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Datasheet for the decision of 25 November 2021

Case Number: T 1634/17 - 3.3.08

Application Number: 12716101.6

Publication Number: 2550363

IPC: C12N15/85, A01K67/027, C12N9/64, C07K16/46, C07K16/28, C07K16/40

Language of the proceedings: EN

Title of invention:
ADAM6 MICE

Patent Proprietor:
REGENERON PHARMACEUTICALS, INC.

Opponent:
Kymab Limited

Headword:
ADAM6 mice/REGENERON PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 123(2), 112, 113, 83, 56, 54
EPC R. 103(1)(a)
RPBA Art. 12(4)
RPBA 2020 Art. 12(3)

Keyword:
Consideration of evidence filed at first instance (yes);
Consideration/admission of evidence filed in appeal (no);
Status of oral/ephemeral disclosure - prior art (no);
Main request - added subject-matter (no);
Main request - sufficiency of disclosure (yes);
Main request - novelty (yes);
Main request - inventive step (yes);
Referral to the Enlarged Board of Appeal (no);
Reimbursement of the appeal fee (no);

Decisions cited:
G 0001/92, T 0019/90, T 1212/97, T 2003/08

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1634/17 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 25 November 2021

Appellant I: (Patent Proprietor)	REGENERON PHARMACEUTICALS, INC. 777 Old Saw Mill River Road Tarrytown, NY 10591 (US)
Representative:	Bentham, Andrew J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Appellant II: (Opponent)	Kymab Limited The Bennet Building (B930) Babraham Research Campus Cambridge Cambridgeshire CB22 3AT (GB)
Representative:	Stephen, Robert John 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 26 May 2017 concerning maintenance of the European Patent No. 2550363 in amended form.**

Composition of the Board:

Chair	B. Stolz
Members:	M. R. Vega Laso
	R. Winkelhofer
	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. European patent no. 2 550 363, based on European patent application no. 12 716 101.6, was originally filed under the PCT and published as International patent application WO 2012/141798 (hereinafter "the patent application"). The patent was granted with 14 claims and an opposition was filed on the grounds set out in Articles 100(a), 100(b) and 100(c) EPC. The opposition division considered the main request and auxiliary request 1 not to fulfil the requirements of Articles 56 and 54 EPC, respectively, and auxiliary request 2 to fulfill the requirements of the EPC.

II. Appeals were lodged by the patent proprietor and the opponent (appellants I and II, respectively).

With the statements setting out their grounds of appeal, appellant I maintained their main request (claims as granted) and filed auxiliary requests 1 to 7 and both, appellant I and appellant II, filed new evidence. As an auxiliary measure, both appellants requested oral proceedings (Article 116(1) EPC).

III. The appellants replied to their respective statements of grounds of appeal. Both appellants filed new evidence and appellant I also filed an auxiliary request 8.

IV. The parties were summoned to oral proceedings. In a communication sent to the parties, they were informed of the board's provisional opinion on the issues of the appeal.

V. Oral proceedings were held on 25 November 2021 in the presence of all parties.

VI. Claims 1, 2, 4 and 14 as granted read as follows:

"1. A mouse having a genome comprising a modification of an immunoglobulin heavy chain locus, wherein the modification eliminates endogenous ADAM6 function, which is associated with a reduction in fertility in male mice, the mouse further comprising nucleic acid sequences encoding a mouse ADAM6a protein, or an ortholog or homolog or functional fragment thereof that is functional in a male mouse, and a mouse ADAM6b protein, or an ortholog or homolog or fragment thereof that is functional in a male mouse.

2. The mouse of claim 1, wherein the nucleic acid sequences are at an endogenous immunoglobulin locus or wherein the nucleic acid sequences are integrated into the mouse genome at a position other than an endogenous immunoglobulin locus.

4. A method for modifying an immunoglobulin heavy chain locus of a mouse, comprising:

(a) making a first modification of the mouse immunoglobulin heavy chain locus that results in an elimination of endogenous mouse ADAM6 activity in a male mouse; and,

(b) making a second modification of the mouse to add nucleic acid sequences that confer upon the mouse ADAM6 activity that is functional in a male mouse, preferably wherein the nucleic acid sequences in step (b) are added at an ectopic position, which nucleic acid sequence encodes a mouse ADAM6a protein or an ortholog,

a homolog, or a functional fragment thereof, and a mouse ADAM6b protein or an ortholog, a homolog, or a functional fragment thereof.

14. A nucleic acid sequence encoding a mouse ADAM6a protein or an ortholog or homolog or functional fragment thereof that is functional in a male mouse, and a mouse ADAM6b protein or an ortholog or homolog or fragment thereof that is functional in a male mouse for use in restoring or enhancing the fertility of a male mouse having a genome comprising a modification of an immunoglobulin heavy chain locus, wherein the modification reduces or eliminates endogenous ADAM6 function, which is associated with a reduction of fertility in male mice, wherein said nucleic acid sequence is to be integrated into the genome of the mouse at an endogenous immunoglobulin locus or at a position other than an endogenous immunoglobulin locus."

Claim 3 and claims 5 and 6 are directed to particular embodiments of claims 1 and 4, respectively. Claim 7 is directed to an isolated cell or an isolated tissue from a mouse of any one of claims 1 to 3. Claim 8 is directed to the use of a mouse according to claim 3 for the generation of different types of antibodies and antibody fragments. Claims 9 and 10 are directed to methods for generating a chimeric antibody and a fully human antibody, respectively, specific against an antigen. Claims 11 to 13 are directed to particular embodiments of claims 9 and 10.

VII. The following documents are cited in this decision:

(1): US-A1-2004/0018626 (pub. date: 29 January 2004);

(3): C. Han *et al.*, Biol. Reprod., 2009, Vol. 80, pages 1001 to 1008;

(4): K. Featherstone *et al.*, J. Biol. Chem., 2010, Vol. 285, No. 13, pages 9327 to 9338;

(7): I. Choi *et al.*, Genomics, 2004, Vol. 83, pages 636 to 646;

(8): WO-A1-2011/004192 (pub. date: 13 January 2011);

(9): WO-A1-2011/158009 (pub. date: 22 December 2011);

(11): D. Murphy, "BAC-based Modifications of the Mouse Genome: The Big and The Backward", in "Welcome Trust Advanced Course: Genetic Manipulation of ES Cells", November 3rd, 2009, Hinxton, UK;

(11)': as defined by the opposition division at the first instance proceedings (page 14, point 3.26 of the decision under appeal);

(13): Declaration Dr A. Murphy, signed on 1? June 2014;

(14): WO-A1-2013/079953 (pub. date: 6 June 2013);

(23) Declaration/Statement of Dr G.A. Friedrich, signed on 3 March 2016;

(24): Declaration/Statement of Professor A. Bradley, signed 13 June 2016;

(25): Declaration/Statement of Dr Meng (Amy) Li, signed on 7 June 2016;

(26): Declaration/Statement of Dr Wei Wang, signed on 13 June 2016;

(27): Declaration/Statement of Dr Hui Liu, signed on 13 June 2016;

(28): Declaration/Statement of Dr. E-Chiang Lee, signed on 13 June 2016;

(30): Declaration/Statement of Dr Meng (Amy) Li, signed on 5 September 2016;

(37): Declaration/Statement of Dr Kosuke Yusa, signed on 2 October 2017.

VIII. The arguments of appellant I, insofar as relevant to the present decision, may be summarised as follows:

Consideration/admission of document (37) in appeal proceedings

Document (37) could and should have been filed at earlier stages of the proceedings. The issues addressed by this document were already raised in earlier stages of the first instance proceedings, in particular in the preliminary opinion of the opposition division and before the oral proceedings at first instance. The evidence provided by document (37) neither added anything to that already on file nor overcame the deficiencies of other documents and evidence on file.

