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Datasheet for the decision of 9 July 2026

Case Number: T 0527/24 - 3.3.04

Application Number: 18183980.4

Publication Number: 3456190

IPC: A01K67/0276, A01K67/0275, C12N15/85, C07K16/00

Language of the proceedings: EN

Title of invention:
Antibody producing transgenic murine animal

Patent Proprietor:
Merus N.V.

Opponent:
Kymab Limited

Headword:
Antibody producing mouse/MERUS

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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T 2140/22

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Case Number: T 0527/24 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 9 July 2026

Appellant: (Opponent)	Kymab Limited The Bennet Building (B930) Babraham Research Campus Cambridge Cambridgeshire CB22 3AT (GB)
Representative:	CMS Cameron McKenna Nabarro Olswang LLP Cannon Place 78 Cannon Street London EC4N 6AF (GB)
Respondent: (Patent Proprietor)	Merus N.V. Yalelaan 62 3584 CM Utrecht (NL)
Representative:	Simmons & Simmons LLP (Munich) Lehel Carré Gewürzmühlstraße 11 80538 Munich (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted/electronically transmitted on 16 February 2024 rejecting the opposition filed against European patent No. 3456190 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	A. Chakravarty
	L. Bühler

Summary of Facts and Submissions

I. The opponent (appellant) filed an appeal against the opposition division's decision to reject the opposition. The patent proprietor is respondent to the opponent's appeal.

II. In the decision under appeal, the opposition division considered and dismissed grounds for opposition raised under Article 100(a), (b) and (c) EPC that the claimed subject-matter lacked novelty and an inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the (earlier) application as filed.

III. The appellant submitted a statement of grounds of appeal to which the respondent replied. With its reply the respondent re-submitted sets of claims of auxiliary requests 1 to 3, which were those filed before the opposition division.

IV. The appellant then responded to the respondent's reply to the statement of grounds of appeal with a letter dated 14 April 2025 together with an Annex 1.

V. The board appointed oral proceedings and subsequently issued a communication under Article 15(1) RPBA, setting out its preliminary opinion on the appeal case.

VI. The respondent replied to the appellant's letter of 14 April 2025 with its own letter dated 24 July 2025, together with an Annex 2. It also submitted a further letter dated 9 June 2026 in reaction to the board's communication under Article 15(1) RPBA.

VII. Claim 1 of the patent as granted (main request) reads

"1. A transgenic murine host capable of producing immunoglobulins comprising a human VL region, said murine host comprising integrated in its germline a rearranged nucleic acid comprising one human germline V and one human germline J gene segment encoding a rearranged human VL region and a light chain constant region of any animal species, wherein said light chain variable region is capable of pairing with at least two different heavy chains encoded by the host, such that variety in specificity of antibodies comprising said human VL region is retained through rearrangements and hypermutations in the heavy chains".

Claim 1 of auxiliary request 1 is the same as claim 1 of the main request.

Claim 1 of auxiliary request 2 is based on claim 17 of the patent as granted, amended to adapt it to the deletion of the previous product claims. It reads:

"1. A method for producing a desired antibody comprising exposing a transgenic murine host capable of producing immunoglobulins comprising a human VL region, said murine host comprising integrated in its germline a rearranged nucleic acid comprising one human germline V and one human germline J gene segment encoding a rearranged human VL region and a light chain constant region of any animal species, wherein said light chain variable region is capable of pairing with at least two different heavy chains encoded by the host, such that variety in specificity of antibodies comprising said human VL region is retained through rearrangements and hypermutations in the heavy chains

to an antigen such that an antibody response is induced and isolating the antibodies specific for the antigen".

Claim 1 of auxiliary request 3 differs from claim 1 of auxiliary request 2 in that after the word "isolating" it reads "a nucleic acid encoding at least part of such an antibody, inserting said nucleic acid or a copy or a derivative thereof in an expression cassette and expressing said antibody in a host cell".

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

D3: WO 2004/106375
D41: US 2006/0015957
D52: Chapter 5 (pages 105-136), Kuby, Immunology, 6th edition, July 2006.

IX. Oral proceedings before the board took place as scheduled. At the end of the proceedings, the Chairwoman announced the decision of the board.

X. The appellant's arguments are summarised as follows:

Admittance of the submission of 14 April 2025

The submission of 14 April 2025 was made in response to assertions made for the first time in the respondent's reply to the statement of grounds of appeal. This could not have been done earlier because the respondent's assertions were not part of the decision under appeal.

The submission also included arguments in relation to the auxiliary requests which could not have been made earlier. It was not known earlier which, if any, auxiliary requests the respondent would maintain. It

was therefore legitimate to include this response.

Main request and auxiliary request 1 - claim 1
Inventive step (Article 56 EPC)

Closest prior art

Document D41 was the closest prior art. It was the most suitable starting point for assessing inventive step because it disclosed a transgenic mouse platform for producing human antibodies, in particular transgenic mice containing a rearranged light-chain transgene and an unrearranged heavy-chain transgene. In fact, D41 already disclosed all features of claim 1, or at least came extremely close to doing so. The opposition division had misunderstood the term "minilocus", which referred only to unrearranged segments (see, for example, in paragraph [0334]). The nucleic acid comprising the rearranged light chain was consistently described in D41 as a "construct".

