not convincing.

Novelty (Article 54(3) EPC) - claim 1

24. The appellant challenged the opposition division's decision that the disclosure in document D1, which constituted prior art under Article 54(3) EPC, did not anticipate the subject-matter of claim 1.

25. It was common ground that documents D1 and D4 disclose mice homozygous at the modified light chain and modified heavy chain loci, respectively. It was disputed between the parties whether or not the disclosure in paragraph [00267] of document D1 amounted to a direct and unambiguous disclosure of the mice defined in claim 1, whose genome is homozygous at one or both immunoglobulin loci.

26. Paragraph [00267] of document D1 reads "*Mice bearing an unrearranged human λ light chain locus are also bred with mice that contain a replacement of the endogenous mouse heavy chain variable gene locus with the human heavy chain variable gene locus (see US 6,596,541 , Regeneron Pharmaceuticals, the VELOCIMMUNE® genetically engineered mouse). [...]. Upon a suitable breeding schedule, mice bearing a replacement of the endogenous mouse heavy chain locus with the human heavy chain locus and an unrearranged human λ light chain locus at the endogenous κ light chain locus is obtained*".

27. The quoted sentence does not disclose the mice obtained by the "suitable breeding schedule" but rather suggests carrying out a suitable breeding. This understanding of the disclosure is supported by the fact that the breeding scheme is not precisely defined, as it would be in an example, but is referred to as a "*suitable*" one. Thus, the mice resulting from this breeding scheme are not disclosed but merely suggested in document D1.

Since it is these mice that are purported by the appellant to be relevant to the novelty of the claimed subject-matter, the board must conclude that the disclosure in document D1 does not affect the novelty of the subject-matter of claim 1.

28. The appellant's further argument based on document D27 is that the suitable breeding scheme mentioned in paragraph [00267] of document D1 discloses the claimed mice because these are the inevitable consequence of carrying it (the breeding scheme) out. However, as is apparent from the appellant's summary of document D27 (see section XI.) which mentions that "*such a schedule requires only the application of highly routine principles of mouse breeding*", the arguments presented could be relevant to an allegation of obviousness but not to an allegation of lack of novelty under Article 54(3) EPC. For this reason, the argument also fails.

Objections under Articles 56 and 83 EPC

29. In the statement of grounds of appeal, objections pursuant to Articles 56 EPC and 83 EPC were briefly mentioned, however without any indication of reasons. It was merely stated in point 6.1 that *"the claims as upheld also lack inventive step and/or are insufficient for essentially the reasons as set out during the opposition proceedings. The OD was incorrect to hold that the claims comply with Article 56 EPC and Article 83 EPC.*"

30. Such a general statement or reference does not meet the requirements under Article 12(2) RPBA 2007. According to this provision the statement of grounds of appeal should contain the appellant's complete case and set

out clearly and concisely the reasons why the decision under appeal should be reversed. All the facts, arguments and evidence relied on should be specified.

31. It is the board's view that the objections relating to Articles 56 EPC and 83 EPC are not substantiated. No further relevant submissions were made in reply to the board's communication under Article 15(1) RPBA and the board thus decided not to take objections under Articles 56 and 83 EPC into account in these appeal proceedings in accordance with Article 12(4) RPBA 2007.

32. In view of the considerations set out above, the patent with claim 1 meets the requirements of the EPC and the appeal is thus not allowable. Since the appellant has not submitted separate objections against any of claims 2 to 14 of the main request, the patent may be maintained on the basis of the set of claims of the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form with the set of claims 1 to 14 of the main request, filed as auxiliary request 1 with the reply to the statement of grounds of appeal, and a description and drawings to be adapted thereto.

The Registrar: The Chair:

I. Aperribay B. Claes

Decision electronically authenticated