Document (11) and the status of document (11)' as prior art

Dr Murphy only believed that document (11) was a copy of the slides used and shown during his presentation (58 slides in less than one hour) and for which no copies were ever distributed (points 5, 9 and 10 of

document (13)). A presentation was an ephemeral event, document (11) could not be equated to and used as a printed publication; a reader could not have relied on all of its details, neither had time and opportunity to review the slides in depth nor to revisit them as needed. It was not correct to consider the entire content of a presentation (all slides) to have entered into the public domain. The crucial point was not what information was presented but what was taken away by the audience. According to the case law, this had to be shown by contemporaneous evidence from neutral, disinterested members of the audience.

The standard for assessing what was made available to the public *via* an oral disclosure was set out in decisions T 1212/97 and T 2003/08. In T 1212/97, the board stated that a lecture was an ephemeral disclosure and the manner/speed of the presentation affected its comprehensibility. For establishing the information content made available to the public, safe/satisfactory evidence had to be provided so as to proof beyond reasonable doubt that a particular information was made available. The lecturer's own evidence by itself was not enough but contemporary written notes made at the lecture by at least two members of the audience were sufficient (points 1 to 4 of the Reasons). In T 2003/08, the board stated that, under certain circumstances, lecturer's evidence and that provided by only one member of the audience was convincing enough to reach the standard of proof, i.e. beyond reasonable doubt (point 42 of the Reasons).

In the case at issue, the evidence on file was neither contemporaneous to Dr Murphy's presentation nor from neutral, disinterested members of the audience. Neither Professor Bradley's notes (document (24)) nor other

evidence on file (documents (23), (25) to (28), (30)) or Dr Amy (Meng) Li's witness testimony, satisfied the criteria set out in the case law. The opposition division did not follow correctly the case law in reaching its conclusion, making findings about Dr Murphy's presentation that were not based on safe and satisfactory evidence, and disregarding thus the core principle of "beyond reasonable doubt".

The purpose of Dr Murphy's presentation was to provide some practical applications of laboratory techniques, not to teach the actual methods or experiments in the presentation (point 8 of document (13)). The focus was on general techniques rather than on ADAM6 gene *per se* and restoration of mouse male fertility by this gene; there was no evidence that the few slides relating to ADAM6 were given any prominence in Dr Murphy's presentation. Indeed, the evidence on file showed that the members of the audience took away information that was different from the subject-matter claimed.

The creation of document (11)' by the opposition division was inadmissible and a substantial procedural violation. Moreover, the information contained in this document was not present in document (11). Whilst document (11)' referred to "infertility" and ADAM6 genes in plural, document (11) mentioned "poor fertility" and ADAM6 gene in singular. Document (11) referred to a targeted ADAM6 insertion ("put back"), whilst document (11)' referred to a random transgenesis of ADAM6. Thus, the evidence on file on Dr Murphy's presentation as interpreted by the opposition division, namely document (11)', contained information that was different from that present in document (11).

Main request (Claims as granted)
Article 100(b) EPC (Article 83 EPC)

The terms "homolog", "ortholog" and "functional fragment" were known in the field and understood by the skilled person. They provided a fair scope of protection and should not be interpreted in a strict, narrow sense requiring an inferred evolutionary relatedness but, in line with the disclosure of the patent application (paragraph [0234]), to embrace variants arisen by evolution *per se* as well as *in vitro* manipulation. There was no difficulty for a skilled person to compare nucleotide/amino acid sequences such as those obtained from databases. The patent application provided guidance to suitable reference sequences as starting points for sequence variation (paragraph [0276]) and information for identifying ADAM6 functionality, such as sperm motility and migration (paragraphs [0393], [0394]), histological assays (paragraph [0395]), and Western blotting in epididymis (paragraphs [0397], [0398]). The opposition division was right as regards the burden of proof and the fact that, in the present case, no evidence was provided to support any serious doubt, let alone substantiated by variable facts, as required by the established case law (T 19/90, EPO OJ 1990, 476).

Article 100(a) EPC (Article 54 EPC)

Reference was made to the submissions filed at first instance proceedings and the opposition division's findings on Article 54 EPC as well as their agreement therewith.

Article 100(a) EPC (Article 56 EPC)

The closest prior art document (1) was silent on fertility in general and referred neither to ADAM6 nor to the role of any ADAM family member on mice fertility. The relevant disclosure of document (1) concerned the use of "large targeting vectors for eukaryotic cells" (LTVECs) for producing chimeric or hybrid human/mouse monoclonal antibodies as described in Example 3 (paragraph [0211]). The resulting transgenic mice served as an initial source of immunological diversity for subsequent screening. The skilled person with a conservative attitude would not have embarked on a risky, expensive and time-consuming research involving the genetic modification of transgenic mice that were already modified and produced at all events the monoclonal antibodies of interest.

A fertility problem was neither obvious nor directly derivable from the transgenic mice disclosed in document (1) but, if at all, from breeding these mice. It was thus an extrinsic characteristic of these transgenic mice within the meaning defined in decision G 1/92 (OJ EPO 1993, 277, point 3 of the Reasons); it was only revealed by exposing the transgenic mice to interaction with specifically chosen conditions and a comparison with non-modified mice. Document (1) did not identify however any breeding problem. The reduction in fertility identified in the patent (paragraphs [0214], [0331]) had no bearing on the question whether a skilled person would have recognised a fertility problem when carrying out the methods of document (1). The data disclosed in the patent actually showed that transgenic mice lacking the ADAM6 gene were capable of breeding, they were successfully bred (Table 9, paragraph [0354]). The reduction in male fertility

would not have been necessarily manifested to, and recognised by, a skilled person when carrying out the teachings of document (1); fertility problems were not an absolute deficiency, they emerged as phenotype in some breeding colonies under certain conditions, manifested in a stochastic manner and colony-dependent, only in homozygous transgenic male mice but not in heterozygous male mice or in female mice. Many factors could affect mice breeding performance other than fertility *sensu strictu* and document (1) contained no information identifying any fertility problem.

Even if, *arguendo*, the reduction in litter size and frequency could have been seen as a problem, it would not have been obvious to a skilled person that this problem was caused by a reduction in fertility *per se*, let alone in male fertility specifically. Litter size and frequency were determined by overall breeding performance which was itself affected by many factors other than fertility; moreover, such a reduction could have also resulted from adventitious mutations arising when carrying out the teachings of document (1). Furthermore, the loss of the ADAM6 function could not have been directly identified as the source of such a problem from document (1). Example 3 of this document described the production of transgenic mice in which all or part of the mouse heavy chain locus variable region was replaced by the human counterparts (paragraph [0222]). Mice with only some of the mouse variable region replaced (by transfection with LTVEC1) did not necessarily have the ADAM6 gene function eliminated (paragraph [0224]). Only mice with all the region removed (by subsequent transfection with LTVEC2 and production of double targeted ES cells) contained a modification that eliminated the endogenous ADAM6 gene function and resulted in a reduction of male fertility

(paragraph [0225]). However, even Professor Bradley acknowledged that no embedded genes had been identified in the murine immunoglobulin loci (page 5, point 14 in document (24)). Thus, extensive experimentation and deconvolution of their results would have been required to identify the relative contribution of the various variables and factors that could have affected litter size and frequency.

In addition, the function of ADAM6 was unknown. Document (7) did not disclosed a definitive function of the murine ADAM6 gene. As evidenced by document (3), even five years after the publication of document (7), the role of murine ADAM6 was unknown; only a non-essential role for ADAM6 in ADAM2 and ADAM3 complexes was described in document (3) (page 1006 and Figure 8(B)) which concluded that the role of the ADAM proteins was complex and involved a tangled relationship between the protein phenotypes and fertilization phenotypes (page 1007, right-hand column, last paragraph).

In conclusion, there was no indication of any fertility problem in document (1) nor was this problem directly derivable from document (1). Therefore, there was no motivation for a skilled person to solve such a problem. The solution to this problem was neither obvious nor derivable from the prior art without hindsight knowledge of the patent; moreover, other solutions were also available to a skilled person such as breeding heterozygous transgenic mice colonies. In addition, there was neither a suggestion in the prior art nor any reason to use two ADAM6 genes, namely ADAM6a and ADAM6b.