As far as there were any differences between the claimed subject-matter and the disclosure in D41, these might be as follows:

The "germline" feature

If the "germline" identity of the V/J segment were to be taken as a difference between the disclosure in D41 and the claimed subject-matter, it had no technical effect. The opposition division had already correctly made this finding in the decision under appeal, see paragraphs 5.2.2 and 5.3.2.

The "wherein said light chain variable region is capable of pairing with at least two different heavy chains encoded by the host" feature

The opposition division held that D41 did not directly and unambiguously disclose a light chain satisfying the above pairing requirement. However, this was not correct. Example 8, paragraph [0481] of D41 described a kappa light chain expression cassette designed to reconstruct rearranged light chain genes. The expression cassette included the VJ segment and Cκ region (see paragraph [0481] and Fig. 33). Paragraph [0482] stated that "*[t]ransgenic mice generated with the rearranged light chain constructs can be bred with heavy chain minilocus transgenics to produce a strain of mice that express a spectrum of fully human antibodies in which all of the diversity of the primary repertoire is contributed by the heavy chain.*" In these mice the light chain necessarily had to be capable of pairing with more than one heavy chain for such a spectrum of fully human antibodies to be produced, particularly where the diversity of the repertoire was contributed by the heavy chain. This capability was fundamental to a platform in which all diversity was provided by the heavy chain.

Furthermore, paragraph [0482] stated that because not all light chains were equivalent in their ability to combine with a variety of heavy chains, different strains of mice comprising different light-chain constructs could be generated and tested. This also indicated that light-chain constructs were selected on the basis of their ability to pair with a broad range of heavy chains.

A similar disclosure was found in Example 14 of D41. Paragraph [0553] stated that "*[b]ecause not all VJκ combinations may be capable of forming stable heavy-light chain complexes with a broad spectrum of different heavy chain VDJ combinations, several different light chain constructs are generated*", i.e. in order to produce VJκ combinations that **were** capable of forming stable heavy-light chain complexes with a broad spectrum of different heavy chain VDJ combinations. This capability was clear from the final sentence of paragraph [0553], which stated that "*[r]earranged light chain transgene constructs that result in the highest level of human heavy/light chain complexes on the surface of the highest number of B cells ... are selected for the generation of human monoclonal antibodies*". This paragraph provided an explicit indication that rearranged light chain constructs were being selected on the basis that they paired with the highest number of heavy chains.

The "rearranged" feature

"Rearranged" was not a difference between the claimed subject-matter and that disclosed in D41. The opposition division was right in the decision under appeal to state that "*the construct of figure 33 [is] a rearranged nucleic acid as recited in claim 1*" (see point 4.6.1). The sub-heading within D41, Example 8, where Figure 33 was discussed in detail (paragraphs [0481] and [0482] of D41), was '*Rearranged Light Chain Transgenes*' – a clear indication that the construct shown in Figure 33 was considered to comprise a rearranged variable light chain region.

It was noted that claim 1 of the main request did not exclude the possibility that more than one V or J

segment was present, provided the VL region was rearranged. Therefore a disclosure comprising multiple J gene segments fulfilled the 'one J segment' requirement of the claim.

Paragraph [0482] of D41 described the amplification of rearranged human kappa light chain genes from human spleen genomic DNA by PCR. The use of oligos o-130 and o-131 generated a 0.7 kb fragment corresponding to VκIII genes joined to Jκ1 segments, confirming that the V and J segments had been rearranged. The PCR product was cloned, and sequence analysis of five clones identified two containing functional VJ joints, i.e. functional rearranged light chain genes. These functionally rearranged clones were then cloned into a light chain expression cassette.

The presence of additional downstream Jκ segments in the construct of Figure 33 did not alter this conclusion. A single V/J rearrangement was sufficient to generate a rearranged VL region and any remaining downstream J segments were functionally irrelevant because they did not interfere with expression of the variable light chain. Unless the rearrangement utilised the terminal Jκ5 segment, additional downstream J segments would have remained in the construct and would subsequently have been removed during RNA splicing.

The "integrated in its germline" feature

So that transgenic mice generated with the rearranged light chain constructs can be bred with heavy chain transgenic mice (paragraph [0482]), the rearranged light chain sequence had to be integrated into the mouse germline. This was explicitly disclosed, for example, in paragraph [0197], which stated: "*In one*

aspect of the invention, transgenic non-human animals are provided that contain rearranged, unrearranged or a combination of rearranged and unrearranged heterologous immunoglobulin heavy and light chain transgenes in the germline of the transgenic animal".

If there were any differences between the disclosure in D41 and the claimed subject-matter e.g. the "germline" identity of the V or J segment and to the extent that there was any validity to the opposition division's conclusion that the claims were novel over D41 because of this feature, these differences were not linked to any technical effect.

Objective technical problem

In view of the above differences and the absence of any technical effect thereof, the objective technical problem was the provision of a platform for the generation of antibodies.

Obviousness

The claimed solution involved the use of a rearranged light-chain variable region capable of pairing with at least two different heavy chains, thereby allowing antibody diversity to arise from the heavy chain. This was taught in D41.

Indeed, D41 itself explicitly taught the skilled person to select light chains that pair with many different heavy chains. Paragraph [0482] stated that mice could express a spectrum of fully human antibodies in which diversity comes from the heavy chain and further taught that different light chains should be tested because

they differ in their ability to combine with a variety of heavy chains.
The same solution was in paragraph [0553], which taught generating different rearranged VJκ constructs and selecting those capable of forming stable complexes with a broad spectrum of heavy chains. These passages were a direct instruction to identify and use light chains compatible with many different heavy chains, which is exactly what the patent claim stated.

The decision under appeal came to the wrong conclusion on inventive step for two reasons:

Firstly, it was wrong to state in point 5.3.5 that at the priority date the field followed a "more is more" philosophy, i.e. preserving or increasing light-chain diversity instead of reducing light chain diversity. In fact, common-light-chain technology was already known, for example from D3. D41 itself also disclosed a common light chain platform.

Secondly, the decision was wrong in point 5.3.5 to hold that the skilled person would have been too cautious to follow D41's suggestion. D41 expressly recommended selecting light chains capable of pairing with many different heavy chains, a suggestion which the skilled person would naturally investigate and apply. There was no technical prejudice, incalculable risk, or unpredictable area that would have discouraged doing so.

In summary, D41 already taught using rearranged light chains that pair with a broad range of heavy chains. The claimed subject-matter was the mere implementation of what D41 expressly proposed. Therefore the claimed subject-matter would have been obvious to the skilled

person starting from D41 and lacked an inventive step under Article 56 EPC.

Auxiliary requests 2 and 3

Claim 1 of these requests lacked an inventive step for the same reasons as claim 1 of the patent as granted because it was directed to a method for producing antibodies using the mouse that itself lacked an inventive step.

XI. The respondent's arguments are summarised as follows:

Admittance of the appellant's submission of 14 April 2025

The appellant's submission of 14 April 2025 should not be admitted into the proceedings. Under Article 12(3) RPBA, the statement of grounds of appeal and the reply should contain a party's complete appeal case, whereas later submissions were to be seen as amendments to the appeal case.

Main request and auxiliary request 1 - claim 1
Inventive step (Article 56 EPC)

Closest prior art

Although D3 was the closest prior art, D41 was a possible starting point for the inventive step assessment. However, D41 suggested a fundamentally different strategy for generating human antibodies than the claim under consideration. Rather than providing a transgenic animal carrying a predefined common light chain, D41 relied on introducing light-chain constructs containing multiple J segments and envisaged generating

and screening different mouse strains containing different light-chain constructs. Accordingly, D41 followed a "more is more" approach aimed at maintaining or increasing light-chain diversity.

Distinguishing Features

The claimed transgenic murine host differed from D41 in several respects:

The "rearranged" feature

D41 did not disclose a rearranged nucleic acid comprising a single human germline V segment and a single human germline J segment encoding a rearranged human VL region. Instead, the constructs of Examples 8 and 14 contained multiple J segments and required further rearrangement. D41 might use the term 'rearranged', however, it was clearly not a rearranged nucleic acid as required in claim 1. Rather, it was nothing but an unrearranged construct which undisputedly contained multiple J segments, where the V gene segment and any J gene segment must undergo rearrangement such that a rearranged VJ region is produced by transcribing and translating the two rearranged segments. This was clear from paragraph [0481] and Figure 33, which depicted the obtention, and hence structure of the vector pK31s that included five Jκ segments together with the Cκ gene segment.

Capable of pairing with at least two different heavy chains encoded by the host

D41 did not disclose a fixed common light chain that was capable of pairing with at least two different heavy chains encoded by the host and in paragraph

[0482] acknowledged that not all light chains were equivalent in their ability to combine with a variety of heavy chains. D41 itself expressly acknowledged that not all light chains will be equivalent with respect to their ability to combine with a variety of heavy chains. This proved the point that not all light chains were capable of pairing with at least two different heavy chains. To overcome this problem, D41 proposed preparing various mice with different light chain loci (see paragraph [0482], '*…different strains of mice, each containing different light chain constructs* ***can be*** *generated and tested…*', emphasis by the respondent).

Example 14 relied upon by the appellant also did not disclose the rearranged nucleic acid as called for in claim 1. Rather, it again disclosed an unrearranged light chain construct containing multiple J segments. Furthermore, there was no evidence in D41 that the light chains used were necessarily capable of pairing with at least two different heavy chains.

Finally, the relevant passages of D41 were merely prophetic and did not provide experimental evidence that any disclosed light chain actually paired with multiple heavy chains or generated a functional repertoire of antibodies.

Further, document D41 did not directly and unambiguously disclose a transgenic murine host comprising integrated in its germline a rearranged nucleic acid comprising one human germline V and one human germline J gene segment encoding a rearranged human VL region. This was also prophetic.

Technical Effect

The above mentioned distinguishing features meant that the platform of D41 is thus not suitable as a platform for the generation of mixtures of antibodies or multispecific antibodies from single cells. The claimed mouse provided a platform in which a single predefined common light chain could be used to generate antibodies against different targets while diversity was contributed by the heavy chains. As a result, the invention enabled efficient identification and production of antibodies sharing a common light chain, which was particularly valuable for generating multispecific antibodies and antibody mixtures. This approach also avoided the need to identify suitable light chains repeatedly for different targets and provided a practical platform for obtaining heavy chains compatible with a common light chain.