Referral to the Enlarged Board of Appeal

There were no reasons for a referral. Appellant II's question to the Enlarged Board of Appeal was based on erroneous assumptions on document (11) and on some of the evidence on file. Moreover, it was not formulated as an actual question but only as a somewhat vague theme, and it could be answered by reference to existing case law and the actual facts at issue.

Reimbursement of the appeal fee

The creation of a new prior art document by the opposition division was inadmissible and represented a substantial procedural violation. It contravened both general principles and the EPO case law to the detriment of one party (appellant I) over the other party (appellant II). There was no provision in the EPC or in the case law of the Boards of Appeal permitting any instance of the EPO to create its own version of evidence or prior art. This was contrary to all known legal principles and to the general principles of procedural laws in the EPC Contracting States. As acknowledged by the case law, the principle of free evaluation did not allow the deciding body to choose the evidence but required an assessment of all the relevant evidence. Therefore, it was even less permissible for a deciding body to create new evidence.

The opposition division was not allowed to decide that three pieces of information (the content of document (11)'), none of which was wholly found in document (11), were disclosed to the audience of Dr Murphy's presentation and that these pieces of information together constituted an item of prior art. By doing so, the opposition division created two

problems. First, the creation of new evidence was procedurally incorrect because this evidence was an interpretation of existing evidence, not a true piece of evidence or prior art in its own right. Second, the parties were taken by surprise by the appearance of document (11)' as closest prior art at a late stage of the proceedings, namely during an ongoing oral hearing, as shown in the Minutes of the oral proceedings at first instance.

Thus, the creation of document (11)' as an item of the prior art represented a substantial procedural violation within the meaning of Rule 103(1)(a) EPC and a refund of the appeal fee was justified.

IX. The arguments of appellant II, insofar as relevant to the present decision, may be summarised as follows:

Consideration/admission of document (37) in appeal proceedings

The filing of document (37) in appeal was a reaction to the opposition division's findings on document (11) regarding the re-introduction of the murine ADAM6 genes into the mouse genome. Document (37) was *prima facie* relevant because it corroborated that a targeted insertion of the murine ADAM6 genes was disclosed in document (11). This issue was not addressed during the written stage of the opposition proceedings, in particular not in the opposition division's preliminary opinion, but only during the oral proceedings at first instance. Whilst granted claim 2 referred to a targeted insertion, this was only a possible embodiment, not standing alone; the scope of this claim was broader, not limited to this embodiment. Thus, there was no opportunity to file document (37) at earlier stages of

the proceedings, the first opportunity being at the onset of the appeal proceedings.

Document (11) and the status of document (11)' as prior art

Decision T 1212/97 did not set an absolute standard of proof for oral/ephemeral disclosures. This decision stated that each disclosure had to be judged on a case-by-case basis and that other type of evidence could also be taken into account. The present case differed from those underlying the decisions T 1212/97 and T 2003/08.

Whilst in decision T 1212/97, the presentation was only oral, without showing any slides to the audience, in the present case all slides of document (11) were shown to the audience during Dr Murphy's presentation. Whilst in decision T 2003/08, the lecturer had only a vague recollection of which slides were shown to the audience, Dr Murphy acknowledged that all slides of document (11), including slides 23 to 26, were shown to the audience. The term "believe" in Dr Murphy's declaration (document (13)) only meant that to the best of his knowledge all slides of document (11) were shown to the audience. Thus, whilst in the cases underlying decisions T 1212/97 and T 2003/08 there was considerably uncertainty as regards what was actually shown to the audience, there was no uncertainty in the present case as stated in Dr Murphy's sworn declaration that all slides of document (11) were shown to the audience.

Moreover, Dr Murphy's presentation was given in a meeting/workshop for lab people; the attendees were interested in, able to understand and take away, the whole content/information given in this presentation.

Contrary to other cases considered in the case law, wherein the presentations/oral disclosures were given to a general audience, the audience in this case had a high level of skill and were highly interested in Dr Murphy's presentation.

The evidence on file (declarations in documents (23) to (28) and (30)) confirmed that all the slides reproduced in document (11) were shown to the audience. The information given in this evidence did not contradict that present in document (11); although these declarations were made in response to the opposition division's preliminary opinion and thus after Dr Murphy's presentation, they were from several attendees who had not been shown the slides of document (11) after Dr Murphy's presentation. This evidence was thus based only on attendees' recollection, a collective memory, of what was really shown and taken away from Dr Murphy's presentation. Therefore, in this sense, all these declarations could be seen as contemporaneous to Dr Murphy's presentation. The credibility of this evidence was further confirmed by Dr Amy (Meng) Li's witness testimony taken by and satisfying the opposition division (page 10, point 3.12 of the decision under appeal). If the credibility of this testimony was put into doubt, the witness had then to be heard anew. Document (11)' was a summary of the information taken away from Dr Murphy's presentation made by the opposition division on the basis of all the evidence on file.

All the declarations on file and Dr Amy (Meng) Li's witness testimony confirmed that the audience of Dr Murphy's presentation took away that the deletion of mouse immunoglobulin (IgH) locus resulted in male infertility and that fertility could be restored by

transgenesis of the ADAM6 gene, two copies of a single gene were required for obtaining an homozygous transgenic mouse. The mistakenly reference to ADAM19 in Exhibit 5 of Professor Bradley's declaration (document (24)) was a typographical error made by the transcriber of Professor Bradley's notes (a person unskilled/non-familiar in the technical field at issue) that was easily identifiable/immediately recognisable by the (skilled) addressees of Professor Bradley's message as acknowledged by Professor Bradley himself.

Thus, in the present case and in contrast to the cases underlying the decisions of the case law cited by appellant I, the relevant subject-matter were proven beyond reasonable doubt and the evidence on file met the standards/criteria set in the case law for acknowledging the content/information conveyed by an oral/ephemeral disclosure.

Main request (Claims as granted)
Article 100(b) EPC (Article 83 EPC)

The patent did not provide any guidance as regards homologs, orthologs and functional fragments of the ADAM6a and ADAM6b proteins that could be used to restore fertility, nor as regards insertion sites for ADAM6 other than at one specific exemplified location in the endogenous mouse immunoglobulin locus.

Evidence was on file showing that other murine members of the ADAM family (ADAM2, ADAM3, ADAM4), were not capable of restoring male fertility in ADAM6 deleted mice (documents (1), (3)). The patent application showed in Table 9 that the presence of these endogenous murine ADAM family members in the ADAM6 deleted transgenic male mice was not enough to overcome their

infertility. Thus, none of the other members of the ADAM family had been shown to be a functional ADAM6 ortholog/homolog. Neither the patent application nor the prior art provided any guidance/information for the skilled person to achieve functional orthologs/ homologs. According to the case law, the skilled person could not rely on try and error but needed some sort of guidance; the finding of appropriate functional orthologs/homologs required to set up a lengthy and burdensome research project. The same applied to functional fragments since no guidance was provided as regards the (minimum) length required for them to remain functional; undue burden was required for raising/checking transgenic male mice and finding these functional fragments.

Article 100(a) EPC (Article 54 EPC)

Reference was made to submissions filed at first instance proceedings. They explicitly confirmed that there was no novelty objection based on document (14) but only on documents (1), (8) and (9).

Article 100(a) EPC (Article 56 EPC)

Example 3 of the closest prior art document (1) disclosed a transgenic mouse containing the human Ig variable regions and the mouse Ig constant regions obtained by inserting the human sequences into the IgH, λ and κ loci, with concomitant deletion of the corresponding endogenous mouse sequences, wherein the mouse was bred to homozygosity for the modification. These transgenic mice with a genome comprising the entire human heavy and light chain variable gene loci operably linked to entirely endogenous mouse constant region, were used as a platform for producing human

variable/mouse constant monoclonal antibodies (*inter alia*, paragraphs [0219], [0229]). The method or technology for producing these transgenic mice, termed VelocImmune mice, had already been acknowledged by the Boards of Appeal to be enabling.