Objective technical problem

In view of the differences between D41 and the claimed invention, and in view of the technical effect of the claimed and differentiating features as discussed above, the objective technical problem was formulated as: the provision of an improved platform for the generation of mixtures of antibodies or multispecific antibodies from single cells.

Obviousness

Given the prophetic nature of the teaching of document D41, it could not have prompted the skilled person to reasonably expect that a light chain variable region 'capable of pairing with at least two different heavy chains' could be provided, and eventually used in the

efficient production of mixtures of antibodies or multispecific antibodies.

D41 provided no teaching that a single common light chain capable of pairing with multiple different heavy chains could reliably be identified. Instead, D41 expressly warned that not all light chains were capable of combining with a variety of heavy chains and proposed screening multiple light-chain constructs in different mouse strains. The skilled person therefore would not have had a reasonable expectation of success in selecting a single light chain capable of functioning as the claimed common light chain.

Secondly, D41 taught away from the claimed invention by promoting a strategy based on multiple light-chain constructs and multiple mouse strains. The claimed invention instead adopted a single common-light-chain platform. The invention therefore represented a conceptual departure from the approach advocated by D41 rather than a routine optimisation of it.

Thirdly, D41 provided no incentive to use a rearranged nucleic acid comprising only one V segment and one J segment. The constructs disclosed in D41 contained multiple J segments, and a skilled person would have been reluctant to remove these elements because they could have been regarded as important for proper expression and regulation. Thus, D41 did not provide a realistic pathway toward the claimed fixed rearranged light-chain construct.

Fourth, the prophetic nature of Examples 8 and 14 meant that D41 contained no experimental confirmation that the proposed light chains would generate functional antibodies with diverse heavy chains. In the absence of

such evidence, the skilled person would not have had a reasonable expectation that D41's proposed constructs could serve as a universal common-light-chain platform.

Finally, D41 contemplated additional diversity arising through light-chain somatic hypermutation. This was inconsistent with the claimed concept of a fixed common light chain whose sequence remained unchanged while diversity was generated through the heavy chains. The teaching of D41 therefore pointed in a different direction from the claimed invention.

In view of all of the above, the skilled person starting from D41 would not have been motivated, nor would they have had a reasonable expectation of success, in replacing D41's speculative and diversity-focused light-chain strategy with a single rearranged common light chain capable of pairing with multiple different heavy chains and generating antibody diversity through the heavy chains alone.

Auxiliary requests

The appellant's objections against auxiliary requests 1 to 3 were late filed and should not be admitted although these requests had been on file before the opposition division. Any objections to these requests should therefore have been included in the statement of grounds of appeal. There was no valid reason for the board to admit any of the contested submissions.

Auxiliary requests 2 and 3
Inventive step (Article 56 EPC)

Claim 1 of these auxiliary requests was for a method for producing a desired antibody using the transgenic

mouse defined in claim 1 as granted. Even if the mouse of claim 1 as granted lacked an inventive step because the antibodies produced could vary from the exact ones encoded by the rearranged human VL region, the methods did not relate to such variants because they were only for the production of a "desired" antibody. This desired antibody was the common light chain antibody which was inventive over the D41 citation, as explained above.

XII. The appellant requests:

- that the decision under appeal be set aside and that the patent be revoked in its entirety.

XIII. The respondent requests:

- that the appeal be dismissed and that the patent be maintained as granted (main request).
- alternatively, that the patent be maintained in amended form on the basis of any of auxiliary requests 1 to 3, filed before the opposition division on 16 November 2023 and refiled with the statement of grounds of appeal.
- that the appellant's submission of 14 April 2025 not be admitted, and if it were admitted, that the proprietor's response be admitted.

Reasons for the Decision

Admittance (Article 13(1) RPBA)

1. The respondent objected to the admittance of the appellant's submissions on novelty based on documents

D2, D36 and D41, made in the letter dated 14 April 2025.

2. At the oral proceedings, the board admitted these submissions. However, D2 and D36 and the related submissions are not relevant to this decision, so no reason need to be given for their admittance.

3. In relation to D41, the board considers that the arguments in the appellant's letter of 14 April 2025 represent a legitimate response to issues raised in the respondent's reply to the statement of grounds of appeal which the appellant could not be expected to include in its statement of grounds of appeal.

4. Similarly, the appellant could not have been expected to raise objections to auxiliary requests which were not dealt with in the proceedings before the opposition division because a higher ranking request was held allowable. At the time of submitting the statement of grounds of appeal, the appellant could not have known which auxiliary requests would be maintained in the appeal proceedings.

5. The respondent requested that if the appellant's submission of 14 April 2025 were admitted, then that the response thereto dated 24 July 2025 be also admitted. The board also admitted this submission. However, it is noted that the majority of the appellant's letter of 14 April 2025 concerns issues not relevant to the decision to be taken. The relevant part concerns inventive step assessed starting from D41. The respondent's letter dated 24 July 2025 merely refers to the statement of grounds of appeal in this respect.

Admittance (Article 13(2) RPBA)

6. During oral proceedings before the board, the appellant objected to specific technical points in the respondent's submissions on paragraphs [0481] and [0482] and Figure 33 of D41, in particular to:

- the reference to paragraph [0190] of D41 in the assessment of whether paragraph [0481] and Figure 33 disclose rearranged germline DNA;
- the factual allegation that the PCR amplification disclosed in paragraph [0482] was unreliable because the first of the two synthetic oligonucleotides disclosed there was an unspecific and degenerate primer;
- the lack of prior art knowledge on how to obtain transgenic mice.

7. The appellant requested the board to disregard these submissions under Article 13(2) RPBA.

8. Article 13(2) RPBA provides that any amendment to a party's appeal case made after notification of a communication under Article 15(1) RPBA shall, in principle, not be taken into account unless the party concerned has shown exceptional circumstances, justified by cogent reasons. Such circumstances may include new or unforeseen developments in the appeal proceedings, such as new objections raised by the board or another party.

9. The respondent argued that the submissions merely further developed the discussion of paragraphs [0481] and [0482] and Figure 33 of D41 in the reply on pages 32 and 33, sections 5.7 to 5.10. However, the submissions at issue introduced new factual allegations

which went beyond the matter addressed in the reply and in opposition. They therefore constituted an amendment of the respondent's appeal case.

10. The respondent did not identify any exceptional circumstances that would justify the late submissions. Nor were the submissions presented in response to new developments in the appeal proceedings following the issuance of the board's communication under Article 15(1) RPBA, or to new matter introduced by the board in that communication. Paragraphs [0481] and [0482] and Figure 33 of D41 had been discussed in detail during the opposition proceedings, in the decision under appeal, and in the parties' written submissions on appeal. The contested submissions could and should therefore have been presented earlier, rather than at this late stage of the appeal proceedings.

11. For these reasons, the board decided not to admit the respondent's argument concerning the alleged lack of specificity of the oligonucleotide primers mentioned in paragraph [0482] of D41.

12. Paragraph [0190] is addressed below in the discussion of Figure 33 of D41 (point 27.). The alleged lack of prior-art knowledge on how to obtain transgenic mice is addressed in point 29. Since consideration of these submissions did not disadvantage the appellant, there is no need to address their admittance.

Main request - the patent as granted

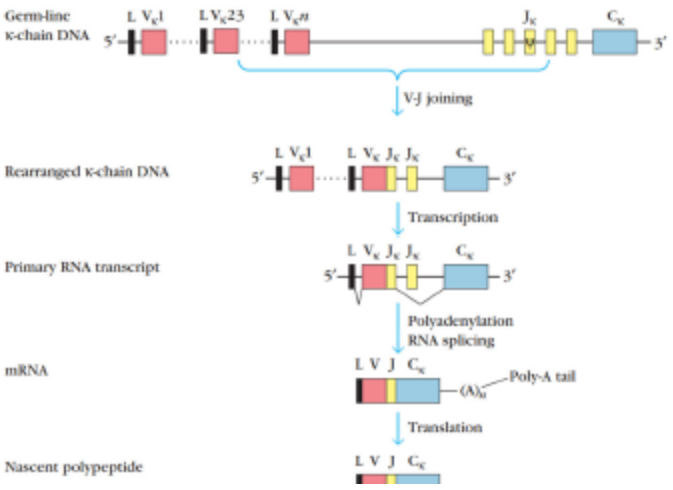
Claim 1

Claim construction

Technical Background

13. The human and mouse immunoglobulin loci comprise gene fragments that serve to build up all immunoglobulin variable domains of heavy and light chains. The genome of undeveloped B cells is organised in gene segments and comprises V (variable), D (diversity), and J (joining) gene segments constituting the variable domain of the heavy chain and only V and J genes for building up the variable domain of the light chain. One of each gene segment is randomly selected by the RAG1/ RAG2 recombinase and joined together to form the variable region (see also paragraph [0002] of the patent).

The scheme is illustrated below and is taken from Figure 5.4 on page 111 of D52. It shows Kappa light-chain gene rearrangement and RNA processing events required to generate a κ light-chain protein. In this example, rearrangement joins Vκ23 and Jκ4.



14. Thus the wording in claim 1 "*a rearranged nucleic acid comprising one human germline V and one human germline J gene segment encoding a rearranged human VL region*" refers to a nucleic acid encoding a variable light chain after recombination of the (human) V-J segments.

15. The claimed subject-matter is a transgenic mouse having integrated in its germline a rearranged nucleic acid comprising:
- at least one human germline V and at least one human germline J gene segment encoding a rearranged human VL region;
- and a light chain constant region of any animal species, meaning at least one specific light chain can be produced.

16. The parties disagreed about whether the claim language excluded animals where the nucleic acid encoding the immunoglobulin light chain has undergone somatic hypermutation. The respondent was of the view that the murine host animal only contained nucleic acids encoding a rearranged human light chain sequence exactly identical to that present in its germline. The appellant, on the other hand was of the view that the claimed murine animal could also be capable of

producing immunoglobulins encoded by nucleic acids derived from the rearranged human germline VL region but which had subsequently undergone somatic hypermutation.

17. Since the claim only defines a rearranged nucleic acid present in the animal's germline, it does not exclude that somatic hypermutation can take place. Therefore the claim encompasses a mouse that can produce immunoglobulins comprising a human VL region whose amino acid sequence is exactly the one encoded by the germline V and the germline J gene segments, but also encompasses mice that can (also) produce immunoglobulins having a VL sequence that differs from the one encoded by the "rearranged" germline nucleic acid by virtue of somatic hypermutation.