The difference between the disclosure of document (1) and the claimed subject-matter was that the nucleic acid sequences encoding the mouse ADAM6a and ADAM6b proteins had been inserted into the human Ig gene sequences. The technical effect of this difference was that the homozygous transgenic male mice were fertile.

Therefore, starting from the closest prior art document (1), the objective technical problem to be solved was the provision of an approach or method for generating a breeding colony of homozygous transgenic mice which were useful for producing therapeutic human monoclonal antibodies. The solution to this problem was the insertion of the nucleic acid sequences encoding the mouse ADAM6a and ADAM6b proteins into the human Ig gene sequences.

This solution would have been obvious to the skilled person. Indeed, a skilled person by setting up a breeding colony of homozygous VelocImmune mice - for using them to produce human monoclonal antibodies as disclosed in document (1) (paragraph [0219]), would have necessarily encountered and realised that these homozygous transgenic male mice were infertile. Mice fertility was inextricably linked to setting up a breeding colony of homozygous mice and problems in the fertility of these homozygous transgenic male mice would have been immediately apparent to, and seen by, a skilled person as shown in Table 9 of the patent (paragraphs [0164], [0214], [0331], [0354]). A skilled

person performing the methods disclosed in document (1) would have thus immediately realised that the resulting homozygous transgenic male mice were infertile when compared to non-homozygous transgenic male mice for the immunoglobulin modification carried out. The infertility of these homozygous transgenic male mice was not an extrinsic characteristic in the sense as defined in decision G 1/92 (*supra*) because it was revealed to the skilled person without requiring the exposure of the homozygous transgenic mice to any interaction with specifically chosen outside conditions.

The average skilled person working in the technical field at issue would certainly have had experience in standard mouse techniques, such as mouse genetic modifications and breeding of mouse colonies, being well acquainted and familiarised with breeding factors and problems, such as colony stress, feeding problems, etc., and knew how to deal with and solve them. Therefore, the skilled person, being conservative and methodic as defined in the case law, when facing the above defined infertility problem, would have routinely checked all these factors and easily discarded them, identifying the genetic deletion of the endogenous mouse sequences at the source or origin of said problem. As also defined in the case law, it was within the normal tasks of a skilled person to eliminate deficiencies, overcome drawbacks and look for improvements. Thereby, it would have been obvious for the skilled person to look for what had been actually deleted, which other genes were comprised in the deleted region and had been deleted, underlying and being associated thus with the identified infertility problem.

In doing so, the skilled person would have checked the information available in the databases (according to the case law, they were part of the skilled person's common general knowledge), such as the database Ensembl. Thereby, the skilled person would have directly identified the gene encoding the ADAM6 protein (and a second gene encoding an ADAM6-like protein which shared 84% sequence similarity to the ADAM6 gene) in the relevant deleted region as shown by the evidence on file. Indeed, the skilled person already knew from document (7) that two ADAM6 genes were located in the immunoglobulin region of the mouse chromosome 12 (Figure 6A) and the role of the ADAM genes in mouse-specific male reproduction (page 643, right-hand column, lines 10 to 13). If the deletion (knock-out) of such a gene resulted in fertility problems, the obvious solution was then, in line with the skilled person's common general knowledge, to rescue/reintroduce or put back, the deleted relevant gene (knock-in) into the genome of the transgenic mice and, in line with the teachings of document (1), two copies of said gene for obtaining homozygous transgenic mice. The skilled person would have arrived thereby at the claimed transgenic mouse in an obvious manner.

Referral to the Enlarged Board of Appeal

What standard was required to illustrate that subject-matter had been made available to the public, when the patentee had confirmed that slides containing the relevant information were presented and the contents of the presentation was corroborated by a number of witnesses.

X. The appellant I (patent proprietor) requests that the decision under appeal be set aside and the opposition be rejected, or the patent be maintained in amended form on the basis of auxiliary requests, and the appeal fee be reimbursed.

XI. The appellant II (opponent) requests that the decision under appeal be set aside and the patent be revoked. Subsidiarily, they request questions be referred to the Enlarged Board of Appeal.

Reasons for the Decision

1. Parts of the present decision are based on the same grounds, arguments and evidence on which the board's provisional opinion, as submitted to the parties in a communication, was based. They were neither questioned by the parties, nor did other aspects come up that would require their re-consideration by the board.

Exclusion of evidence considered by the opposition division

2. Appellant I requested to exclude documents (23) to (28), document (30), and Dr Meng (Amy) Li's witness testimony (recorded at the oral proceedings on 27 March 2017) from the appeal proceedings.

3. In the board's communication, it was stated that the EPC does not provide a basis for excluding, in appeal proceedings, documents that were correctly admitted into the opposition proceedings, the more so when the impugned decision was based thereupon.

3.1 The board also concluded therein that the opposition division had exercised its discretion correctly and in a reasonable way, and that documents (23) to (28),

document (30), and Dr Meng (Amy) Li's witness testimony, would not be excluded from the appeal proceedings.

4. At the oral proceedings before the board, the parties relied on their written submissions and there was no further discussion regarding this issue.

5. Therefore, there is no reason for the board to take a different stand on this issue.

Consideration/admission of document (37) in appeal proceedings

6. With the statement of grounds of appeal, appellant II filed document (37). Appellant I opposed the admission of this document in appeal proceedings.

7. Since the statement of grounds of appeal and the reply thereto were filed before the date of entry into force of the RPBA 2020, the transitional provisions set out in Article 25(2) RPBA 2020 apply and, in the present case, the discretion of the board has to be exercised in accordance with Article 12(4) RPBA 2007. According to this article, the board may hold inadmissible, *inter alia*, evidence that could have been presented in the first instance proceedings.

8. Document (37) is a declaration/statement of Dr Kosuke Yusa on her recollection regarding the presentation given by Dr Murphy at the Sanger Centre in November 2009; Dr Kosuke Yusa was a post-doctoral researcher at the Sanger Institute in November 2009. The declaration/statement is signed on 2 October 2017.

9. There are declarations/statements of other members of the audience of Dr Murphy's presentation on file,

namely documents (23) to (28) and (30); most of these members were PhD students or post-doctoral researchers at the Sanger Institute in November 2009. All these declarations/statements were signed on 2016 (most in June 2016) and provide the recollection of these members on Dr Murphy's presentation.

10. According to appellant II, document (37) was filed in direct reaction to a feature introduced into claim 1 of auxiliary request 2, namely "wherein the nucleic acid sequences encoding said ADAM6 proteins ... are inserted into the human immunoglobulin gene sequences".

11. Claim 1 of auxiliary request 2 underlying the decision under appeal, the sole claim of this request, is identical to claim 1 of the auxiliary request 5 filed on 27 January 2017 in reply to the opposition division's preliminary opinion and in preparation of the oral proceedings on 27 and 28 March 2017. It is also worth noting that granted claim 2 already refers to the locus of integration of the nucleic acid sequences encoding mouse ADAM6a and ADAM6b proteins.

12. In view thereof, document (37) could and should have been filed at the proceedings before the first instance, not in appeal proceedings. The admission of this document in appeal proceedings would be at odds with the primary object of the appeal proceedings, namely to review the decision under appeal in a judicial manner and not a mere continuation of the first instance proceedings (cf. "Case Law of the Boards of Appeal of the EPO", 10th edition 2022, V.A.1.1).

13. Therefore, there was no room to admit document (37) into the appeal proceedings.

Consideration/admission of further new evidence filed in appeal proceedings

14. Both appellants submitted further new evidence in appeal proceedings. In the board's communication, the board also insofar provided a provisional opinion on the relevance of this new evidence and their consideration/admission in appeal proceedings. At the oral proceedings before the board, there was no further discussion regarding this issue.

15. In view thereof and since none of these documents is relevant for the decision, the question of consideration/admission of any of these documents in the appeal proceedings can be left open.

Document (11) and the status of document (11)' as prior art

16. According to Dr Murphy (document (13)), document (11) is a copy of the slides used by him during the presentation held on 3 November 2009 at Hinxton, UK. The presentation with the title "BAC-based Modifications of the Mouse Genome: The Big and the Backward" took place at the Wellcome Trust in an advanced course entitled "Wellcome Trust Advanced Course: Genome Manipulation of ES Cells". According to Dr Murphy, neither hard copies were handed out to the audience nor electronic copies of the slides were distributed (cf. page 2, point 5 of document (13); see also page 13 of Dr Meng (Amy) Li's witness testimony annexed to the Minutes of the oral proceedings at first instance).

17. It is common ground between the parties that Dr Murphy's presentation took place on the date and place described above. In addition to Dr Murphy's

declaration, there is also other evidence on file provided by several attendees of Dr Murphy's presentation to support that this presentation took place as described (documents (23) to (28) and (30), and Dr Meng (Amy) Li's witness testimony).

18. Although appellant I has raised doubts on whether all slides were actually shown to the audience during Dr Murphy's presentation, the fact remains that a presentation with the title indicated above and subject-matter related thereto was presented by Dr Murphy to an audience on the above date and place. In this context, decisions T 1212/97 of 14 May 2001 and T 2003/08 of 31 October 2012 have been cited by appellant I to illustrate "the correct legal standard" to apply.

18.1 These decisions held that the standard of proof for ascertaining the contents of an oral disclosure to be high, "[w]hat has been said, or to use the terms of Article 54(2) EPC, what has been "made available to the public" has to be put beyond reasonable doubt" (cf. T 2003/08, point 37 of the Reasons; T 1212/97, point 2 of the Reasons). Both decisions acknowledge that "the amount of evidence necessary to establish the content of an oral presentation beyond reasonable doubt is to be judged on a case to case basis, i.e. it depends on the quality of the evidence in each case" (cf. T 2003/08, point 38 of the Reasons; T 1212/97, point 4 of the Reasons).

18.2 In decision T 1212/97, the board stated that "[t]he lecturer's evidence can be taken as defining the maximum amount of knowledge that may have conveyed to the audience, but cannot be relied on to establish even what minimum of new knowledge was necessarily conveyed

to the audience". Therefore, the lecturer's evidence by itself was considered not to be sufficient in their case. The board went on to state that "[i]nformation appearing in each of the contemporary written notes made at the lecture by at least two members of the audience can usually be regarded as sufficient" (cf. T 1212/97, points 3 and 4 of the Reasons).

18.3 The relevance of contemporary written notes in the context of an oral/ephemeral disclosure has also been emphasized in decision T 2003/08 (point 39.2 of the Reasons). However, the board also stated that "there may be circumstances where evidence from the lecturer and only one member of the audience is convincing enough to reach the standard of proof - i.e. beyond reasonable doubt" (cf. T 2003/08, point 42 of the Reasons).

19. There is no need to take a stand on the question which standard of proof to apply, if different standards of proof should be applied in proceedings before the boards, depending on the context, and if "proof beyond reasonable doubt" is indeed the right yardstick. There is also no need to take a stand on the question if the categorical reference to contemporary written notes made at a lecture by at least two members of the audience so as to "usually" be sufficient (see again T 1212/97, point 4 of the Reasons) is compatible with the principle of free evaluation of evidence.

What is decisive is that, in view of the evidence before the first instance department or the board in an individual case, the deciding body is persuaded that a particular oral disclosure has taken place and a particular information has been conveyed to the audience, or not.

The circumstances of the present case are such that the opposition division's conclusions cannot be followed.

19.1 In the present case, slides 23 to 26 of Dr Murphy's presentation - referring to the presence of poor male fertility in the homozygous transgenic mice and the role of the ADAM6 gene to restore male fertility, are relevant. Although according to Dr Murphy, all slides were shown to the audience (cf. page 3, point 9 of document (13)), the opposition division, after assessing all evidence on file, considered it to be "very likely" but that "still this fact could not be finally proven beyond reasonable doubt" (cf. page 13, point 3.24 of the decision under appeal). Be that as it may, this evidence is from the lecturer himself and thus, may by itself not be sufficient to proof that the relevant slides were indeed shown.

19.2 It is worth noting here that, to the best of Dr Murphy's recollection, the presentation took less than one hour, i.e. the 58 slides reproduced in document (11) were shown in less than one hour (cf. page 3, point 9 of document (13); see also page 12, last paragraph of Dr. Meng (Amy) Li's testimony).

The "manner or speed of presentation may affect the comprehensibility of a lecture" (cf. T 1212/97, point 4 of the Reasons), and the amount of material/information covered by the lecture may be another factor to affect said comprehensibility. Therefore, "it is the wrong approach to try and answer successive factual questions such as whether a slide was shown at or not, and then what the audience would understand from it. The board is concerned with the information content made

available to the public" (cf. T 1212/97, point 7 of the Reasons).

19.3 The current board agrees therewith. As stated by appellant I, the relevant question is not what was presented or shown to the audience but what was actually conveyed to the public, i.e. what the audience took away from Dr Murphy's presentation. In line with the examples in the case law, providing (at least) a contemporary written note from a member of the audience present at this presentation might be an important and decisive element in the evaluation of evidence (cf. T 1212/97, point 7 of the Reasons; T 2003/08, point 42 of the Reasons).

20. None of the declarations on file (documents (23) to (28), (30), and Dr Meng (Amy) Li's witness testimony) is indeed a contemporary written note taken at Dr Murphy's presentation. Although shortly after Dr Murphy's presentation some members of the audience were asked to bring such contemporary notes to a meeting organised by Professor Bradley on 5 November 2009 (cf. page 5, points 13 and 15, and Exhibits 2 and 3 of document (24)) and some members acknowledge in their declarations to have taken such notes, none of them has actually been ever produced (cf. page 2, point 8 of document (25); page 2, point 8 of document (26); page 1, point 4 of document (27); page 1, point 4 of document (28); page 13 of Dr Meng (Amy) Li's witness testimony).

21. Nonetheless, the opposition division took "into account the amount and quality of all evidence produced, particularly the reliability of the witness recollections and the high relevance of D11" and, on the basis of all this evidence, concluded that the

information content referred to as D11' in the decision under appeal was made available by Dr Murphy's presentation (cf. pages 13 and 14, points 3.25 and 3.26 of the decision under appeal).

The board however cannot agree therewith.

21.1 Neither the amount nor the quality of all this evidence or, for that case, the reliability of the witness recollection taken at the oral proceedings at first instance, needs to be assessed by the board. As stated above, whilst all this evidence might be used to support, complement, interpret or explain the content of a contemporary written note, none of them might be as reliable as such a contemporary note.

21.2 According to Professor Bradley's declaration, he spoke to Dr Murphy on the evening of the presentation's day, i.e. 3 November 2009, and their conversation "was focused on deletions of BACs during integration". This was so because, as acknowledged by Professor Bradley, "my laboratory had noted this issue and described it in one of our prior publications" (cf. page 5, point 12 of document (24)). On the next day, and after this conversation, Professor Bradley called a laboratory meeting and an invitation was sent by his secretary on 4 November 2009 to, *inter alia*, some members of the audience of Dr Murphy's presentation, who are signatories of the declarations/statements of documents (23) and (26) to (28) on file (cf. page 5, point 13, and Exhibit 2 of document (24)).

21.3 On the morning of the scheduled laboratory meeting, Dr Friedrich, the signatory of the statement of document (23), sent an electronic message (e-mail) to the participants of this meeting, requesting them to

put their impressions on Dr Murphy's presentation down in writing and to reply to the e-mail "with the contents of your notes from the talk or what you remember he said". In the same e-mail, he acknowledged to have briefly discussed with Professor Bradley "what was learned from the Regeneron fellow [i.e. Dr Murphy] at the recent advanced course" (cf. page 5, point 15, and Exhibit 3 of document (24)).