18. The encoded light chain variable (VL) region is functionally defined in the claim as being "capable of pairing with at least two different heavy chains encoded by the host, such that variety in specificity of antibodies comprising said human VL region is retained through rearrangements and hypermutations in the heavy chains". The use of "*such that*" is an indication of an intended result of the functional feature but no structural information is conveyed.

19. The term "germline sequence" refers to the DNA present in germline cells, although it does not define any particular sequence. As the claim refers explicitly to germline nucleic acid sequences, the board cannot accept the appellant's suggestion that "*claim 1 should be construed as if the term "germline" was not present*". However, the board also does not share the respondent's view that the term "germline" denotes nucleic acid sequences which encode for protein

segments of the light chain having a germline sequence, but which nucleic acid sequence may be modified in comparison to the germline nucleic acid sequences because in that case the sequences would no longer be "germline" sequences.

Inventive step (Article 56 EPC)

Closest prior art

20. In the decision under appeal, the opposition division assessed inventive step starting from both document D3 and document D41 as the closest prior art. The respondent considered D3 as a better starting point than D41. However, as noted in T 2140/22 (see Reasons 1.9.1 and 1.9.2), any prior disclosure may be used as the starting point for the assessment of inventive step.

21. The board assessed inventive step starting from D41, which was the appellant's preferred starting point.

22. D41 discloses transgenic non-human animals capable of producing a heterologous antibody, such as a human antibody (see paragraph [0021]). In a section entitled "*Rearranged light chain transgenes*", expression cassettes designed to reconstruct functionally rearranged light chain genes that have been amplified by PCR from human B-cell DNA are disclosed (see paragraphs [0481] and [0482]). In paragraph [0482] further details about the cloning scheme are disclosed. In particular, oligonucleotides were used to amplify rearranged kappa light chain genes from human spleen genomic DNA. The amplified fragment had 0.7 kb and individual PCR products were cloned into a plasmid. The paragraph goes on to suggest that "*The functionally*

rearranged clones can be individually cloned into light chain expression cassette described above (FIG. 33). Transgenic mice generated with the rearranged light chain constructs can be bred with heavy chain minilocus transgenics to produce a strain of mice that express a spectrum of fully human antibodies in which all of the diversity of the primary repertoire is contributed by the heavy chain. One source of light chain diversity can be from somatic mutation. Because not all light chains will be equivalent with respect to their ability to combine with a variety of different heavy chains, different strains of mice, each containing different light chain constructs can be generated and tested".

23. The parties did not agree on the differences between the relevant disclosure in D41 and the claimed subject-matter, although they did agree about which passages of D41 were most relevant.

24. The appellant was of the view that, if not already anticipating the claimed subject-matter, the only differences lay either in the features "capable of pairing with at least two heavy chains" or the "germline" feature (with respect to the V or J segment). This was in agreement with the opposition division in the decision under appeal (see point 5.3.1).

25. The respondent agreed that these were differences but was of the view that there were further differences. In particular, D41 did not disclose a rearranged nucleic acid at all, let alone one comprising one human germline V and one human germline J gene segment encoding a rearranged human VL region. It also did not disclose a transgenic animal comprising such a rearranged nucleic acid. Any references to "rearranged"

in D41 were undermined by the disclosure in Figure 33 (referred to in paragraph [0482]) which clearly showed the presence of multiple J segments. Moreover, the disclosure in D41 in regard of rearranged VL regions was prophetic and had never been put into practice.

26. In the board's view, D41 discloses a rearranged nucleic acid comprising a rearranged human VL region. This is because this is explicitly stated in paragraphs [0481] and [0482] and is supported by the disclosure of the size of the amplified 0.7 kb DNA fragment, consistent with a rearranged VJ region. As noted by the appellant "*The size of the DNA fragment, which is specified as being 0.7kb, confirms the VJ segments are rearranged, as an unrearranged VJ from human spleen DNA would be impossible to amplify using PCR with the stated oligos as the V segment would be tens of thousands of base pairs away from the J segment*" (see letter of 14 April 2025, page 4). Moreover, paragraph [0482] of D41 reports that "*The DNA sequence of 5 clones was determined and identified two with functional VJ joints (open reading frames)*". This supports the previous disclosure that relevant experimental work was actually done. A further disclosure in D41 of a nucleic acid comprising a rearranged human VL region is in paragraph [0552] under the heading "*Generation of Transgenic Mice Containing Rearranged Human Light Chain Constructs*". This reads "*Fragments containing functional VJ segments (open reading frame and splice signals) are subcloned into the unique XhoI sites of vectors pCK1 and pCK2 to generate* ***rearranged kappa light chain transgenes***" (emphasis by the board).

27. The respondent's reference to Fig. 33 to support its view that D41 only discloses an unrearranged VL region is not convincing. Firstly, Fig. 33 shows a "scheme",

meaning that the actual cloning strategy might not be fully represented. More importantly, as noted by the opposition division in the decision under appeal, "*Although the construct comprises more J segments, no further rearrangement is possible in the absence of additional upstream V segments. The construct must thus be considered as "rearranged*" (see point 4.6.1). The board notes that the claim is not worded to exclude the presence of further unrearranged J segments, in addition to the rearranged VL region. Furthermore, the definition of "rearranged" in paragraph [0190] of D41 does not exclude further J segments and is thus not in contradiction to Fig. 33.

28. To support its view that D41 does not disclose a nucleic acid encoding a rearranged VJ region, the respondent also argued:

i) that the skilled person would have doubts about the probative value of the disclosure in D41 because the disclosure in D41 concerning a rearranged VL region was prophetic (meaning suggestions for future work) and therefore of less probative value.

ii) that the date of D41's priorities (in the 1990s), would have caused the skilled reader to doubt that such a rearranged nucleic acid had been obtained.

On the topic of whether the disclosure in D41 related to work that had been done or was "prophetic" it submitted

iii) that D41 did not disclose transgenic mice producing the corresponding, single light chain immunoglobulins. Such mice were merely suggested and there was nothing in D41 or in any other document to

show that they could have been obtained using the teaching available at the date.

29. As to arguments i) and ii), the board notes that the relevant date for the present considerations on patentability is the effective (priority) date of the patent in suit, not the date of the priority documents of D41. The skilled person reading D41 has all the common general knowledge available at that date. The respondent's arguments relating to the prophetic nature of the Examples and the priority dates of D41 could be understood as suggesting that the disclosure in D41 is not sufficiently disclosed, in analogy with Article 83 EPC. However, no relevant evidence or technical argument was submitted in support of such a position.

30. In any case, as far as a nucleic acid encoding a rearranged VL region is concerned, the disclosure in D41 is more than "prophetic", because it includes experimental results, such as the 0.7 kb DNA fragment amplified from human spleen DNA corresponding to rearranged V_KIII genes joined to J_K1 segments (paragraph [0482]). The use of the past tense also indicates that the experiments were done.

31. In relation to argument iii) the respondent is right in stating that D41 only suggests that transgenic mice be produced. Reference to mice is not made in the past tense but as follows "*Transgenic mice generated with the rearranged light chain constructs* ***can be bred*** *with heavy chain minilocus transgenics to produce a strain of mice that express a spectrum of fully human antibodies in which all of the diversity of the primary repertoire is contributed by the heavy chain*" (paragraph [0482]; emphasis by the board).

32. A further difference between the disclosure in D41 and the claimed subject-matter put forward by the respondent and one that was crucial to the opposition division's decision on inventive step, was the functional feature "*wherein said light chain variable region is capable of pairing with at least two different heavy chains encoded by the host*".

33. Here the board differs from the opposition division in its reading of D41. As set out in its communication pursuant to Article 15(1) RPBA, said feature is not a difference between the rearranged nucleic acid defined in claim 1 and the rearranged nucleic acid comprising a rearranged human VL region disclosed in D41: if the rearranged nucleic acid disclosed in Example 8 (paragraph [0482]) was not able to pair with more than one heavy chain, then the (suggested) transgenic mice generated using it would not be expected to be able to express a spectrum of fully human antibodies in which all of the diversity of the primary repertoire is contributed by the heavy chain as set out later in the same paragraph.

34. The respondent also argued that the passage in paragraph [0482] of D41 that "*One source of light chain diversity can be from somatic mutation. Because not all light chains will be equivalent with respect to their ability to combine with a variety of different heavy chains, different strains of mice, each containing different light chain constructs can be generated and tested*" implied that antibody diversity was disclosed as being due to variation on the light chain (and not to ability to pair various heavy chains) and also as confirming that not all light chains are equal when it comes to promiscuity in heavy chain pairing.

35. The board accepts that the skilled person knew that not all light chains are equal when it comes to promiscuity in heavy chain pairing. However, the above cited passage merely offers a second mechanism for generating antibody diversity and further suggests screening for light chains capable of combining with a variety of different heavy chains. It does not imply that the previously disclosed nucleic acid encoding rearranged light chain variable region are not capable of pairing with at least two different heavy chains encoded by the host. The board has not seen any evidence to suggest that the known difference in pairing promiscuity of VL regions means that VL regions exist that can only pair with a single VH region.

36. Example 14 (see paragraph [0553]) also discloses rearranged nucleic acid constructs having this functional feature. In paragraph [0553] it is stated that "*not all VJκ combinations may be capable of forming stable heavy-light chain complexes with a broad spectrum of different heavy VDJ combinations*" and suggests testing different VJκ clones and to select those which "*result in the highest level of human heavy/light chain complexes on the surface of the highest number of B cells*".

37. The opposition division concluded from this that "*It is thus not a given (it cannot directly and unambiguously be concluded) that a rearranged light chain pairs with several heavy chains*" (see point 4.6.2 of the decision under appeal).

38. Even if the opposition division's decision in this respect was based on a view that D41 did not directly and unambiguously disclose rearranged nucleic acids having this functional feature because these still

needed to be identified by testing, the board is unable to understand why in its considerations on inventive step it stated "*there was no reasonable expectation ... that these light chains (or at least some of them) would indeed be able to pair with different heavy chains*" (see point 5.3.5). This conclusion goes against what is explicitly taught in D41 without a technical explanation based on common general knowledge or a document from the state of the art.

39. For the sake of completeness, the board has noted that the respondent's argument that the opposition division accepted was that D41 differs from the claimed invention in that it teaches that "*[a]t the time of filing of the patent, the philosophy was still to apply the "more is more" technology, i.e the use of a variety of immunoglobulin gene segments to mirror the in vivo situation as much as possible*" (see point 5.3.5 of the decision under appeal). This submission is not relevant to the decision because, although D41 does disclose such embodiments (i.e. those using a variety of light chain constructs), it also discloses constructs having a rearranged light chain, as set out above. These are the starting point for the assessment of inventive step.