21.4 Following the laboratory meeting, Professor Bradley compiled on 6 November 2009 a summary of "what we had learnt from Dr Murphy's presentation" that was circulated to the participants of this meeting on 9 November 2009 (cf. page 5, point 16, and Exhibits 4 and 5 of document (24)). None of these documents is thus contemporary to Dr Murphy's presentation and all of them were produced after conversations, discussions and a meeting that took place well after Dr Murphy's presentation among members of the audience who, to use Professor Bradley's own words, "had a particular interest in attending the 2009 presentation by Dr Murphy from Regeneron, because ... had great relevance to our own work" (cf. page 3, point 8 of document (24)).

21.5 Indeed, Dr Meng (Amy) Li, the signatory of the statements of documents (25) and (30), confirms the interest and relevance of Dr Murphy's presentation in her witness testimony (cf. *inter alia*, pages 8 and 9 of said witness testimony). There is no doubt that the skills of these members of the audience, namely PhD students, post-doctoral researchers and professors leading research groups, are those acknowledged in the case law to define a person skilled in the art in the field of biotechnology, if not even higher (cf. "Case Law", *supra*, I.D.8.1.3). Nor can there be any doubt

that, in view of the interest/relevance of Dr Murphy's presentation, conversations, discussions and comments on this presentation took place among such a group of skilled persons immediately after this presentation (as acknowledged by Dr Meng (Amy) Li in her witness testimony; cf. page 19, third witness' reply of said testimony). Such discussions also took place shortly after the presentation between Professor Bradley and Dr Murphy himself (cf. point 21.2, *supra*), and before the laboratory meeting arranged by Professor Bradley (as acknowledged by Dr Friedrich; cf. point 21.3, *supra*).

21.6 In fact, a laboratory meeting for such a group of skilled persons to be effective and rewarding usually requires, and it is to be expected, from the participants of such a meeting to attend it with a certain degree of preparation and readiness to provide a positive contribution (cf. page 19, last sentence of second witness' reply of Dr Meng (Amy) Li's testimony). This might have been the purpose of Dr Friedrich's e-mail sent on the day of the laboratory meeting at issue (cf. point 21.3, *supra*). It is worth noting here that, whilst Dr E-Chiang Lee, a participant of said laboratory meeting, acknowledges to have presented "some slides on our research progress" at this meeting and that Dr Amy (Meng) Li was a participant of this meeting (cf. page 2, point 7 of document (28)), Dr Amy (Meng) Li did not recollect her attendance to this meeting during her witness testimony at first instance (cf. paragraph bridging page 24, last paragraph to page 25, second witness' reply to said witness testimony).

22. The fact that all these discussions, conversations and comments took place after Dr Murphy's presentation and

before the compilation of a summary of this presentation by Professor Bradley (cf. Exhibits 4 and 5 of document (24)) as well as before the statements/ declarations of the members of the audience of Dr Murphy's presentation on file (documents (23) to (28), and (30)), is to be taken into account. This has not been done by the opposition division. After all, the board can thus not agree with the opposition division's conclusion that the relevant "information content" was indeed made available and conveyed to the audience in Dr Murphy's presentation.

23. Since, as a consequence, document (11) does not form part of the state of the art, no information can be derived therefrom nor, for that case, from Dr Murphy's presentation, let alone an "information content" that is "proven beyond reasonable doubt" (see pages 13 and 14, points 3.24 to 3.26 of the decision under appeal). Thus, the so-called document (11)' does not form part of the state of the art.

24. In the light of the above considerations, neither document (11) nor document (11)' form part of the state of the art within the meaning of Article 54(2) EPC.

Main request (Claims as granted)
Article 100(c) EPC (Article 123(2) EPC)

25. On page 16, section 2 of the decision under appeal, the opposition division considered the arguments of the parties on added subject-matter and concluded that the claims of the main request fulfil the requirements of Article 123(2) EPC.

26. In the board's communication, it was stated that "[i]n section 4 of the statement of grounds of appeal and

section 3 of the reply to appellant I's grounds of appeal, appellant II appears to contest this finding by referring generally to the reasons set forth in the notice of opposition and the subsequent written and oral submissions in opposition proceedings. However, it is not specified expressly why the opposition division's decision on Article 123(2) EPC should be incorrect". With reference to Article 12(3) RPBA 2020, the board further stated that a "sweeping reference to the submissions in the previous proceedings is not sufficient to substantiate an objection to findings in a decision under appeal. In the absence of sufficient substantiation, the objection cannot be taken into account by the board for its decision on the appeal".

27. At the oral proceedings before the board, the parties relied on their written submissions and there was no further discussion regarding this issue.

28. Thus, the ground for opposition under Article 100(c) EPC in conjunction with Article 123(2) EPC is not prejudicial to the maintenance of the patent.

Article 100(b) EPC (Article 83 EPC)

29. The compliance of the main request with Article 83 EPC was not assessed in the decision under appeal. However, as regards auxiliary request 2, the opposition division with reference to Example 8 of the patent application and documents (3) and (7), held that a skilled person, with the guidance of the patent application, could test and identify without undue burden homologs, orthologs and functional fragments as cited in the claims, i.e that are able to restore the functionality of the mouse ADAM6 protein (cf. pages 30 and 31, points 4.3 and 4.4 of the decision under appeal).

30. Whilst in appeal appellant I provided further arguments to support this decision, appellant II contested it arguing that the disclosure of the patent application did not provide any guidance on homologs, orthologs and functional fragments of the mouse ADAM6 protein that could restore fertility, nor on insertions sites for ADAM6 other than the specific one exemplified in the patent application.

31. The board agrees with appellant I that the terms "homologs" and "orthologs" in the context of the claims of the main request cannot be interpreted narrowly.

31.1 In paragraph [000234] of the patent application, homologs and orthologs are defined as proteins that are "at least 89% to 99% identical to a mouse ADAM6 protein". No inventive skill or undue burden is required for a skilled person to assess whether a protein fulfils this degree of identity, regardless of whether this protein is obtained from natural sources or *in vitro* methods. Nor does the production of such a protein, starting from the known mouse ADAM6 protein, require any particular skill.

31.2 The opposition division referred to document (7) and stated that human ADAM6 is a pseudogene, but considered that the patent application and the prior art provided sufficient guidance for the skilled person to achieve suitable homologs and orthologs of the mouse ADAM6 protein (cf. page 30, point 4.3, last full sentence and sentence bridging to page 31 of the decision under appeal). Indeed, paragraph [000230] of the patent application refers to the superfamily *Muroidea* and several families related thereto, such as *Calomyscidae, Cricetidae, Muridae*, etc., all of them are appropriate

starting candidates for the skilled person to look for natural homologs of the mouse ADAM6 gene/protein, either by wet-lab or *in silico* methods (see also, in this context, paragraph [000276]). Likewise, if the term ortholog is to be narrowly understood, namely as a gene/protein in a different species that evolved from a common ancestral gene, a skilled person would start from closely related species. Nothing more than routine work, even though time consuming and tedious, would be required.

31.3 The fact that other members of the ADAM family, such as ADAM2, ADAM3 and ADAM4, are not capable to restore male fertility in ADAM6 deleted mice, even though they might be involved in the fertilisation process and have a role in male reproduction (testicular germ cells and sperm maturation), is not relevant. Document (3) refers to 33 known ADAM members, 18 of them being expressed exclusively or predominantly in the male reproductive tissues, wherein these 18 members are divided into phylogenetically three major groups, namely ADAM group I, II and III. ADAM6 is described as a member of group I together with, among others, ADAM1 and ADAM4 (cf. page 1001, left-hand column of document (3)). As described in this document, the specific functions and roles of each ADAM member are not necessarily identical and interchangeable to those of other ADAM members. Thus, other members of the ADAM family would, and are, not necessarily expected to be (functional) homologs and/or orthologs of the known mouse ADAM6 protein.

31.4 As regards "functional fragments", a reasonable interpretation of this term in the context of the claims requires neither the disclosure nor the characterisation of a so-called minimal functional fragment of the known mouse ADAM6 protein with

determination and identification of the regions, domains and/or residues of this protein that are functionally essential for restoring mice fertility. The term is not limited to short or very short fragments of the known mouse ADAM6 protein, but embraces a large number of long fragments that may well be, at least most of them, functionally active.

31.5 In this respect, as stated by the opposition division, the patent application, in particular Example 8, provides sufficient information for the skilled person to check and assess the functionality of such homologs, orthologs and fragments of the mouse ADAM6 protein. Appellant I has cited several paragraphs of the patent application that disclose suitable tests for carrying out such analysis (cf. paragraphs [000393] to [000398]).

31.6 There is no evidence on file showing that homologs, orthologs and functional fragments of the known mouse ADAM6 protein such as those referred to in the paragraphs above, are not available to the skilled person or else that inventive skill or undue burden are required from the skilled person to achieve them. Even if doubts may have been raised by appellant II, they are not serious and supported by verifiable facts as required by the case law (cf. "Case Law", *supra*, II.C. 7.1.4; *inter alia*, T 19/90, OJ EPO 1990, 476).

32. As regards the insertion sites for ADAM6, the board observed in its communication that appellant II had not put forward any arguments against the findings of the opposition division on this issue. Neither were such arguments put forward at the oral proceedings before the board nor were the board's observations further discussed at these oral proceedings.

33. Therefore, the ground for opposition under Article 100(b) EPC in conjunction with Article 83 EPC is also not prejudicial to the maintenance of the patent.

Article 100(a) EPC (Article 54 EPC)

Entitlement to priority - Transfer of priority right

34. In the communication sent to the parties, the board observed that the findings of the opposition division in section 2 on pages 4 to 7 of the decision under appeal, namely the entitlement to priority for the subject-matter of the granted claims (transfer of priority right), were contested in appeal only by sweeping reference to the submissions made at first instance (cf. page 8, point 6 of appellant II's grounds of appeal, and section 3.1 of appellant II's submission of 1 February 2018). With reference to Article 12(3) RPBA 2020, the parties were informed that this objection could not be taken into account by the board for its decision (see also, "Case Law", *supra*, V.A. 2.6.5). At the oral proceedings before the board, the parties relied on their written submissions and there was no further discussion regarding this issue.

35. Therefore, the findings of the opposition division as regards this issue, namely that "at the date of filing of the application from which the opposed patent derives, Regeneron is considered to be the successor-in-title of the priority application and is therefore entitled to claim priority from it", are maintained (cf. page 7, section 2.3.12, last sentence, in the decision under appeal).

Relevant prior art and novelty

36. With reference to documents (1), (8), (9), (11)' and (14), the opposition division held the main request to fulfil the requirements of Article 54 EPC (cf. page 16, point 3 of the decision under appeal).

37. In the written phase of the appeal proceedings, appellant II contested this decision by reference to submissions made at first instance (page 8, points 4 and 7 of appellant II's statement of grounds of appeal, and page 6, point 3.1 of appellant II's submissions dated 1 February 2018). At the oral proceedings before the board, the parties only referred to, and relied on, their written submissions on Article 54 EPC. Upon request, appellant II clarified that no objection was raised under Article 54 EPC against the main request based on document (14) (cf. page 3, second paragraph of the Minutes of the oral proceedings).

38. In view of the parties' submissions in appeal proceedings, the objection raised under Article 54 EPC based on documents (1), (8) and (9) cannot be taken into account by the board for its decision (Article 12(3) RPBA 2020). Documents (11) and (11)' do not form part of the state of the art within the meaning of Article 54(2) EPC (*supra*) and thus, they are not relevant for the purpose of Article 54 EPC.

39. Therefore, the ground for opposition under Article 100(a) EPC in conjunction with Article 54 EPC is likewise not prejudicial to the maintenance of the patent.

Article 100(a) EPC (Article 56 EPC)

40. The opposition division identified document (11)' as the closest prior art and, starting therefrom, formulated the objective technical problem as "the provision of means to restore fertility in IgH locus modified mice that show a reduced fertility". With reference to "databases entries" and to documents (4) and (7), the main request was held not to fulfil the requirements of Article 56 EPC (cf. page 21, point 4.3 of the decision under appeal). Document (1) was cited as an alternative closest prior art in the context of auxiliary request 2. According to the opposition division, a skilled person, starting from document (1), could arrive at the claimed subject-matter only with hindsight (cf. page 29, point 3.5 of the decision under appeal).

41. Since documents (11) and (11)' do not form part of the state of the art (Article 54(2) EPC) (*supra*), they are not relevant for the purpose of Article 56 EPC.

42. In appeal proceedings, the parties identified document (1) as the closest prior art and acknowledged the relevance of Example 3 of this document.

43. Example 3 describes a method for obtaining a transgenic mouse producing "hybrid antibodies containing human variable regions and mouse constant regions ... accomplished by a direct, *in situ* replacement of the mouse variable region genes with their human counterparts" (cf. paragraph [0213]). This method is based on the "large (DNA) targeting vector for use in eukaryotic cells (LTVECs)" disclosed in document (1) (cf. *inter alia*, paragraphs [0002], [0009] to [0013], [0026]). Example 3 refers to a first and second steps

using LTVEC1 (Figure 4D) and LTVEC2 (Figure 4C), respectively (cf. paragraphs [0224] and [0025]). After subsequent steps (cf. paragraphs [0226] to [0228]), it is stated that "[t]he final steps in creating the human variable/mouse constant monoclonal antibody producing-mouse will be performing the equivalent variable region substitutions on the lambda and kappa light chain loci and **breeding** all three hybrid loci to homozygocity together in the same mouse" (emphasis by the board) (cf. paragraph [0229]).

44. The technical difference between the claimed mouse and those obtained by the method described in Example 3 of document (1) is that the former comprises the "nucleic acid sequences encoding a mouse ADAM6a protein, or an ortholog or homolog or functional fragment thereof that is functional in a male mouse, and a mouse ADAM6b protein, or an ortholog or homolog or fragment thereof that is functional in a male mouse". The effect of this difference is that the claimed homozygous transgenic male mice are fertile (cf. page 11, point 8.2 of appellant II's statement of grounds of appeal).

45. Starting from this prior art, appellant II formulated the objective technical problem as the provision of "an approach for generating a breeding colony of homozygous mice, which are useful for producing therapeutic antibodies" (cf. page 11, point 8.2 of appellant II's statement of grounds of appeal).

46. As stated above, Example 3 of document (1) already refers to the breeding of the resulting (final) transgenic mice. Indeed, after the first and second steps and before the final steps described in this example, there are several references to a possible breeding of the (intermediate) transgenic mice (cf.

paragraphs [00226] and [0228]). The "production and maintenance of a breeding mouse colony" is also explicitly mentioned in the description of the method of Example 3 (cf. paragraph [0219]). Thus, document (1) already provides a solution to the objective technical problem formulated in the above terms; document (1) provides an approach or a method for generating a breeding colony of homozygous mice useful for producing the (hybrid) antibodies of interest.

47. Moreover, there is no suggestion, let alone an explicit reference, to the presence of any problems or technical difficulties in the breeding of such a mouse colony in Example 3 or, for that case, in the whole disclosure of document (1). It is thus arguable whether a skilled person, starting from document (1), would have identified and recognised the infertility of the transgenic male mice obtained by the method described in this document as a technical problem.

48. In this context, appellant II stated that "fertility of the mice is inextricably linked to setting up a breeding colony". And, with reference to G 1/92 (OJ EPO 1993, 277), appellant II argued that, when carrying out the method described in document (1), in particular the production or generation of a breeding colony of the homozygous transgenic mice, a skilled person would necessarily have become aware and identified the infertility of the homozygous transgenic male mice. The results shown in Table 9 of the patent were cited to support this argument.

49. The data in Table 9 show a "representative breeding comparison of $H^{+/+}\kappa^{+/+}$ and $H^{+/+}A6^{res}\kappa^{+/+}$ mice" (cf. paragraph [0354]), wherein the former are mice homozygous for both human heavy chain variable gene

loci and human κ light chain variable gene loci, and the latter are (rescued) mice having the ectopic mouse genome fragment encoding the mouse ADAM6a and ADAM6b genes with both alleles of the human chain locus (cf. paragraph [0341]). The infertility of the $H^{+/+}\kappa^{+/+}$ homozygous transgenic male mice shown in Table 9 may be severe (cf. paragraph [0179]), but it is not absolute or total, because successful litters with offspring are obtained, even though in lower numbers than that of the (rescued) $H^{+/+}A6^{res}\kappa^{+/+}$ homozygous transgenic male mice.

50. Thus, a skilled person would have faced, if at all, a reduction in fertility, as acknowledged in the patent (cf. *inter alia*, paragraph [0009]). However, several methods for maintenance of the mouse strain would have also been available to a skilled person, as also acknowledged in the patent (cf. paragraphs [0173] to [0176]), not all of them resulting in a reduction of fertility that could have been immediately identified and recognised by a skilled person. The board thus agrees with appellant I that, when breeding the mouse colony of interest by following the teachings of document (1), the identification of the infertility - actually a reduced or poor fertility - in the homozygous transgenic male mice would not necessarily be straightforward and arguably involves or requires certain skills from the average person working in the field.

51. In view thereof, the infertility or reduced fertility cannot be recognised as part of the objective technical problem. A formulation of the objective technical problem in such terms, when starting from the closest prior art document (1), requires the benefit of hindsight knowledge of the patent in suit. Therefore, starting from this closest prior art, the objective

technical problem must be formulated in more general terms such as, in line with the technical problem formulated by appellant II above, the provision of an alternative approach or method for generating a breeding colony of homozygous mice, which are useful for producing therapeutic antibodies. The subject-matter of the main request, in particular that of claim 1, solves this technical problem as shown by the disclosure and results provided by the patent.

52. In absence of any hint or suggestion in the closest prior art document (1) leading the skilled person towards this solution, the claimed subject-matter would not have been obvious to a skilled person. As argued by appellant I and acknowledged also by the opposition division (cf. page 29, point 3.5 of the decision under appeal), the combination of the closest prior art document (1) with document (7) would have required the benefit of hindsight knowledge of the patent; especially when bearing in mind that, as stated by Professor Bradley, no genes had been identified or were known to be present (embedded) within the long stretches of DNA making up the murine immunoglobulin loci (cf. page 5, point 14 of document (24)), certainly not a gene or a nucleic acid sequence encoding a member of the ADAM family. As an aside, it is also worth noting here that, as reported in document (7), members of this family had been found to be active in various biological processes other than fertilization, such as neurogenesis, myogenesis, and inflammatory response (cf. page 636, left-hand column, first paragraph).

53. Therefore, the ground for opposition under Article 100(a) EPC in conjunction with Article 56 EPC is, finally, also not prejudicial to the maintenance of the patent.

Referral to the Enlarged Board of Appeal

54. According to Article 112 EPC, the Board of Appeal shall, during proceedings on a case and either of its own motion or following a request from a party to the appeal, refer any question to the Enlarged Board of Appeal if it considers that a decision is required for the purpose of ensuring uniform application of the law or for a point of law of fundamental importance. In the present appeal, none of these cases arises.

55. In the present appeal, the case law referred to by the parties regarding oral or ephemeral disclosures, in particular decisions T 1212/97 and T 2003/08, is not divergent and does not provide opposite guidance. Both decisions, and the case law in general, outline and emphasise the role and relevance of contemporary notes taken by (at least) a member of the audience during these oral or ephemeral disclosures as essential means of (supporting) evidence of the actual content and/or merits of these ephemeral disclosures. There is thus neither a need to ensure uniform application of the law nor a need to clarify or determine a point of law of fundamental importance.

56. Above all, and as outlined above, the specific circumstances of the case in hand allow for the conclusion that the relevant "information content" of document (11)' was not conveyed to the audience of Dr Murphy's presentation. There was no need to take a general stand on the value of contemporary notes, going beyond the case at hand, and on the required standard of proof.

57. Thus, there is no room to refer any question to the Enlarged Board of Appeal on this issue.

Request for reimbursement of the appeal fee

58. Appellant I requests the reimbursement of the appeal fee arguing that the opposition surprised the parties by the "creation of a new piece of evidence or prior art", namely document (11)', at a late stage of the proceedings. This was a substantial procedural violation within the meaning of Rule 103(1)(a) EPC that justified the reimbursement of the appeal fee.

59. The board cannot follow this line of argument.

59.1 As regards the "creation of a new piece of evidence or prior art", appellant I themselves acknowledge that this evidence was "created" on the basis of existing evidence, for simplicity. Document (11)' is not a new piece of evidence as such or a new prior art document. The content of document (11)' results from the conclusions made by the opposition division of Dr Murphy's presentation, i.e. the information which according to the opposition division the members of the audience would have taken away from Dr Murphy's presentation of the slides reproduced in document (11).

59.2 Document (11) was filed with the Notice of opposition and, in its preliminary opinion, the opposition division had already drawn the parties' attention to the ephemeral character of such a presentation and referred also to the case law regarding oral or ephemeral disclosures, including the decisions T 1212/97 and T 2003/08. The parties were informed that "the slides alone are not a proof beyond any reasonable doubt that indeed the information" at issue was

actually made available to the public. The opposition division explicitly stated that it remained "an open question ... what was the exact content of the presentation held by Dr. Murphy and if said content was understood by the attendees" (cf. pages 7 to 9, points 2.4.2 to 2.4.5, and point 2.4.10 of the preliminary opinion issued on 29 July 2016).

59.3 At the oral proceedings and in view of the relevance of document (11), the opposition division established the "exact content of the presentation held by Dr. Murphy" in accordance with the case law referred to above (cf. pages 13 and 14, points 3.25 and 3.26 of the decision under appeal). Appellant I disagreed - and still disagrees in appeal proceedings - with the opposition division's established "exact content" of document (11), i.e. document (11)', noting and emphasizing the differences between the slides reproduced in document (11) and the information or content of document (11)' (cf. page 14, point 4.4 of the decision under appeal). The fact that the opposition division, after hearing the parties' arguments, was allegedly wrong in the establishment of the content of a piece of evidence or the disclosure of a document - in the present case, the content of an oral or ephemeral disclosure - might have constituted an error of judgment by the opposition division on the substance at issue, but it would in no case amount to a procedural violation, let alone a substantial one, within the meaning of Rule 103(1)(a) EPC (cf. "Case Law", *supra*, V.A.11.6.10.b)).

59.4 As regards the allegation that the parties were surprised, in view of the course of events at the first instance proceedings as described above, the parties were in fact informed of the relevant issue in the

opposition division's preliminary opinion and, during the oral proceedings at first instance, they were all given the opportunity to argue and present their arguments on this issue (cf. page 14, points 4.2 to 4.5 of the decision under appeal). Indeed, even though there was a request by the opponent/appellant II for a postponement of these oral proceedings, the patent proprietor/appellant I saw no reasons for such a postponement, and the opposition division provided the reasons for not allowing that request in the decision under appeal (cf. page 14, points 4.3 and 4.5 of the decision under appeal; see also page 4, fourth to sixth paragraphs of the Minutes of the oral proceedings at first instance).

59.5 The parties were thus heard by the opposition division and the decision under appeal was taken by the opposition division after having heard the parties' arguments regarding Dr Murphy's presentation of the slides reproduced in document (11) and the content conveyed to the audience of said presentation as established by the opposition division, namely document (11)'. Thus, the right of the parties to be heard under Article 113 EPC was also respected by the opposition division (cf. "Case Law", *supra*, V.A. 11.6.8).

60. Therefore, a reimbursement of appellant I's appeal fee is not justified (Rule 103(1)(a) EPC).

Order

For these reasons it is decided that:

1. The request of appellant II (opponent) for referral of questions to the Enlarged Board of Appeal is refused.

2. The decision under appeal is set aside.

3. The opposition is rejected.

4. The request of appellant I (patent proprietor) for reimbursement of the appeal fee is refused.

The Registrar: On behalf of the Chair (according to Art.8(3) RPBA 2020):

L. Malécot-Grob P. Julià

Decision electronically authenticated