40. In view of the above considerations and in summary, the differences between the disclosure in D41 and the claimed subject-matter are as follows:

i) D41 does not disclose a transgenic murine host. Instead, it discloses nucleic acids suggested as suitable for generating such an animal.

ii) D41 does not disclose a rearranged nucleic acid encoding a rearranged human VL region comprising "germline" gene segments.

41. As to the technical effect of these differences, the board agrees with the decision under appeal that no case has been made that the "germline" feature results in any technical effect. This difference therefore has no bearing on the formulation of the objective technical problem. The technical effect of the first difference is to actually put into practice what is suggested in D41.

Objective technical problem

42. In view of the differences between the subject-matter disclosed in D41 and the claimed subject-matter, the objective technical problem can be formulated as *putting into practice the suggestion in paragraphs 481 and 482 of D41 to produce immunoglobulins having a common light chain*.

43. The problem adopted in the decision under appeal was "*provision of a platform for the generation of antibodies*". Although the claimed mice do represent a solution to this problem, it is not adopted because the differences between the disclosure in D41 and their technical effect include the generation of transgenic mice using the rearranged human VL region.

44. The respondent considered that the objective technical problem was "*the provision of an improved platform for the generation of mixtures of antibodies or multispecific antibodies from single cells*". This problem was not adopted because the board came to a different conclusion about the differences between the

disclosure in D41 and the claimed subject-matter and the technical effects thereof.

Obviousness

45. The claimed subject-matter represents an obvious solution to the above objective technical problem because the skilled person starting from the kappa light chain expression cassettes disclosed in paragraphs [0481] and [0482] of D41 and seeing in the latter paragraph that "*Transgenic mice generated with the rearranged light chain constructs can be bred with heavy chain minilocus transgenics to produce a strain of mice that express a spectrum of fully human antibodies in which all of the diversity of the primary repertoire is contributed by the heavy chain*", was motivated to generate those transgenic mice expressing the rearranged light chain expression cassette and breed them with mice expressing the full repertoire of human heavy chains to obtain the mice suggested in paragraph [0482]. These mice would have been expected to be capable of producing fully human antibodies. It is also considered that the skilled person embarking on such a course had a reasonable expectation of success because no evidence has been put forward that the skilled person would have had doubts about the feasibility of carrying out the suggestions in D41 at the relevant date. The respondent referred to the date of the priority documents of D41 in this regard but provided no concrete technical arguments to support the idea that the skilled person was aware of technical obstacles at the relevant date.

46. The same conclusion is reached when starting from Example 14 disclosing the construction of rearranged light chain transgenes (see paragraph [0551]).

Paragraph [0552] again suggests "*Generation of Transgenic Mice Containing Rearranged Human Light Chain Constructs*" (see title) and then suggests that "*Animals expressing human kappa chain are bred with heavy chain minilocus containing transgenic animals to generate mice expressing fully human antibodies*". Following these suggestions would lead the skilled person directly to subject-matter falling within claim 1 at issue.

47. Even taking the respondent's argument that D41 does not actually disclose the production of any transgenic mice into account, the conclusion on obviousness remains because no technical argument or evidence has been provided that the skilled person following the course of action suggested in D41 would expect any technical difficulties which would go beyond the capacity of the skilled person at the relevant date.

48. In view of the above considerations, claim 1 of the main request (the patent as granted) lacks an inventive step and the main request is not allowable.

Auxiliary requests 1 to 3

49. Claim 1 of auxiliary request 1 is identical to claim 1 of the main request. Auxiliary request 1 is therefore not allowable for the same reasons as the main request.

50. Claim 1 of auxiliary requests 2 and 3 is directed to a method for producing a desired antibody using the transgenic mouse defined in claim 1 as granted. Since the mouse of claim 1 of the patent as granted lacks an inventive step, and its purpose (defined in the claim) is the production of common light chain antibodies, the finding of lack of inventive step applies to the

subject-matter of claim 1 of both of these auxiliary requests. In other words, the overarching idea behind the mouse of claim 1 of the main request was the production of common light chain antibodies. Claim 1 of auxiliary requests 2 and 3 merely requires that the mouse be exposed to an antigen. Claim 1 of auxiliary request 3 merely adds the steps of isolating the relevant nucleic acid from the mouse and its expression in a host cell. None of these features go beyond the common knowledge of the skilled person at the relevant date. Indeed, the respondent has not relied on any argument based on these additional steps.

51. The respondent did argue that the word "desired" in claim 1 of auxiliary requests 2 and 3 implied that the "desired" antibody was different from one which was not "desired". In its view, the "desired" antibody was the antibody encoded by the rearranged nucleic acid, without somatic hypermutation having taken place.

52. This argument is neither persuasive nor could it alter the board's finding of lack of inventive step, which was based on exactly this embodiment. For the sake of completeness, the board notes that the word "desired" does not change the subject-matter claimed because "desire" is a subjective quality, and thus a desired antibody can be any antibody.

53. Auxiliary requests 1 to 3 are not allowable for lack of an inventive step. Since no auxiliary request is allowable, the patent must be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated