Case No: A3/2016/1993 & A3/2016/1994

Neutral Citation Number: [2018] EWCA Civ 671
IN THE COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM HIGH COURT OF JUSTICE
CHANCERY DIVISION, PATENTS COURT
MR JUSTICE HENRY CARR
[2016] EWHC 87 (Pat)

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 28/03/2018

Before :

LADY JUSTICE ARDEN
LORD JUSTICE KITCHIN
and
LORD JUSTICE FLOYD

- -

Between :

REGENERON PHARMACEUTICALS, INC	**Appellant in Appeal No: A3/2016/1993** **Respondent in Appeal No: A3/2016/1994**
- and -	
(1) KYMAB LIMITED	**Respondent in Appeal No: A3/2016/1993** **Appellant in Appeal No: A3/2016/1994**
(2) NOVO NORDISK A/S	**Respondent in Appeal No: A3/2016/1993**

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Justin Turner QC with Joe Delaney and William Duncan (instructed by **Allen and Overy LLP**) for **Regeneron Pharmaceuticals, Inc**
Michael Tappin QC and James Whyte (instructed by **Powell Gilbert LLP**) for **Kymab Limited**

Hearing dates : 17- 20 October 2017

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Judgment

Lord Justice Kitchin:

1. The claimant and appellant ("Regeneron") appeals from the decision of Henry Carr J that European Patent (UK) No 1 360 287 and its divisional European Patent (UK) No 2 264 163 ("the 287 patent" and "the 163 patent" respectively) are invalid. The first respondent ("Kymab") cross-appeals against the judge's finding that its various strains of transgenic mice would infringe claims 5 and 6 of the 287 patent and claim 1 of the 163 patent if those patents had not been invalid. The second respondent, Novo Nordisk, although formally a party to Regeneron's appeal, has not taken any active part because Regeneron discontinued its infringement claim against it shortly before the trial. Its counterclaim for revocation survives, and for that purpose it adopts Kymab's submissions. This is the judgment of the court on the appeal.

2. The disclosure of the two patents is substantially the same, the material differences lying in the claims. For that reason we will refer to paragraphs in the description of the 287 patent, as the judge did.

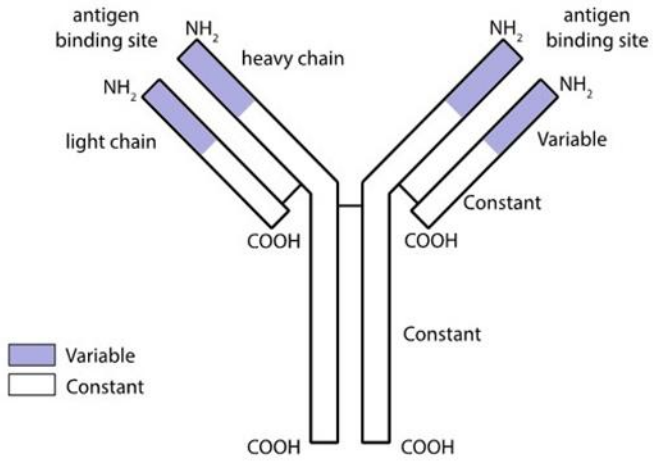
The technical background in outline

3. The patents are concerned with biotechnology, and in particular the production of human antibodies using transgenic mice. This is a field of great technical complexity. The judge began his judgment by describing some of the basic concepts in a passage which was not the subject of any dispute either before him or before us: see [2016] EWHC 87 (Pat) at [8]-[79] to which the reader can refer for the fine detail. In the summary which follows we draw heavily on that description. All of it formed part of the common general knowledge of the relevant skilled team at the priority date of the patents, which was 16 February 2001.

Antibodies

4. By the priority date, the potential uses of antibodies (also known as immunoglobulins) for use in treating human disease had been well recognised, and a number of different antibodies had been developed and approved for such use. These included mouse antibodies, chimeric antibodies and humanised antibodies.

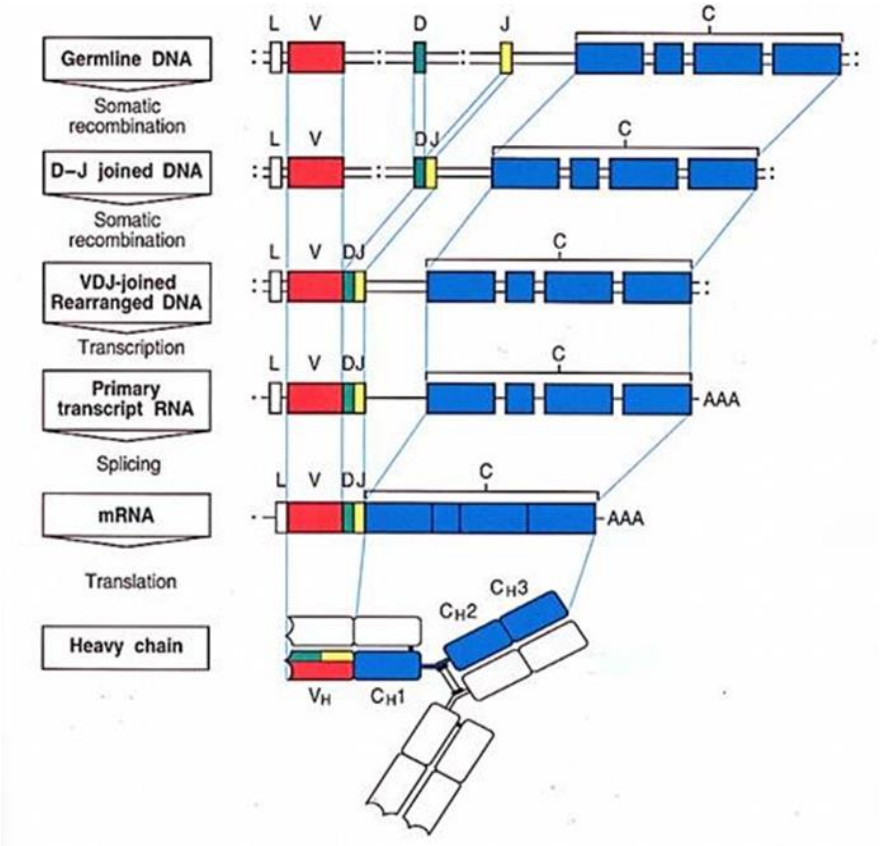
5. Antibodies all share a characteristic unit structure consisting of four polypeptide chains: two identical "heavy" chains and two identical "light" chains. The structure of an antibody (or "Ig") is traditionally depicted as having a Y-formation as shown below. The light and heavy chains are so called because the former are made up of only two immunoglobulin domains, while heavy chains are made up of four (or five). One end of both the heavy and light chains is variable in sequence and is known as the variable region, whilst the other end is constant in sequence (for a given class or isotype) and is known as the constant region.



6. The light chains are found in two isotypes, kappa ("κ" or "K") and lambda ("λ" or "L"). There is no known functional difference between antibodies having K and L chains but they are encoded by genes on different chromosomes.

7. The immunoglobulin genes, which are responsible for encoding the heavy and light chains, are not present in germline B cells in a form which is transcribed as a functional unit that encodes an antibody. Instead the relevant loci contain a series of segments which recombine during the B cell maturation process to form unique immunoglobulin heavy and light chain loci. These segments are known as variable (V), diversity (D), joining (J) and constant (C) gene segments. The heavy chain of an antibody has V, D, J and C segments. The light chains have only V, J and C segments.

8. During B cell development the V, D, and J segments (in the case of the heavy chain) and the V and J segments (in the case of the light chain) are joined together at the DNA level in a process known as VDJ recombination or somatic gene rearrangement. The eventual result is the production, after transcription and translation, of a huge array of different antibodies. The process of rearrangement, and then transcription and translation of the heavy chain of an antibody is shown schematically below:



9. After VDJ rearrangement, if a B cell is engaged by a fully mature and activated T cell of appropriate specificity, the B cell turns on activation induced cytidine deaminase which results in a wide spectrum of mutations in the antibody genes. Any given V segment may undergo anything from zero to dozens of mutations leading to numerous amino acid substitutions in the V regions. Favourable mutations confer an increase in affinity for the antigen, and B cells harbouring such mutations have a selective advantage, whereas deleterious mutations eventually ensure that the irrelevant B cells are eliminated. This process of mutation is known as somatic hypermutation and it improves still further the strength of the antibody response.

Antibodies in therapy

10. Antibodies incorporating mouse regions can create an immune response in humans (known as the HAMA response or human anti-mouse antibody response). To avoid the HAMA response it was known to be preferable to use an antibody that was fully human, as opposed to a murine antibody or a chimeric antibody (which has mouse variable regions and human constant regions) or a humanised antibody (which has the complementarity determining regions of a murine antibody grafted onto a human antibody).

11. The antibodies used for therapy at the priority date were monoclonal antibodies. Monoclonal antibodies were first described in Köhler and Milstein's 1975 paper in the journal Nature where they proposed a technique whereby a transformed (cancerous) B cell (i.e. myeloma) was fused with a normal antibody producing B cell to create a "hybridoma" that grows freely in vitro while continuing to produce an antibody. The hybridoma thus carried a single rearranged immunoglobulin heavy (“IgH”) gene, and a single rearranged immunoglobulin kappa (“IgK”) or lambda (“IgL”) gene, and

secreted antibody molecules of a single specificity into the culture supernatant. The ability to produce monoclonal antibodies specific to particular human receptors opened up the possibility of major advances in the treatment of disease.

Immunoglobulin locus size

12. The mouse and human Ig loci are of different sizes and contain different numbers of V, (D) and J gene segments. The human IgH locus is approximately 1,250 kb long. The human IgK locus is approximately 1,820 kb long, and the IgL locus is approximately 1,050 kb long and is located on chromosome 22.

13. The murine IgH locus is approximately 3 Mb in length. The murine IgK locus is approximately 3.2 Mb in length, and the murine IgL locus is smaller than the other loci at just 240 kb in length.

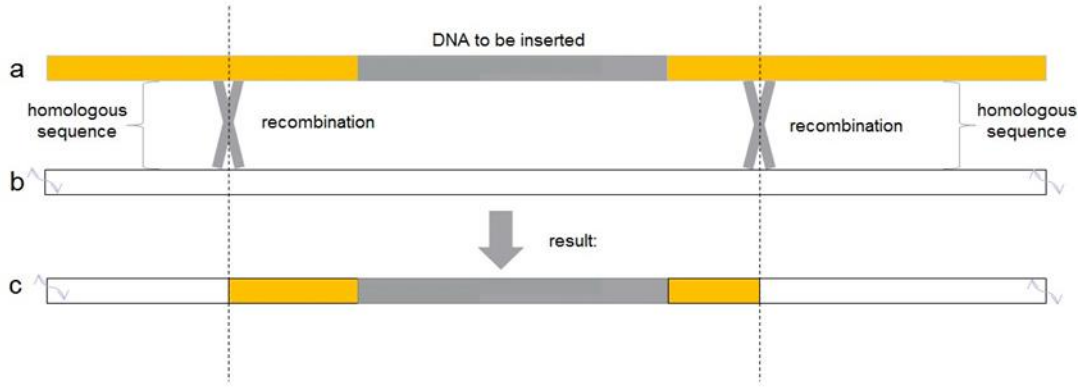
Transgenics

14. Transgenics is the term used to describe the introduction of a DNA fragment encoding a functional gene product into the germ line of a different species. In transgenics, one can take a human antibody gene and insert it into the mouse genome. If one challenges the mouse with a target antigen of interest the mouse will produce antibodies with its B cells. One can then screen for the B cell which is producing the antibody of interest.

15. Transgenics can be carried out broadly by two techniques. The first is random integration into the target genome, and the second is by targeted integration. Random integration was a technique practised by groups including those of Brüggeman, Lonberg and Abgenix before the priority date. Targeted integrations can be achieved by two methods, namely homologous recombination and site-specific recombination ("SSR").

16. Most methods of gene targeting involve rare events so it is very desirable to be able to select or screen for the desired gene alteration and to discriminate against the others. Most methods of gene targeting use embryonic stem ("ES") cells. Selectable markers can be used to select for ES cells in which the targeting construct has integrated.

17. Vectors to carry the DNA fragment to be incorporated into the host genome differ depending on whether they are to be used for homologous recombination or SSR. A targeting vector for homologous recombination includes flanking homology arms which are selected so that they are highly related and preferably identical in DNA sequence to the sequences that flank the target sequence being modified or replaced in the genome. The length and degree of sequence homology of the homology arms is an important factor in determining the efficiency of incorporation of the targeting construct. The process is illustrated in the following diagram:



18. A targeting vector for SSR uses a site-specific recombinase enzyme and its target sequence. The enzyme cleaves the DNA at a distinct target sequence and ligates it to the cleaved DNA of a second target of the same nature to generate a specific recombination event. The SSR sequence is first introduced into the host (by homologous recombination), followed by the use of the site for site-specific recombination. SSR can be used for targeted insertion or replacement of an endogenous gene in whole or in part. This system was particularly efficient at making deletions from the host genome.

19. Site directed integration by SSR can be achieved by recombinase-mediated cassette exchange ("RMCE"). This involves flanking the insert with two different recombination sequences and using these to exchange the insert with the sequence flanked by the sites in the host genome.

20. Traditional cloning techniques involved the use of the polymerase chain reaction ("PCR") to generate DNA fragments, and the use of DNA ligase to join these fragments together. These constructs could be used with bacterial plasmid vectors, but were limited to constructs of up to 20 kb in size due to a lack of restriction sites.

21. By the priority date, recombineering was a well-known alternative method for constructing targeting vectors. Recombineering is a form of bacterial homologous recombination that does not use restriction enzymes, and is therefore suited to the engineering of long complex DNA structures.

22. Bacterial artificial chromosomes ("BACs") are single-copy, high capacity plasmids propagated in *E. coli*. BAC clones can be used to clone large segments of genomic material, up to at least 300 kb in length. BACs are easy to handle and stable. BAC libraries provide a resource for storing, accessing and cloning genes of interest.

The experts

23. The judge heard evidence from four expert witnesses. For Regeneron, Professor Sir Martin Evans FRS gave evidence in the field of genetic engineering, and Professor Ploegh gave evidence in the field of immunology.

24. The judge found Professor Evans to be highly experienced in handling ES cells and that he had a broad knowledge of the relevant molecular biology techniques. The

judge found to him to be an exemplary witness who gave his evidence clearly and fairly.

25. As for Professor Ploegh, the judge rejected criticisms that he was not a specialist in B cell biology and lacked familiarity with the work of companies producing transgenic mice at the priority date. He also rejected criticisms that Professor Ploegh was biased in favour of Regeneron and that he took unmeritorious points.

26. For Kymab, Professor Stewart gave evidence in the field of genetic engineering and Professor Howard gave evidence in the field of immunology. Save for one matter which we do not think bears on this appeal, the judge rejected all criticism of Professor Stewart's evidence and found the manner in which he gave that evidence to be instructive and engaging, and the evidence itself to be of great assistance.

27. Professor Howard FRS is a leader in the field of immunology but had not worked on producing antibodies for use in therapy and was not a B cell specialist. Nevertheless, the judge found his evidence of great assistance.

The invention disclosed in the patents

28. The invention disclosed in the two patents in suit has two principal aspects. A first aspect is the *in situ* replacement of mouse variable region immunoglobulin gene segments with human variable immunoglobulin gene segments, maintaining the mouse constant regions, so as to create what is called the "reverse chimeric locus". A second aspect of the disclosure concerns methods which can be used to target, via homologous recombination, and modify, endogenous genes and chromosomal loci in eukaryotic cells.

29. The concept of the reverse chimeric locus is described in the patent as part of Example 3. At [0113] the patent refers to prior art transgenic mice being used to produce fully human antibodies. As it explains, endogenous genes are "knocked out" of mice, and the genes replaced with their human counterparts (including both variable and constant sequences) to produce entirely human antibodies. The specification goes on to say that mice producing fully human antibodies have a reduced immune response. It is suggested that this may be because human antibodies produced by transgenic mice with entirely human constructs have reduced affinity compared with mouse antibodies. Reduced affinity could affect B-cell maturation and survival.

30. In discussing these prior art transgenic mice the judge found that the patent was referring to mice with a fully human immunoglobulin locus developed by groups such as Brüggeman, Lonberg and Abgenix. It is important to recognise that, in these prior art mice, the human immunoglobulin variable gene segments (together with the human immunoglobulin constant segments) are inserted randomly into the mouse genome, resulting in fully human antibodies.

31. The specification then goes on to explain at [0115] that the transgenic mouse with the reverse chimeric locus produces antibodies with human variable regions and mouse constant regions. The resultant hybrid immunoglobulin loci undergo the natural process of rearrangement during B-cell development to produce hybrid antibodies. It is further explained that these hybrid antibodies are not the final therapeutic product because they contain mouse constant regions which would be liable to induce the

HAMA response. They can however be engineered to produce fully human antibodies in a subsequent step by replacing the mouse constant regions with human constant regions. In this way the specificity of the human variable region is retained and immunogenicity is avoided.

32. The specification also advances an explanation of why the antibodies generated by the new transgenic mouse are superior to antibodies generated by the prior art mice. The murine constant regions retained in the new mouse will interact more efficiently with the other components of the mouse B cell receptor complex. In addition, the murine constant regions will be more specific than human constant regions in their interactions with corresponding receptors on mouse cells and complement molecules. These interactions are important for a strong and specific immune response, for the proliferation and maturation of B cells and for affinity maturation of antibodies.

33. At [0117] the specification explains that, because there is a direct substitution of human V, D and J or just V and J regions for the equivalent regions of the mouse loci, all of the sequences necessary for proper transcription, recombination, and/or class switching will remain intact. These include the murine immunoglobulin heavy chain intronic enhancer, Em, and the immunoglobulin 3' enhancer region, both of which play important roles in recombination and expression.

34. Kymab no longer contends, as it did at the trial, that the reverse chimeric locus was an obvious advance over the prior art. Dr Yancopoulos, one of the inventors of the patents and the President and Chief Scientific Officer of Regeneron, gave unchallenged evidence before the judge, which he accepted, as to how the invention of the reverse chimeric locus came about. Before the priority date Regeneron was a customer of a company called Medarex who, in collaboration with Kirin, another well-known company in this field, had produced transgenic mice with additional transchromosomal components, but without a reverse chimeric locus. Regeneron was dissatisfied with the performance of Medarex fully human immunoglobulin transgenic mice, which were failing to produce antibodies to targets which were known to induce antibody responses in wild type mice. The mice were what has been described as "immunologically sick". This resulted in the need to inoculate many more mice with the target of interest in order to identify an appropriate antibody than would be the case with the wild type, and in some cases an antibody could not be identified at all. It occurred to Dr Yancopoulos that the problem could be addressed by retaining the mouse constant regions and creating a hybrid locus. Such a mouse would theoretically not only be much more efficient and optimised in its immune function but also simultaneously avoid all the inherent breeding problems seen in the Medarex and Kirin mice, in terms of having to account for multiple transgenic loci at multiple non-endogenous locations, as well as instability problems with the Kirin mini-chromosome.

35. Until Dr Yancopoulos introduced the idea to Medarex, no scientist there had raised the possibility of any solution similar to that proposed by him. In particular nobody raised the possibility that putting human variable segments into the endogenous mouse locus would have any advantage, or that retaining mouse constant regions would have any utility or advantage.

36. Dr Yancopoulos had his idea at a time when, as the judge found, the thinking of those skilled in the art was "unidirectional, narrowly focussed, myopically obsessed one might say, with the production of human antibodies".

37. Professor DeFranco, an eminent scientist in this field, served on the scientific advisory board of Abgenix between 1998 and 2004 when Abgenix produced transgenic mice called XenoMouse I and XenoMouse II. He gave unchallenged evidence that the idea of the reverse chimeric locus did not occur to him or, so far as his knowledge went, to anyone else associated with Abgenix. There was also similarly unchallenged evidence from Professor Ishida who worked at Kirin. Kirin produced transgenic antibodies in mice by chromosomal transfer, i.e. by introducing a human chromosomal fragment into the mouse. Kirin later collaborated with Medarex to produce the Kirin/Medarex mouse which comprised both transgenic and chromosomal components. He was aware of the immunological deficiency of these mice as compared with wild type, as well as the fact that the mice showed defects in class switching. The idea of the reverse chimeric locus never occurred to him or his colleagues. It was never suggested to him in the course of this work that these defects had anything to do with the nature of the human constant region and its interaction with the mouse B-cell receptor complex and this idea did not occur to him either.

38. The unexpected nature of the advantage of the reverse chimeric locus was subsequently recognised by Kymab in a 2014 paper which was published in the journal *Nature* entitled "*Complete humanization of the mouse immunoglobulin loci enables efficient therapeutic antibody discovery*" Lee, E-Chiang et al, Nature Biotechnology (2014), 32.4;356-363. Having described the randomly integrated transgenes of the prior art, the authors continued:

> "The technology used to establish these first-generation mice had several inherent limitations, including position effects due to the random integration of the transgene and upper limits on the length of the DNA that could be introduced into the mouse genome by means of zygote injection. As a result these mice had incomplete human antibody repertoires. In addition, these first-generation transgenes included both human variable and constant regions. Although these mice would be expected to produce fully human antibodies, there are sequence differences between human and mouse IgM constant regions and signaling proteins Igα and Igβ. As a result, during the stage when an antibody functions as a B-cell receptor (BCR), the interaction between the human constant region and the mouse signaling proteins Igα and Igβ may not be optimal, and reduced signaling could limit antibody class switching and affinity maturation, as well as B-cell differentiation into mature antibody-secreting plasma cells."

39. The invention of the reverse chimeric locus was accordingly, a striking, radical and highly original departure in the art.

40. The second aspect of the invention disclosed in the patents in suit is a novel molecular biology technique. As explained at [0002] the patent describes methods which target,

via homologous recombination, and modify endogenous genes and chromosomal loci in eukaryotic cells. As set out at [0010] these methods involve:

i) bacterial homologous recombination to engineer a desired genetic modification within a large cloned genomic fragment to create large targeting vectors ("LTVECs") for use in eukaryotic cells;

ii) introducing these LTVECs into eukaryotic cells to modify the endogenous chromosomal locus of interest; and

iii) using an assay for modification of allele ("MOA") of the parental allele that does not require sequence information outside of the targeting sequence, such as, for example, quantitative PCR to determine those eukaryotic cells in which the targeted locus has been modified as desired.

41. In summary, therefore, the patent is teaching an approach which uses LTVECs in combination with a particular assay, the MOA. At [0003] it explains that LTVECs have advantages over existing methods in that they can be rapidly and conveniently generated from available libraries of large genomic fragments (such as BAC libraries). Larger modifications as well as modifications spanning larger genomic regions can be more conveniently generated. Further, longer regions of homology increase the targeting frequency of "hard to target" loci.

42. As for the MOA assay, the specification explains at [0078] that prior art assays could not be used to detect successful homologous recombination events in eukaryotic cells when using LTVECs because of the long homology arms. The use of LTVECs is made possible by the MOA assay which detects unmodified alleles, so that a cell in which one allele has been modified can be distinguished from a cell in which neither has been modified. Thus at [0091] the patent explains:

> "In contrast to traditional methods, in which a difference in restriction fragment length spanning the entire homology arm or arms indicated the modification of one of two alleles, the quantitative TaqMan® method [an example of the MOA assay] will detect the modification of one allele by measuring the reduction in code number (by half) of the unmodified allele. Specifically the probe detects the unmodified allele and not the modified allele."

43. The assay is based on the fact that ES cells are diploid and so contain two copies of the allele of interest. An ES cell in which the native allele has been successfully altered loses one copy of that allele whereas ES cells which have been the subject of unsuccessful modification retain both copies of that allele. The MOA assay detects those ES cells in which the loss of one native allele has occurred, and it does so by measuring the reduction in the frequency of the unmodified allele from two to one. The approach obviates interference in the analysis by the integrated targeting vector and it facilitates the use of large targeting vectors.

The claims

44. Claim 1 of the 163 patent is in the following terms:

> "1. A transgenic mouse that produces hybrid antibodies containing human variable regions and mouse constant regions, wherein said mouse comprises an *in situ* replacement of mouse VDJ regions with human VDJ regions at a murine chromosomal immunoglobulin heavy chain locus and an *in situ* replacement of mouse VJ regions with human VJ regions at a murine chromosomal immunoglobulin light chain locus."

45. Claims 1, 5 and 6 of the 287 patent are as follows:

> "1. A method of modifying an endogenous immunoglobulin heavy chain variable region gene locus in an isolated mouse embryonic stem (ES) cell by an *in situ* replacement of V, D, and J gene segments of the endogenous locus with orthologous human V, D and J gene segments, to create a modified immunoglobulin locus that produces hybrid antibodies containing human variable regions and mouse constant regions, said method comprising:
>
> a) obtaining a large cloned genomic fragment greater than 20kb containing orthologous human V, D, and J gene segments;
>
> b) using bacterial homologous recombination to genetically modify the cloned genomic fragment of (a) to create a large targeting vector for use in a mouse ES cell (LTVEC);
>
> c) introducing the LTVEC of (b) into a mouse ES cell to replace said V, D, and J segments *in situ* with the orthologous human V, D and J gene segments; and
>
> d) using a quantitative assay to detect modification of allele (MOA) in the mouse ES cell of (c) to identify a mouse ES cell in which said V, D and J segments have been replaced *in situ* with the orthologous human V, D and J gene segments.
>
> 5. A genetically modified eukaryotic cell or a mouse comprising a genetically modified immunoglobulin heavy chain variable region locus obtainable by the method of any one of the preceding claims *in situ* in place of the endogenous
>
> 6. A mouse embryonic stem (ES) cell containing a genetically modified immunoglobulin heavy chain variable region gene locus obtainable by the method of any one of claims 1 to 4 *in situ* in place of the endogenous immunoglobulin heavy chain variable region gene locus."

Construction

46. The issue of construction which divides the parties is the meaning of "*in situ* replacement" in claim 1 of the 163 patent and claim 1 of the 287 patent. It is common ground that the term has the same meaning in all the claims. Kymab's case was and

remains that an *in situ* replacement requires a deletion (in the sense of a physical removal from the genome) of the murine variable gene segments, coupled with the insertion of the human variable segments in the same place. Regeneron's case was that all that is required by "*in situ* replacement" is a replacement "in the position of" the murine variable gene segment, and does not require deletion, a process which it described as "positional replacement". The issue is relevant to infringement because, in the Kymab constructs, the murine variable segments are inverted so that they appear in a different place in the genome where they substantially cease to function, but are not physically removed or deleted.

47. The judge considered the rival arguments on construction (which have, subject to some refinement, been repeated before us), before concluding at paragraphs [172] to [173]:

> "172. In my judgment, in situ replacement means replacing 'in the position of". The phrase is apt to describe a positional replacement and this is how it is used in context. The human sequences are to be inserted in the original position of the mouse segments juxtaposed with the mouse constant regions. The skilled person would appreciate that the patentee is using this language to distinguish targeted replacement from random insertion into the genome. This includes the case where the relevant murine sequence is deleted, and also the case where it is moved to a different location and inactivated.
>
> 173. The word "replacement" is used in the specification to describe both deletion and displacement/inactivation. The invention is concerned with the use of LTVECs and the MOA assay to enable the targeted insertion and detection of human variable V, D and J gene segments, in place of mouse variable V, D and J gene segments, whilst retaining the mouse constant segments. Given that inactivation was a well-known alternative to deletion at the priority date, I do not consider that it would make technical sense for the patentee to have excluded embodiments where the murine sequence had been moved to a different location and rendered inactive."

48. Mr Michael Tappin QC, who has appeared for Kymab with Mr James Whyte, submits that there were three constructions in play. These were (a) Kymab's construction, according to which there was a requirement for physical deletion; (b)(i) Regeneron's primary construction according to which all that was necessary was positional replacement, the ultimate destination of the replaced segments being immaterial; and (b)(ii) Regeneron's alternative construction, which was accepted by the judge, according to which the word "replacement" required insertion and deletion or insertion with displacement and inactivation. He submits that the judge did not accept (b)(i), Regeneron's primary construction, and was right to do so because it would allow the claim to cover the case where the endogenous genetic material had merely been displaced and remained active. There was no sense in which those displaced gene segments could be regarded as having been replaced when they were still present and active. That is why the judge had to build in to the definition of "replacement"

the additional requirement of inactivation. However, he submits, in doing so the judge erred in principle by having too much of an eye on the alleged infringement.

49. Mr Tappin submits that the skilled person would approach the patent with the knowledge that, in the field of homologous recombination or site-specific recombination, the word "replacement" had a specific and well-understood meaning. It was used by Professor Stewart, Kymab's expert witness, in his expert report in the present case, to distinguish replacement (with insertion and deletion) from mere insertion (without deletion) and mere deletion (without insertion). This passage was put in cross-examination to Sir Martin Evans, Regeneron's expert, who did not disagree with the distinctions being made.

50. Turning to the patent Mr Tappin submits that much of the description goes much broader than the claims. Thus, whilst the description refers to modification in any eukaryotic cell, the claims are limited to mouse ES cells. The description refers to modifications to any endogenous gene or chromosomal locus, whereas the claims are restricted to mouse immunoglobulin variable loci. In the same way, the description refers to a wide range of modifications, but the claims are to replacements of mouse V, D and J segments. Accordingly the skilled person would appreciate that the patentee consciously limited the scope of the claims from the broader range of modifications referred to in the description.

51. Mr Tappin draws particular attention to [0012] of the specification, which is in a part of the specification which sets out some embodiments of the invention:

> "Another embodiment of the invention is a method wherein the genetic modification to the endogenous gene or chromosomal locus comprises **deletion** of a coding sequence, gene segment, or regulatory element; **insertion** of a new coding sequence, gene segment, or regulatory element; creation of a conditional allele; or **replacement** of a coding sequence or gene segment from one species with an homologous or orthologous coding sequence from a different species." (emphasis added).

52. In similar vein, [0084] of the specification sets out the same list of potential modifications. Mr Tappin submits that these passages, as well as passages elsewhere in the specification, make it clear that the specification is using the term replacement in the way in which the skilled person would have understood it in any event, namely as requiring both insertion and deletion, in contrast to mere insertion or mere deletion. That submission is, he says, reinforced by the fact that all the examples in the patent are of replacements in this sense, namely examples of removal of a segment of genetic material and the insertion of something else. In particular, when one comes to Example 3, which contains the description particularly relevant to the invention, it describes the replacement of the mouse variable loci by deletion, and insertion of the human variable loci.

53. Mr Tappin places reliance on [0140] of the specification which states:

> "The 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

> homozygosity in the same mouse. The resultant transgenic mouse will have a genome comprising **entirely** human heavy and light chain variable gene loci operably linked to entirely endogenous mouse constant regions". (Emphasis added).

54. Mr Tappin asks forensically how it can be said that the mouse genome contains *entirely* human variable gene loci if it continues to contain the murine loci, albeit displaced from their original position? A genome which contains displaced murine loci, even if inactivated, does not fit this part of the description.

55. In connection with Regeneron's alternative construction, in which "*in situ* replacement" covers displacement and inactivation, Mr Tappin draws attention to the process steps of claim 1 of the 287 patent. In step (a) a large cloned genomic fragment is obtained, and, in step (b) the fragment is subjected to bacterial homologous recombination to create an LTVEC. In step (c) the LTVEC is introduced into a mouse ES cell "to replace" mouse V, D and J segments *in situ* with the orthologous human V, D and J segments. On Kymab's construction step (c) will, because of the word "replace", both insert the human gene segments and delete the mouse segments. By contrast, there is no process step in the claim to effect inactivation, which is not inherent in the word "replace".

56. Further, as Mr Tappin goes on to submit, step (d) of claim 1 of the 287 patent, which utilises the MOA assay, is directed at showing whether the gene has been modified. It cannot detect whether a part of the gene has been shifted upstream. If "*in situ* replacement" means insertion, displacement and inactivation, then the MOA assay will not be able to detect whether the gene has been replaced because it will not be able to tell whether it has been inactivated.

57. Mr Turner QC, who has appeared for Regeneron with Mr Joe Delaney and Mr William Duncan, maintains that the judge has correctly construed the phrase "*in situ* replacement" in the sense of positional replacement. He places reliance, as did the judge, on the overall purpose of the invention. The overall purpose of the invention is to insert the human sequences in the original position of the mouse segments, juxtaposed with the mouse constant regions. This creates, first, the reverse chimeric locus and the potential to produce chimeric antibodies without the immunological sickness of the prior art. Secondly, as explained in the patent at [0117], the mouse intronic enhancer, Em, which is critical for VDJ recombination, is maintained intact. What happens to the mouse sequences originally in that position is at most a subsidiary question.

58. Mr Turner also relies on a number of passages in the specification, which, he submits, show that the specification does not consistently use the word replacement to indicate both insertion and deletion. Thus [0113], when referring to the prior art mice in which the human genes are randomly inserted, explains that the endogenous genes have been "knocked out" of the mice and "the genes <u>replaced</u> with their human counterparts" (our emphasis). [0063] defines a "gene knockout" as "a genetic modification resulting from the disruption of the genetic information encoded in a chromosome locus." Such a knockout can be achieved simply by employing a stop codon, but without deleting any part of the relevant murine sequence, as the skilled reader would appreciate. Accordingly, in these mice, the endogenous locus is not deleted, yet the

patentee uses the word "replace" to describe this process. It was wrong to assume that, when one comes to the claims, "*in situ* replacement" requires deletion.

59. Whilst Kymab has relied on the distinctions made in paragraphs [0012] and [0084] between insertion, deletion and replacement, Mr Turner draws attention to the introduction to [0084] which reads:

> "The region to be modified and replaced using bacterial homologous recombination can range from zero nucleotides in length (creating an insertion into the original locus) to many tens of kilobases (creating a deletion and/or a replacement of the original locus)…"

60. The first use of "replaced" in that passage, submits Mr Turner, indicates that insertion can encompass insertions, deletions and a combination of the two.

61. Mr Turner also relies, as did the judge, on [0125] of the specification, which contemplates two scenarios. In one scenario mouse V, D and J segments are deleted and human V, D and J segments inserted. In the second scenario only mouse D and J segments, but not V segments are deleted. The mouse V segment remains but is displaced. That passage shows that the invention does not require the deletion of mouse V, D and J segments for them to be treated as replaced.

62. Mr Tappin's response is that this argument leads to an absurd result. First, it leads to the result that the mouse V segment is replaced even though it is still plainly present. Secondly, it is not just the immediately adjacent mouse V segment which is displaced, but all the V segments. On Regeneron's construction, in the second alternative within [0125], all the V segments are replaced by being displaced by the insertion. That does not make sense, because the specification goes on to explain that it is "preferable" to eliminate all the mouse variable segments, which is not possible if they have already been "replaced". Instead, the judge should have appreciated that only the first alternative within [0125] is actually within the claim.

63. Mr Tappin also points to [0118] of the specification which states, in the final sentence, when making a comparison with the prior art:

> "Since there will be only one, chimeric, heavy or light chain locus (as opposed to mutated immunoglobulin loci and with human transgenic loci integrated as distinct chromosomal locations for heavy and light chains in the currently available mice) there should be no trans-splicing or trans-rearrangements of the loci which could result in non-productive rearrangements or therapeutically irrelevant chimeric antibodies."

64. This passage is promising the reader that there exists the possibility of preventing the rearrangement of loci so as to produce therapeutically irrelevant antibodies. If the mouse variable regions are allowed to remain, this advantage will not be achieved, because the displaced mouse V regions will still be able to re-combine with human D and J regions to form unwanted chimeric antibodies.

Assessment

65. The parties framed the list of issues for our decision on construction of the claims of the patents in the following way:

> " 1. What is the correct construction of the term "*in situ* replacement" in claim 1 of the 287 patent and claim 1 of the 163 patent? In particular, does it mean:
>
> (a) mouse V, D and J gene segments (or, as the case may be, mouse VDJ or VJ regions) have been deleted from the genome;
>
> or does it also include cases in which:
>
> (b) mouse V, D and J gene segments (or, as the case may be, mouse VDJ or VJ regions) have been
>
> (i) displaced; or
>
> (ii) displaced and inactivated?"

66. Construction (a) is said to represent Kymab's construction, whilst (b)(i) is said to be Regeneron's primary construction and (b)(ii) its alternative construction. We think there is a danger inherent in the way these issues are phrased, in particular with the composite question "…does it mean [X] … or does it include cases [Y] and [Z]?" There is a fundamental distinction between what a claim means, in the sense of what it requires as a minimum, and what it includes or covers, in the sense of what is included within the monopoly. A claim which requires X as a minimum also covers X in combination with other things. We think that these questions unhelpfully mix up what the claim means with what it covers.

67. Based on this formulation of the issues, Mr Tappin submits that there are three constructions in play: (a), (b)(i) and (b)(ii). The judge rejected (a) and (b)(i) and accepted (b)(ii). This allows him to attack construction (b)(ii) as if it were an independent *meaning* to be given to the claims, requiring both displacement and inactivation. It is on this basis that he is able to submit that the promise of [0140] is not fulfilled, because "entirely human heavy and light chain variable gene loci" can never be made if the murine sequences are allowed to remain in the genome. In like vein he can submit that the process claims do not include a de-activation step, which on that construction would be a necessary one.

68. We do not think it is helpful to analyse the case, at least as advanced on this appeal, as involving three potential constructions. We have no difficulty in understanding Regeneron's primary position, namely that the phrase "*in* situ replacement" only calls for positional replacement, that is to say the insertion of human variable sequence into a specific position previously occupied by the murine variable sequence. As finally advanced before us, we did not detect much enthusiasm in Mr Turner's submissions for an intermediate meaning to be given to the claims between Regeneron's primary case and Kymab's. On Regeneron's primary argument of positional replacement, the scope of the claimed monopoly extends to the cases where there is (a) positional replacement accompanied by displacement and inactivation of the murine sequences, (b) positional replacement accompanied by deletion of the murine sequences and (c) positional replacement where the murine sequences are simply displaced upstream.

The only other candidate construction, therefore, is Kymab's construction, which interprets the claim as requiring more than positional replacement, i.e. the deletion of the murine sequence. Viewed in this way the issue on construction is a two, not a three horse race.

69. We are not persuaded that the judge did in fact reject Regeneron's primary construction. Certainly, when describing Regeneron's argument before him at [148] of his judgment he says:

> "…so the relevant murine variable segments must at least be moved (and inactivated) so that the human variable segments can be inserted in their position…"

70. However, the construction which he adopted at [172] was simply that "*in situ* replacement means replacing 'in the position of'" (emphasis added). He went on to say that it covered both the cases of deletion and moving to a different location and inactivation. That passage is consistent with his having accepted Regeneron's primary argument. We do not read his judgment as rejecting the third alternative, which is the logical consequence of Regeneron's construction, namely insertion and displacement (without inactivation).

71. We would also acquit the judge of the criticism levelled at him that he had too close an eye on the infringement when deciding the issue of construction. Whilst Mr Tappin is right that it is sometimes said that one must construe the patent as if the defendant had not ever been born, it is necessary to refer to the alleged infringement in order to identify the claim features which must be construed. Moreover it is necessary to keep in mind that the relevant word or phrase has to be construed in context. The judge made it clear that he had this principle well in mind at [149] of his judgment. He cited what Jacob LJ said in *Technip France SA's Patent* [2004] RPC 46:

> "..questions of construction seldom arise in the abstract. That is why any sensible discussion of the meaning of language runs along the lines 'does it mean this, or that, or the other?', rather than the open-ended 'what does it mean?"

72. We can see no reason why the court cannot ask itself the question whether the phrase "*in situ* replacement" means positional replacement, or whether it means insertion and deletion. What the court must not permit itself to do is to be inspired by the acts of the infringer to cause the language to have a meaning it will not sensibly bear.

73. We were not impressed by the excursion into the cross-examination of the experts, which showed that, as a matter of language, it is possible to draw clear dividing lines between deletion, insertion and replacement. We accept that this may be so. It is, however, common ground that the phrase "*in situ* replacement", and *a fortiori* the word "replacement", are not terms of art with a fixed meaning. We are concerned, as we believe the skilled reader would be, with the meaning to be given to the phrase in the context of this specification and in its claims.

74. The starting point for Regeneron's primary argument is that the phrase "*in situ* replacement", because of its focus on positional replacement (as compared with the random insertion employed in the prior art) is apt as a matter of language to

encompass the insertion of a human gene segment into the place formerly occupied by the mouse segment, and thereby replacing it. The fact that the mouse segment is displaced rather than deleted does not, at least as a matter of language, prevent that positional replacement from having taken place. Mr Turner drew a linguistic analogy of a person being replaced at the front of the queue, when the person formerly in that position has been moved into second place. Replacement does not imply that the person is removed from the queue altogether. Whilst analogies can be unhelpful, this one assists an understanding of what could be meant.

75. The second point to note is that the skilled reader of the patents would understand that the primary purpose of creating the reverse chimeric locus is the insertion of the human variable locus into the position occupied by the mouse locus, juxtaposed with the mouse constant regions. What happens to the mouse locus is of subsidiary importance, provided it is removed from that position.

76. We can see no technical reason why the skilled person would understand that the patentee was using the phrase "*in situ* replacement" to mean more than positional replacement. The specification does not contain any teaching that the mouse segments must necessarily be deleted or inactivated. This is made clear at [0125] of the specification which points out that the process may give rise to hybrid heavy chains, "but it is preferable to proceed with subsequent steps that will eliminate the remainder of the mouse variable segments". The suggestion that removal of all the mouse segments is "preferable" makes it clear that mouse segments can be tolerated.

77. The evidence also fails to support Mr Tappin's reliance on [0118] for this purpose. That is the paragraph which holds out the possibility of avoiding therapeutically irrelevant chimeric antibodies by, it is said, a purely human variable locus. Thus, Professor Ploegh said that the production of some unwanted chimeric antibodies (which would be the case if the mouse variable region was retained) was "*not an issue that I would be overly concerned with*" given the ability to distinguish the desired product from the undesired. He went on to explain that, according to his understanding of the patent, the advantage of the avoidance of therapeutically unwanted antibodies is achieved if "*one takes all the possible steps*" in the patent. However, he said:

> "… as I have pointed out before, even if you had only a few human Vs properly positioned relative to the mouse constant regions, you reap the full benefit of the invention. You would allow class switch recombination, somatic hypermutation all to benefit from the presence of these mouse constant regions."

78. No doubt on the basis of that evidence the judge held (at [170] of his judgment) that [0118] of the patent did not provide a technical reason for the patentee to have limited his monopoly in the manner suggested by Kymab. Indeed, as Mr Turner pointed out, Kymab's construction itself allows for only a single murine V, D and J segment to be deleted and a corresponding human insertion made. In those circumstances the remaining murine sequences will not be inactivated, and the same consequences will follow. The possibility of unwanted antibodies if murine sequences are not deleted cannot therefore provide a pointer in favour of Kymab's construction.

79. Given that conclusion, there is no basis either for the reader to conclude that [0125] of the specification is seeking to draw a distinction between the alternative modifications

there described, to the effect that only one of them falls within the claims. Given that the skilled reader would understand that the advantages of the invention can be reaped without deletion of displaced mouse Vs, there is no reason to assume that both modifications are not equally encompassed within the claim.

80. Thirdly, the description of the invention is regularly contrasted with the prior art in which the integration of the human sequences occurs at random positions. As the judge held, the skilled reader would understand that the patentee is using the composite phrase "*in situ* replacement" to distinguish targeted positional replacement from random integration.

81. Fourthly, whilst there are indeed many passages in the specification which distinguish between insertion, deletion, and replacement, we do not think that the skilled reader who took the time to think about it would conclude from those passages that the patentee was intending to limit his claim to insertion and deletion. Although it is dangerous to home in on isolated passages in the specification, we think it significant that when the word "replaced" is used in [0113] to describe what occurs with the prior art mice, it is used in a sense which does not require physical deletion. The mouse locus is replaced even though it is not deleted from the genome. It is true that, in the prior art, the inactivated locus stays where it is and is not displaced, as Mr Tappin pointed out, but that merely shows the capacity of the word "replace" to encompass other specific mechanisms of replacement which do not involve the deletion of the gene. One may ask forensically why, when one has regard to the purpose of the invention, would the patentee be using the word "*in situ* replacement" in a narrower sense than this in the claim?

82. Fifthly, we do not think that the skilled reader would be prevented from reaching the conclusion that *in situ* replacement does not necessarily require deletion either by the use of the word "entirely" in [0140] or by the fact that the examples all include deletion. Taking the second point first, the fact that the examples show only one type of replacement, namely that which includes deletion, is not a sufficient indication that replacement is similarly restricted in the claims. As to [0140], the paragraph, read fairly, is not promising that the use of the invention will invariably result in mice having a genome comprising entirely human heavy and light chain variable gene loci. Mr Tappin accepts this, but says that if "replacement" means displacement with inactivation, then the genome will never be composed entirely of human variable loci, and the statement is falsified. He is right about that as well, but, as we have said, we do not understand Regeneron to contend that inactivation is a requirement of the claim. The entirely human result can be achieved by insertion and deletion.

83. Sixthly, we turn to Mr Tappin's argument that process steps (c) and (d) of claim 1 of 287 do not fit with Regeneron's construction. In essence the argument on step (c) is that the disclosure of the patent is deficient in failing to provide a description of a method in which the murine sequence is displaced and inactivated, because the only method described in the patent is one in which there is direct replacement of the murine sequence in the manner argued for by Kymab. We do not think that this is a tenable argument. Once it is appreciated that Regeneron's construction does not require inactivation, inactivation is simply an optional further step which the claim does not need to specify any more than it needs to specify deletion. If the argument is that the claim is broader than the subject matter which it enables, then that is an argument directed to sufficiency, not construction.

84. As for the MOA assay, (step (d)), the evidence showed that the MOA assay could detect insertions where no deletion had been made. Although Professor Stewart considered that the skilled team might prefer to use regular junction PCR instead of MOA, he accepted that it was plain in the light of the patent that MOA could be used for this purpose. It is true that the MOA assay will not detect whether the murine genes have been inactivated, but the claim, on Regeneron's construction, does not require it to do so. The MOA assay is required by step (d) to "to identify a mouse ES cell in which said V, D and J segments have been replaced *in situ* with the orthologous human V, D and J gene segments." On the evidence accepted by the judge it can plainly do so.

85. We therefore accept Regeneron's construction, and reject Kymab's. The claim, on its proper construction, requires positional replacement only.

Infringement

86. There are three strains of Kymab mice in issue, referred to as HK, HL and HKL. All three are alleged to infringe claims 5 and 6 of the 287 patent and HK and HKL are alleged to infringe claim 1 of 163.

87. Kymab's process does not infringe the process claims of either patent because it does not use LTVECs or MOA assays. Instead they insert a series of large segments using sequential RMCE. The details do not matter for our purposes. In short, the mouse locus is modified by insertion of part or all of the human variable region between the mouse variable region and the mouse constant region, followed by an inversion of the mouse variable region which is displaced upstream. The effect is not only to reverse the order of the mouse VDJ sequences, but also to move these inverted sequences many mega-bases upstream of their original position. For the IgH locus, the mouse VDJ sequence is moved upstream so that the now most proximal mouse V is 3.8 Mb away from the 5' distal human V. In the IgK locus it will be even further away, approximately another 20 Mb upstream.

88. Kymab's primary point on non-infringement is that the mouse sequence has not been deleted from the genome. That point depends on acceptance of Kymab's construction argument, which we have rejected.

89. Before the judge, Kymab submitted that the presence of the mouse variable regions, albeit inverted and upstream from the human insert and the mouse constant regions, still permitted unwanted recombination. In other words, if "*in situ* replacement" requires inactivation, Kymab's displaced gene is not fully inactivated. The judge found on the evidence that the displaced gene was substantially inactivated and that there was therefore infringement. Before us, Mr Tappin does not seek to dislodge the judge's conclusion that on Regeneron's secondary case on construction, there was infringement. On Regeneron's wider construction there is obviously infringement as well.

90. We have heard limited argument on whether, if we had accepted Kymab's construction of "*in situ* replacement", we could nevertheless have found infringement on the basis of the Supreme Court's recent decision in *Actavis UK Limited and others v Eli Lilly and Company* [2017] UKSC 48. In that case the Supreme Court held that, in deciding infringement in the case of a variant from the language of the claim, there are two issues to be addressed. The first issue is whether the variant infringes "as a

matter or normal interpretation". The second issue is whether the variant nevertheless infringes because it varies from the invention in a way or ways which are immaterial. It is necessary to consider this second issue because article 2 of the Protocol on the Interpretation of article 69 of the European Patent Convention (as amended in 2000) requires account to be taken of equivalents. We have considered the first issue, and have concluded as a matter of normal interpretation that the Kymab mice infringe. It follows that it is not necessary for us to consider the second issue. Had it been necessary, we would have been troubled by the suggestion that we could have approached this issue for the first time on this appeal. The case was not advanced on this basis before Henry Carr J. On balance we would have remitted the matter to him to consider the second *Actavis v Lilly* issue, had it been necessary for us to do so.

Insufficiency

Introduction

91. The judge found that each of the claims in issue, that is to say claims 1, 5 and 6 of the 287 patent and claim 1 of the 163 patent, was invalid for insufficiency. He concluded that the whole subject matter of claim 1 of 287, the method claim, was not capable of being performed at the priority date without undue burden and without invention. In his view the difficulty related not just to a puzzle at the edge of the claim but to the central disclosure of the specification for none of the processes described in Example 3 would have worked in the hands of the skilled team at the priority date. The task contemplated by the patent was unprecedented and could not have been achieved without a great deal of creative thinking. Moreover, the reverse chimeric locus did not constitute a principle of general application because it was not a principle that enabled the method to be performed across the scope of the claim. It was instead the result of successfully carrying out the method. The judge also found that the other claims in issue, which were all product claims, were considerably wider and so necessarily insufficient too.

92. Upon this appeal Regeneron contends the judge made a series of errors of principle which fatally undermine his decision. In outline, it contends, first, that the judge failed properly to appreciate the true nature of the reverse chimeric locus and that he ought to have found that it embodies a new principle of general application which is common to all the processes and products falling within the claims.

93. Secondly, the judge approached the issue of insufficiency on the wrong basis. Instead of considering, as he should have done, whether the claims were properly enabled across their breadth having regard to the technical contribution of the patents, he sought to identify whether there were any products or processes which fell within the claims which were not enabled. Then, having identified a product and process which were not enabled, he held all the claims to be insufficient.

94. Thirdly, the judge failed properly to consider the scope of claim 1 of the 287 patent. Having correctly held that the claim did not require deletion of the relevant coding sequence but embraced positional replacement, he held that the minimum replacement required an insertion of a fragment of at least 75 kb, when the claim in fact only requires the insertion of a fragment of greater than 20 kb.

95. Fourthly, having found claim 1 of the 287 patent to be insufficient, the judge applied this finding in a mechanistic way to the product claims. Here he fell into error. He ought to have considered the sufficiency of the product claims on their own merits.

96. Finally, the judge approached the evidence on the wrong basis in several respects. First, he failed to take into account the common ground between the experts that the processes described in the 287 patent would work with obvious minor adjustments. In particular, this patent teaches and the skilled team would have appreciated that the reverse chimeric locus could be built up in a series of steps. Secondly, he repeatedly elided the question whether the claims were enabled with the question whether processes or products falling within their scope could be performed (in the case of method claim 1 of the 287 patent) or made (in the case of product claims 5 and 6 of the 287 patent and claim 1 of the 163 patent) by non-obvious means.

97. In assessing the judge's approach to and findings of insufficiency we shall refer (as the parties did) primarily to the 287 patent. References to "the patent" should therefore be taken as references to the 287 patent save where we indicate to the contrary.

The technical contribution of the patent

98. As we have explained, the invention of the patent hast two aspects: first, the reverse chimeric locus; and secondly, the use of LTVECs as targeting vectors to engineer and the MOA assay to detect recombination events in a target gene.

99. The reverse chimeric locus was not only a striking, radical and highly original departure in the art but Regeneron's "Velocimmune ®" mouse, with this locus, has now become the gold standard for *in vivo* antibody production, as Dr Yancopoulos explained in his unchallenged evidence.

100. There is another arresting and conspicuous feature of the reverse chimeric locus which merits some discussion, and was explained by both Dr Yancopoulos and Dr Murphy, the other named inventor of the patent and Senior Vice President of Research at Regeneron. Dr Yancopoulos gave unchallenged evidence that although it took some time to create the final Velocimmune ® mouse they were aiming towards, in about mid-2003 they obtained the first mice containing three human variable chain regions and that their antibody responses were good and the antibodies responded well to *in vitro* assays. Further, the B cell response of these mice was far closer to that of wild type mice than competitor mice. He also expressed the opinion that the reverse chimeric locus was key to Regeneron's success in producing antibodies. The process of producing antibodies from transgenic mice was laborious and by significantly improving the efficiency of the process, Regeneron was able to produce better antibodies to more targets than was possible using fully human constructs.

101. Dr Murphy's undisputed evidence was to much the same effect. He explained that Regeneron's Velocimmune ® VI strain of mouse, with only three human heavy chain variable gene segments, had an immunological performance which was similar to that of wild type mice and significantly better than that of the transgenic mice of any competitor.

102. Turning to the contribution made by the disclosure of LTVECs and the MOA assay, this technology creates the possibility of using longer homology arms to achieve

targeted recombination. This improves the frequency of homologous recombination events and is beneficial, as Professor Stewart explained in cross-examination and the judge accepted at [264]. These benefits were described in a paper by Valenzuela and others, including Professor Stewart, entitled *High-throughput engineering of the mouse genome coupled with high-resolution analysis* Nature Biotechnology (2003), Vol 21. No 6, 6522. We recognise, however, that the judge's finding was qualified. He did not accept that this improvement came near to enabling deletions and insertions on the scale contemplated by the patent, and this is a matter to which we must return.

The examples of the patent

103. We must now say a little more about the relevant examples of the patent. The judge described the teaching of Examples 1 and 2 from [116]-[118] of his judgment in terms which neither side has criticised. In summary, Example 1 describes a practical instance of the use of LTVECs and the MOA assay to increase the frequency of recombination events concerning the OCR 10 gene and then to detect those cells in which the desired recombination has occurred. Example 2 provides additional data supporting the use of this technique. But as the judge explained, the LTVEC of Example 1 was intended to lead to the insertion of a sequence of 6 kb and the deletion of a sequence of 20 kb, described in the specification as "a very large deletion"; and Example 2 describes the introduction of sequences of under 10 kb and the deletion of no more than 30 kb.

104. Example 3 describes the reverse chimeric locus and was discussed by the judge from [119]-[140]. It has three parts: an introduction, a brief description and a section on materials and methods. The introduction and the brief description disclose the concept of the reverse chimeric locus, as we explained earlier in this judgment (at [29]-[33]). For the purposes of this aspect of the appeal, we must focus on the further aspects of the disclosure which are contained within the material and methods section of the example.

105. The materials and methods section opens at [0123]:

> "Precise replacement of the mouse heavy chain locus variable region (VDJ) with its human counterpart is exemplified using a combination of homologous and site-specific recombination in the following example, which utilizes a two-step process. One skilled in the art will recognize that replacement of the mouse locus with the homologous or orthologous human locus may be accomplished in one or more steps. Accordingly, the invention contemplates replacement of the murine locus, in whole or in part, with each integration via homologous recombination."

106. As the judge observed at [129], this passage contemplates that the replacement of the heavy chain mouse locus with the heavy chain human locus may be accomplished in more than one step.

107. The specification proceeds to describe two general approaches for implementing the invention, but as Regeneron fairly points out, the skilled team would approach this aspect of the disclosure with two techniques already in mind by which heterologous sequences could be inserted into ES cells. The first was homologous recombination,

although the skilled team would not have known, before reading the specification, of the use of BACs with long homology arms or the MOA assay. The second was SSR which involves the insertion of SSR sites into a sequence which can then be used to effect an insertion or a deletion, a matter to which we will return when dealing with enablement.

108. The first of the general approaches is set out in the specification from [0124]-[0129] and was described by the judge from [130]-[136] of his judgment in terms which Mr Turner for Regeneron accepted were fair. In broad summary, this approach involves the following steps. The first is to construct an LTVEC, described as LTVEC 1, by bacterial homologous recombination in *E coli*. This contains, in order (and among other things), a large mouse homology arm derived from a region upstream of the mouse DJ region; a large human insert spanning several V segments and the entire DJ region; and a mouse homology arm containing the region adjacent to but not including the mouse J segments. This is introduced into the mouse ES cells to replace the mouse DJ segments with several human V segments and all the human DJ segments. The human insert in this LTVEC is said to be about 200-300 kb in length, and the mouse sequence to be replaced is about 100 kb in length.

109. The second step involves another LTVEC, described as LTVEC 2. This is produced in the same way as LTVEC 1 and is introduced into the ES cells to replace the distal mouse V segments with the most distal human V segments. This human insert is again about 200-300 kb in length.

110. That leaves a large number of mouse V segments between the inserted human segments; and the specification teaches at [0127] that these can be deleted by routine techniques. The specification also teaches at [0128] that additional V segments can be inserted into the locus and that one approach to achieve this is to use SSR which Professor Stewart explained in his first report at [56] could be used to make insertions of a relatively small size, that is to say no more than 10 kb in length.

111. The second general approach is described in the specification from [0130]-[0139] and involves replacing the whole of the mouse locus with human sequence using RMCE. It is explained by the judge from [137] to [139] and he held at [229] that it would not have worked. This finding is not challenged by Regeneron on this appeal and so we need say no more about it.

112. Finally, we should say a word about the light chain. The specification teaches at [0140] that the same steps may be carried out on the relevant light chain loci so that, in the words of the patent, the resultant transgenic mouse will have a genome comprising entirely human heavy and light chain variable gene loci.

The claims

113. We have recited the relevant claims from [44]-[45] and considered one aspect of their proper interpretation in some detail from [46]-[85]. That analysis was primarily concerned with the issue of infringement, however. We must now say a little more about their scope.

114. We begin with claim 1 of the 287 patent, as did the judge. This claim was not asserted against Kymab (which does not use LTVECs or the MOA assay) but its validity was in issue. It is a method claim directed to the modification of an endogenous

immunoglobulin heavy chain locus in a mouse ES cell such that murine V, D and J gene segments are replaced by human V, D and J segments, and the locus produces hybrid antibodies containing human variable regions and mouse constant regions.

115. The claim then sets out four steps of the method. The first is to obtain a cloned genomic fragment of greater than 20 kb which contains human V, D and J gene segments. Secondly, homologous recombination is used to modify the genomic fragment to produce a LTVEC. Thirdly, the LTVEC is introduced into a mouse ES cell to replace the endogenous murine V, D and J segments with the orthologous human V, D and J segments. Finally, the MOA assay is used to detect correctly targeted cells. As Regeneron says, this is not a claim to any way of creating a reverse chimeric locus; it is instead a claim to a particular way of making a reverse chimeric locus.

116. The judge held at [145]:

> "… the claim requires at least one endogenous V gene segment (as well as D and J gene segments), i.e. at least about 150 kb of mouse sequence, to be replaced with at least one orthologous V human gene segment (as well as D and J gene segments), i.e. at least about 75 kb of human genomic sequence. There is no doubt that at least about 75 kb of human genomic sequence is required to be inserted. Whether, in addition, at least about 150 kb of mouse sequence is required to be deleted depends upon the meaning of "*in situ* replacement" which I shall consider below. I will also consider whether claim 1 covers the case where the mouse sequence is deleted. "

117. We have dealt with the meaning of *in situ* replacement earlier in this judgment. Here the focus is on the size of the insert. As we have explained, the specification describes (at [125]) deletion of 100 kb of mouse sequence (the D and J regions) and the insertion of 200-300 kb of human sequence. Further, the judge found that the minimum required by the claim is the deletion of 150 kb of mouse sequence and the insertion of about 75 kb of human sequence. He held that this was clear from the cross-examination of Professor Evans who accepted that if the skilled team wanted to replace at least one mouse V segment and all the mouse D and J segments with one human V and all the human D and J segments, that would require the replacement of 150 kb of mouse sequence with about 75 kb of human sequence.

118. Regeneron says that at this point the judge fell into error for whilst he was correct to hold that the language of the claim required the replacement of at least one mouse V segment by one human V gene segment, he was wrong to hold that it required all the mouse D and J segments to be replaced by all the human D and J segments. It argues that there is no basis in the language of the claim to treat the D and the J segments any differently from the V segments, and the judge gave no reason for doing so. It contends that the judge was therefore wrong to say that at least about 75 kb of human genomic sequence must be inserted.

119. We agree with Regeneron that the claim does not require a fragment containing all the human J segments to be inserted. Nor, in our judgment, does it require a fragment containing all the human D segments to be inserted, even though the human D segments lie between the V and the J segments on the genome. It requires a fragment

containing at least one V, one D and one J segment to be inserted. Nevertheless, we agree with the judge that the claim encompasses the insertion of at least one human V and all the human D and J segments.

120. We draw the following further conclusions about the scope of this claim:

i) The claim does not require the deletion of any sequence. It requires the replacement of at least one V, one D and one J mouse segment with the orthologous human V, D and J segments. But we accept the judge's finding that one V, and all the D and J segments of the mouse genome have a length of about 150 kb, including all the intergenic regions.

ii) We also have no doubt that the judge was entitled to find that a fragment containing one human V and all the human D and J segments will be about 75 kb in length, assuming it contains all the intergenic regions. There was an amply sufficient basis for this finding in the evidence of Professor Evans and Professor Howard. We return later in this judgment to the question of the length of the intergenic regions and whether they could be deleted.

iii) The specification describes at [0125] (among other things) the replacement of 100 kb of mouse sequence with 200-300 kb of human sequence.

iv) The parties were agreed and the judge found that the claimed method imposes a practical limit on the size of the cloned fragment that can be introduced because an LTVEC produced by recombineering cannot be larger than about 300 kb in length.

v) It is a requirement of the claim that the cloned genomic fragment which is used to create the first LTVEC must be at least 20 kb in length and contain orthologous human V, D and J segments, and that is so whether or not the intergenic regions are deleted. However, that said, there is no limit to the number of steps that can be used to build up the rest of the reverse chimeric locus described in the specification.

121. Claims 5 and 6 of the 287 patent are product by process claims. The meaning of claims such as these was explained by Lord Hoffmann in *Kirin Amgen Inc v Hoechst Marion Roussel Ltd* [2005] RPC 169 at [87] to [91] and explored by Birss J in *Hospira v Genentech Inc* [2014] EWHC 3857 (Pat). In short, a product by process claim is a claim to a product which is defined by and has the characteristics conferred by the process described in the claim. If the claimed product is old, the process described in the claim cannot confer novelty upon it. But equally, if the claimed product is novel and inventive, then the claim will be infringed by making that product, and that will be so whether the product is made by the process in the claim or any other process.

122. Claim 5 is a claim to a genetically modified eukaryotic cell or a mouse, and claim 6 is a claim to a mouse ES cell, in each case comprising (in the case of claim 5) or containing (in the case of claim 6) a genetically modified immunoglobulin heavy chain variable region gene locus obtainable by any one of claims 1 to 4 in place of the endogenous immunoglobulin heavy chain variable gene locus. So, as Regeneron contended at trial and the judge accepted, the claims extend to cells and mice

containing heavy chain variable region loci in the endogenous position of the mouse heavy chain variable region loci.

123. The judge also made findings about the scope of these claims at [183] with which we agree:

i) As with claim 1, they include products in which 100 kb of endogenous sequence has been deleted and 200-300 kb of orthologous sequence has been inserted and products in which 150 kb of endogenous sequence has been deleted and 75 kb of orthologous sequence has been inserted.

ii) Unlike claim 1, they contain no limitation as to the use of LTVECs or the MOA assay. Provided that the product in issue has the characteristics of a product made by the process of the claim, it does not matter how it is in fact produced.

iii) They contain no limit as to the amount of endogenous sequence which must be deleted and so include products in which the entire endogenous heavy chain sequence has been deleted.

iv) They contain no limit as to the amount of orthologous sequence which has been inserted and so include products in which the entire orthologous heavy chain sequence has been inserted.

124. It follows that, as the judge correctly observed, claims 5 and 6 extend to cells and mice in which the entire mouse variable heavy chain locus has been replaced by the entire human variable heavy chain locus. But we would add once again that the replacement may be achieved in a number of steps. Further, there is nothing in the claims to preclude the deletion of intergenic regions and in that way to reduce the size of any particular fragment to be introduced.

125. Claim 1 of the 163 patent is directed to a transgenic mouse in which there has been *in situ* replacement of mouse V, D and J regions on the heavy chain by human V, D and J regions; and in which there has been *in situ* replacement of mouse V and J regions on the light chain by human V and J regions.

126. The claim contains no requirement that any particular size of DNA fragment is inserted or replaced; nor is there any limit to the number of steps by which the claim requirements may be met. Further, the reference to V, D and J regions must mean one or more V, D and J segments respectively.

127. As the judge explained at [186], the following further points may be made about the scope of this claim:

i) The claim is not confined to a single product. It includes mice in which different amounts of mouse V, D and J regions (of the heavy chain) and mouse V and J regions (of the light chain) have been replaced by human V, D and J regions and V and J regions, respectively. So it includes, for example, a mouse in which one V, one D, and one J region (of the heavy chain) and one V and one J region (of the light chain) have been replaced, and mice in which several such regions have been replaced.

ii) As with claim 1 of the 287 patent, it includes products in which 100 kb of endogenous sequence have been deleted and 200-300 kb of orthologous sequence have been inserted; and products in which 150 kb of endogenous sequence have been deleted and 75 kb of orthologous sequence have been inserted.

iii) Unlike claim 1 of the 287 patent, this claim contains no requirement that LTVECs or the MOA assay must be used.

iv) The expressions "VDJ regions" and "VJ regions" as used in this claim are broad and encompass the whole mouse and human variable gene loci. Accordingly the claim extends to a mouse in which the entire murine variable gene locus has been replaced with the entire human variable gene locus.

What the skilled team could do

The findings of the judge

128. Here we must begin with the relevant findings of the judge, some (but by no means all) of which Regeneron seeks to challenge on this appeal.

129. The judge focused on claim 1 and Example 3 of the 287 patent. He reiterated his conclusion that:

i) the minimum replacement by LTVEC1 as described in [0125] is a deletion of 100 kb of mouse sequence and an insertion of 200-300 kb of human sequence;

ii) the minimum replacement required by claim 1 involves a larger deletion (of 150 kb) but a smaller insertion (of 75 kb);

iii) the claim also includes the case where the relevant mouse sequence has been displaced and deactivated, and the case where the relevant mouse sequence has been deleted.

130. The judge then held from [218]-[223] that, in light of the evidence of Professor Evans and Professor Stewart, neither replacement of 100 kb of mouse sequence by 200-300 kb of human sequence (termed "100 kb out, 200-300 kb in"), nor replacement of 150 kb of mouse sequence by 75 kb of human sequence (termed "150 kb out, 75 kb in") would have been considered feasible at the priority date. In the judge's mind, these combined unprecedented insertions with unprecedented deletions. He found that it was likely that neither would have worked.

131. Regeneron's own work and attempts to put the invention into practice were considered by the judge from [224]-[228]. These confirmed his view that replacements on the scale of "100 kb out, 200-300 kb in" or "150 kb out, 75 kb in" would not have worked. He also found at [229] that the second approach of Example 3, that is to say using RMCE instead of homologous recombination, would not have worked either.

132. The judge considered next alternative approaches that the skilled team might apply using their common general knowledge. He directed his attention first to the work of Lynn Macdonald and others, including Dr Yancopoulos and Dr Murphy, published in

a paper entitled *Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes*, Proceedings of the National Academy of Sciences (2014), 111, 5147. This described later work by Regeneron in which the authors replaced six Mb of mouse genes in a precise manner and *in situ* with human gene sequences. The judge accepted the evidence of Professor Stewart that this work was an outstanding piece of thinking and very creative. It would not have occurred to the unimaginative skilled team.

133. The second was an approach put to Professor Stewart in the course of his cross-examination by Mr Turner on behalf of Regeneron. This involved using a targeting vector to make a series of modest insertions (without deletion) by homologous recombination, starting at the proximal end of the locus and then proceeding towards the distal end, one insertion followed by another, each sufficiently small that it could be achieved, and in this way "shunting up" the native mouse sequence. The judge did not accept that this approach would have occurred to the unimaginative skilled team in light of the evidence of Professor Evans and Professor Stewart.

134. The third was to carry out a series of more modest insertions and deletions of perhaps 10 kb in length using LTVECs and the MOA assay and in this way achieve in the end the deletion of 150 kb of mouse sequence and the insertion of 75 kb of human sequence. The judge rejected the submission that this would allow the method of claim 1 of the 287 patent to be performed for the following reasons. To begin with, it would not carry out the method of the claim which required the replacement of at least one mouse V segment and the mouse D and J gene segments by at least one orthologous human V segment and the orthologous human D and J segments, that is to say about 75 kb of the human gene sequence. Further, the claim included within its scope single step replacements of "100 kb out, 200-300 kb in" and "150 kb out, 75 kb in", and these could not be achieved. What was more and whilst it was true to say that the specification did refer to the repetition of steps (at [0036]-[0038]), this was a more generalised disclosure of the claimed method which involves a targeted replacement at the proximal end, followed by a targeted replacement at the distal end, followed by other steps in the middle. Finally, the specification did not contemplate this approach, neither of the experts had endorsed it and it ignored all the difficulties that the skilled team would have encountered in practice, as corroborated by the difficulties that Regeneron itself encountered.

135. The judge summarised his conclusions on enablement at [257]-[258] in these terms:

> "257. For these reasons, I have concluded that the whole subject matter defined in the claim 1 of the 287 Patent was not capable of being performed at the priority date without undue burden and without invention. The difficulty does not relate to some hypothetical puzzle at the edge of the claim, but rather to the central disclosure of the specification, and the amounts of genetic sequence of which it contemplates the deletion and insertion. None of the methods of the 287 Patent for achieving this, as disclosed in Example 3 would have worked. The task contemplated was unprecedented and could not have been achieved, if at all, without a great deal of creative thinking at the priority date. I do not accept that all embodiments within the claim are unified by a single principle of a reverse chimeric

> locus. This is not a principle that enables the method to be performed, rather it is the result of successfully carrying out the method. Accordingly, the insufficiency objection succeeds in respect of claim 1 of the 287 Patent.
>
> 258. It follows that claims 5 and 6 of the 287 Patent and claim 1 of the 163 Patent are also invalid for insufficiency. I have concluded that they are of considerably wider scope than claim 1 of the 287 Patent. Even if I had concluded that claim 1 of the 287 Patent was not of excessive breadth, I would still have concluded, for the reasons set out above, that these wider claims were insufficient."

136. The judge turned next to various additional insufficiency objections. He rejected those relating to the benefit of long homology arms, the use of MOA assay improvements and difficulties in identifying the 5' end of the mouse locus. However, he accepted a submission by Kymab that a "16.6 kb out, 144 kb in" replacement achieved by Regeneron in the course of its development work was achieved using an improvement which was not disclosed in the patents and which would not have occurred to the skilled person, namely the use of a reduced amount of DNA. He thought this was an additional support for his conclusion that the claims were insufficient.

137. After the circulation of the draft judgment, Regeneron raised two further issues. It contended first, that following the teaching in the patents, the skilled person could insert human DNA comprising at least one V segment, and the D and J segments having a length of about 75 kb and invited the judge so to find.

138. The judge dealt with this issue from [278]-[281]. He concluded that this was another attempt by Regeneron to argue that that the claims were enabled across their breadth; that he had rejected all of the different ways that contention had been presented at trial; that this particular point had been before him; and that the evidence did not establish that the skilled team could have achieved an insertion of 75 kb and a deletion of 17 kb without undue effort. He held at [280]:

> "[280] … Regeneron cites certain passages from the cross-examination of Prof. Stewart. I have already considered Prof. Stewart's evidence on this issue, and the parties' submissions in their written and oral closings. In my judgment, this evidence did not establish that a '17 Kb out, 75 Kb in' replacement could have been achieved by the skilled person in 2001 using the methods disclosed in the patent or other standard techniques. I have reached the opposite conclusion, for the reasons set out in detail in this judgment."

139. The second issue concerned the possibility of additional insertions. Regeneron argued that the skilled person could perform additional insertion steps following the initial insertion of one V and the D and J segments of the human sequence and it invited the judge so to find. As an alternative, it asked the judge to confirm that he had not made a finding that the person skilled in the art, having inserted such a human sequence into the murine locus could not thereafter without undue effort insert further sequences. In the further alternative, it invited the judge to address its submission that it was not

open to Kymab to take this point on the basis that it had not been pleaded or addressed in evidence.

140. The judge dealt with the second issue from [282]-[286]. He rejected all of Regeneron's arguments. He held that this was a matter he had already addressed in finding that the reverse chimeric locus could not be built up in a series of steps and so shunting up the mouse sequence; that Kymab's case had been adequately pleaded; and that the reason the issue had not been addressed by the experts in their reports was that it had only emerged during the cross-examination of Professor Stewart.

The arguments on appeal – an outline

141. Upon this appeal, Regeneron does not challenge all of the judge's findings. In particular, it does not question his finding that, at the priority date of the 287 patent, the skilled team could not have deleted 100 kb of mouse sequence and inserted 200-300 kb of human sequence in a single step. Nor does it challenge his finding that it was not possible to delete 150 kb of mouse sequence and insert 75 kb of human sequence in a single step.

142. It contends instead that the judge has focused unduly on the details of Example 3 and failed properly to consider whether the skilled team could have made mice falling within claim 1 of the 163 patent and cells and mice within claims 5 and 6 of the 287 patent by gene targeting and, in particular, by inserting a minigene construct containing a subset of the V, D and J segments at the proximal end of the mouse immunoglobulin variable region using traditional techniques of homologous recombination. It says there was no dispute that such a construct of up to 20 kb in length could have been made and inserted successfully.

143. Further, it continues, the judge ought to have found that the skilled team could have implemented the reverse chimeric locus without undue effort by using the LTVEC and MOA technology the patent describes and making simple and obvious adjustments to Example 3.

144. The first of these adjustments would have been to reduce the size of the inserts in the LTVECs by cutting down the number of V, D and J regions they contain and then to carry out the deletion of the mouse sequence in a separate step. In particular, it continues, the skilled team could have implemented the teaching with an insert in LTVEC 1 of about 50-75 kb in length. Further, the team could have shortened the insert further still by cutting out the intergenic regions to make a minigene.

145. Then, as taught in the specification at [0126], the skilled team could have inserted an additional variable region sequence of 50-75 kb in length at the distal end of the mouse locus, using a similarly modified LTVEC 2.

146. Finally, having performed an insertion at the proximal and distal ends of the mouse gene locus, the skilled team could have deleted the intervening mouse sequence without difficulty using SSR, as Professor Stuart accepted in his second report at [104]. The team could also have added more human V segments having a length of up to about 10 kb between the LTVEC 1 and LTVEC 2 insertions.

147. For these reasons, continues Regeneron, the specification of each of the patents did enable the skilled team to implement the invention and make products and perform the method described in the claims in issue and the judge ought so to have found.

148. In its written submissions Regeneron has taken a further point. It contends that the judge fell into error in accepting Kymab's submission that its success in inserting 144 kb of human sequence and deleting 16.6 kb of mouse sequence in one step was attributable to an improvement which was not disclosed in the patents and would not have occurred to the skilled person, namely the use of a reduced amount of DNA. It says that this was a contrived point with which Regeneron was ambushed at trial and upon which the judge should have placed no reliance at all.

149. Kymab responds that on the judge's findings of fact and his analysis of the scope of the claims, his conclusion that each of the claims in issue was invalid for insufficiency was inevitable. It says that Regeneron deployed a number of ways the skilled team could perform the claimed inventions, and that the judge addressed and rejected each of them. It necessarily follows that the claims are insufficient, and that remains the case despite all the points now advanced by Regeneron on this appeal.

150. Kymab also argues that the reason the judge did not address the contentions now advanced by Regeneron on this appeal is that he was never asked to, and that it is far too late for Regeneron to raise them now. The factual aspects of those contentions should have been raised in evidence and put to Kymab's experts; and then the contentions should have been developed before the judge in submissions. If and in so far as the judge failed to deal with them, they should have been raised with him after he provided his judgment to the parties in draft and before he handed it down, but they did not do so.

151. What is more, Kymab continues, the arguments now developed by Regeneron are unsound in fact and in law and do not in any way undermine the overall conclusions to which the judge came.

152. These rival submissions therefore give rise to a number of issues: first, whether it is open to Regeneron to rely upon its arguments before this court or whether it is foreclosed from doing so by the position it took before the judge; secondly and on the assumption it is open to Regeneron to rely upon these arguments, whether they have any factual foundation; and thirdly, whether these arguments and any findings we consider it appropriate to make provide a basis for reversing the judge's findings of insufficiency. These issues inevitably overlap but in the interests of clarity we will consider them separately. We address the first and second in this section of our judgment. We shall deal with the third later in our judgment after considering the law.

153. We must start, however, by explaining the concept of the minigene. This was addressed by Professor Howard in his first report when addressing the common general knowledge. There he described a minigene as a genetically engineered construct which includes the rearrangeable V, D and J segments, whilst non-essential DNA sequences (such as introns) have been removed. Professor Stewart provided much the same explanation of the term minigene in the annex to his first report which contained a glossary of terms and definitions which were common general knowledge at the priority date.

154. Professor Howard also described from [94]-[100] how minigenes had been used in the approach first proposed in the 1980s for the generation of mouse strains transgenic for human immunoglobulin genes which involved transferring human immunoglobulin genes to mice using plasmids, yeast artificial chromosomes or phage vectors. These vectors were constructed to carry either a transgene reflecting the native sequence of human immunoglobulin loci, or alternatively a minigene.

155. Professor Stewart gave a similar account in his first report at [67]. There he said that it was common general knowledge during the 1990s that a number of transgenic mice were generated which carried human immunoglobulin genes in germ-line configurations on minigene constructs.

Is Regeneron too late?

156. Our consideration of this issue must start with Kymab's pleaded case of invalidity. Kymab attacked each of the patents on various grounds. For the purposes of this appeal, we can focus on the following. It alleged first, that the patents lacked novelty in light of PCT/US91/00245 published as WO 91/10741 on 25 July 1991 ("Kucherlapati").

157. Secondly, the patents were obvious in the light of three publications: Kucherlapati; a US Patent 5,770,429 ("Lonberg"); and a publication entitled "*The Preparation of Human Antibodies from Mice Harbouring Immunoglobulin Loci*" published in 1997 in the textbook "Transgenic animals; generation and use" ("Brüggemann").

158. Thirdly, the patents were insufficient. This allegation had many different limbs, some of which fell away. Others were resolved by the judge in favour of Regeneron. So, for the purposes of this appeal, we can focus on the following. Kymab contended first, that claim 1 of the 287 patent encompassed but did not enable the *in situ* replacement of an entire endogenous murine immunoglobulin heavy chain variable region gene locus with an entire orthologous human gene locus carried in a single vector.

159. Kymab also contended that claim 1 of the 287 patent was not enabled because (among other things) the skilled team could not without undue effort:

    i) use an LTVEC to delete at least 100 kb of an endogenous murine variable region gene locus in a single homologous recombination step;

    ii) insert 200-300 kb of an orthologous human gene locus carried on the same LTVEC and as part of the same homologous recombination step as (i); or

    iii) use a modified human BAC to insert a fragment of at least 75 kb of an orthologous human variable region gene locus, or to replace at least 100 kb of an endogenous murine gene locus with at least 75 kb of an orthologous human variable region gene locus in a single RMCE step.

160. Similar allegations were made in relation to the product claims of the 287 patent and claim 1 of the 163 patent.

161. It is to be noted that Kymab did not assert that it was not possible to insert 75 kb (or less) of human sequence using the LTVECs of the specification. Nor did it assert that it was not possible to make smaller insertions by conventional techniques of

homologous recombination. Indeed, as we will see in a moment, it was part of Kymab's case that such smaller insertions could be made and that it was obvious to make cells and mice falling within the product claims of both patents in light of the cited prior art.

162. Coming now to the reports of the experts, Professor Evans expressed the opinion that the person skilled in the art could have made a mouse with a reverse chimeric immunoglobulin heavy or light chain locus comprising human orthologous variable V, D and J gene segments using the techniques described in the 287 patent and the common general knowledge. He acknowledged, however, that the skilled team would have been unlikely to attempt to conduct the *in situ* replacement of the entire mouse locus in a single step using homologous recombination. He thought that the skilled team would instead modify the mouse locus in a series of steps as described in the specification at [0128] and [0129].

163. Professor Evans also addressed the particular allegations made by Kymab and which we have set out at [158] above. As part of his evidence, he expressed the view that it would not have been any problem for the skilled person to insert at least 75 kb of an orthologous human sequence by a single site SSR step.

164. Professor Stewart focused a good deal of his attention on the teaching of the patents when considering what they enabled. He provided a commentary on the various methods that are taught and, in coming to Example 3, identified the various difficulties the skilled team would have had in trying to implement what it teaches.

165. Professor Howard and Professor Stewart also addressed the prior art that Kymab had cited and, in particular, Kucherlapati and Lonberg. In this connection and as we elaborate below, Professor Howard explained that it would have been obvious to the skilled team to include as many human variable segments as possible and to replace the mouse variable region, and that this might be achieved using a minigene construct engineered to include the re-arrangeable human V, D and J segments. Professor Stewart thought it would have been feasible to replace part of the mouse immunoglobulin variable locus with the corresponding part of the human immunoglobulin variable locus using a minigene construct up to about 20 kb in length containing a subset of the human variable region gene segments to replace the mouse J gene segments.

166. It was against this background that the action came on for trial. The parties had to address a large number of issues, many of considerable complexity. In these circumstances we do not find it surprising that each was not able to anticipate precisely how the other would develop its case. However, we have been taken to aspects of Regeneron's written and oral submissions from which we are satisfied that in opening it did make it clear that it was part of its case not only that the claims in issue do not require *in situ* replacement of all or even a substantial part of the endogenous locus in a single step, but also that it was not necessary to insert the entire human locus or to delete the entire mouse locus to obtain the benefits of the invention. It also contended that the teaching of the patents could be implemented by inserting shorter sequences than those described, carried on a BAC and engineered to contain the V, D and J segments without the intergenic regions, that is to say using a minigene approach.

167. At the trial the experts were cross-examined and, as we shall see, Mr Turner explored with Professor Stewart the ability of the skilled team to implement the teaching of Example 3, and to make and use not only the constructs which are disclosed there but also shorter constructs of, say, 75 or 50 kb in length, with and without the intergenic regions. There was no challenge to the evidence of Professor Stewart and Professor Howard about the ability of the skilled team to make a minigene construct.

168. In its written closing submissions, Regeneron maintained its position that the skilled team could perform the method of claim 1 of the 287 patent by inserting into the mouse immunoglobulin locus at least one human V segment and the human D and J segments upstream of the mouse constant regions, either with or without the deletion of mouse D and J segments, and that this would involve the insertion of about 75 kb of the orthologous human sequence. Mr Turner elaborated these points in his oral closing submissions and in doing so again made the point that if the team had any difficulty inserting a construct of 75 kb in length, it could be shortened by deleting the intergenic regions and making a minigene.

169. As we have explained, the judge did not address the issue of minigenes in the draft of the judgment he supplied to the parties. Upon receipt of that draft, Regeneron then drew to the judge's attention two matters which it believed to be material and with which, so it said, the judge had failed to deal: first, that following the teaching in the patents the skilled team could insert a human sequence of about 75 kb in length and comprising at least one V segment and D and J segments; and secondly, that after inserting such a sequence the skilled team could perform additional insertions. It did not invite the judge to address minigenes, however.

170. Having covered the ground, we can now return to the issue before us and whether it is open to Regeneron to rely upon the use of minigenes in support of this appeal. We consider the following points to be particularly material.

171. First, Kymab's pleaded allegations of insufficiency were carefully framed. We find it striking that, in giving details of what the skilled team could not achieve without undue effort, it did not assert that the specification did not enable the insertion of a fragment of an orthologous human variable gene locus up to 75 kb in length using the first approach of Example 3, that is to say homologous recombination using BACs with long homology arms and the MOA assay. A fragment of this size has particular significance because, as Mr Tappin emphasises, it can encompass one human V segment and the human D and J segments.

172. Secondly, we consider it was in these circumstances reasonable for Regeneron's experts to focus their attention in their reports on the allegations of insufficiency which Kymab had made, of which there were many.

173. Thirdly, Kymab was itself asserting that it was obvious at the priority date in the light of the cited prior art to make cells and mice falling within the product claims by using homologous recombination and a minigene construct of up to 20 kb in length engineered to include human orthologous variable V, D and J segments. Regeneron took issue with the suggestion that the cited art rendered it obvious to make a reverse chimeric locus but it has never disputed that, given that idea, the skilled team could carry out the necessary insertion without undue effort using a minigene. In our judgment Mr Turner's submission that this much appeared to be common ground has considerable force.

174. Fourthly, we are satisfied that, at trial, Mr Turner made clear in his opening submissions that Regeneron relied upon the use of minigenes as a way of implementing the teaching of the patents. This gave Mr Tappin, on behalf of Kymab, an opportunity to question Regeneron's experts if he wished to do so. Mr Turner then explored the issue with Professor Stewart in the course of his cross-examination. Finally, Mr Turner reiterated Regeneron's reliance upon the use of minigenes in his closing submissions in the manner we have described.

175. In our view these matters point in favour of allowing Regeneron to rely upon the evidence concerning the use of minigenes in support of its appeal. The one matter that has caused us considerable concern is that Regeneron did not raise the issue with the judge when it received the draft judgment. It is axiomatic that if an advocate believes that a judge has not dealt with a material issue then it should be drawn to the judge's attention pursuant to that advocate's duty to assist the court and to further the overriding objective. In *Re T (Contact: Alienation: Permission to Appeal)* [2002] EWCA Civ 1736; [2003] 1 FLR 531, Arden LJ said at [50]:

> "In a complex case, it might well be prudent, and certainly not out of place, for the judge, having handed down or delivered judgment, to ask the advocates whether there are any matters which he has not covered. Even if he does not do this, an advocate ought immediately, as a matter of courtesy at least, to draw the judge's attention to any material omission of which he is then aware or then believes exists. It is well-established that it is open to a judge to amend his judgment, if he thinks fit, at any time up to the drawing of the order. In many cases, the advocate ought to raise the matter with the judge in pursuance of his duty to assist the court to achieve the overriding objective (CPR 1.3, which does not as such apply to these proceedings); and in some cases, it may follow from the advocate's duty not to mislead the court that he should raise the matter rather than allow the order to be drawn. It would be unsatisfactory to use an omission by a judge to deal with a point in a judgment as grounds for an application for appeal if the matter has not been brought to the judge's attention when there was a ready opportunity so to do. Unnecessary costs and delay may result. I should make it clear that there are general observations for assistance in future cases, and that I make no criticisms of Counsel in this case."

176. We think it highly unsatisfactory that this course was not followed by Regeneron in this case. Quite apart from the consequences to which Arden LJ referred, it means that, if we allow Regeneron to develop its arguments before this court, we must either make an assessment of the evidence without the benefit of a reasoned decision of the trial judge, or remit it to him for his assessment with all the costs and delay that would entail.

177. In the end, however, we have come to the conclusion that the failure by Regeneron to raise the issue with the judge after receiving the draft judgment should not preclude it from relying upon it upon this appeal. As we shall explain, the relevant evidence is not extensive and was given primarily by Kymab's experts. Further, it is evidence

which we can assess with the benefit of the full submissions we have had from both parties.

178. For all of these reasons, we decide the first issue in favour of Regeneron. It is not precluded from developing before this court its contention that the judge fell into error in failing to find that the skilled team could have implemented the teaching of the patents by using their common general knowledge and adopting simple and obvious adjustments to Example 3, including the use of minigenes.

Implementation of the teaching

179. We begin with the question whether it was possible to make a reverse chimeric locus and so also products falling within each of the product claims in issue by using techniques which were part of the common general knowledge at the priority date. For this we must go to the evidence of Professor Stewart and Professor Howard and two of the publications to which they referred.

180. Professor Stewart pointed in his first report to Kucherlapati and explained at [193] that this application disclosed the creation of mouse ES cells in which the immunoglobulin heavy chain variable region had been replaced in whole or in part by the equivalent portion of the human immunoglobulin heavy chain variable region using homologous recombination. Professor Stewart continued at [194] that the skilled team would have appreciated at the priority date that the largest replacement that could be made by homologous recombination would be less than 20 kb. Therefore, the replacement of the mouse immunoglobulin heavy chain region with the human heavy chain region would require more than 100 rounds of homologous recombination. In Professor Stewart's view, this would have represented a massive project at the priority date which would have taken many years to complete. Regeneron accepts for the purposes of this appeal that this could not have been achieved at the priority date without undue effort.

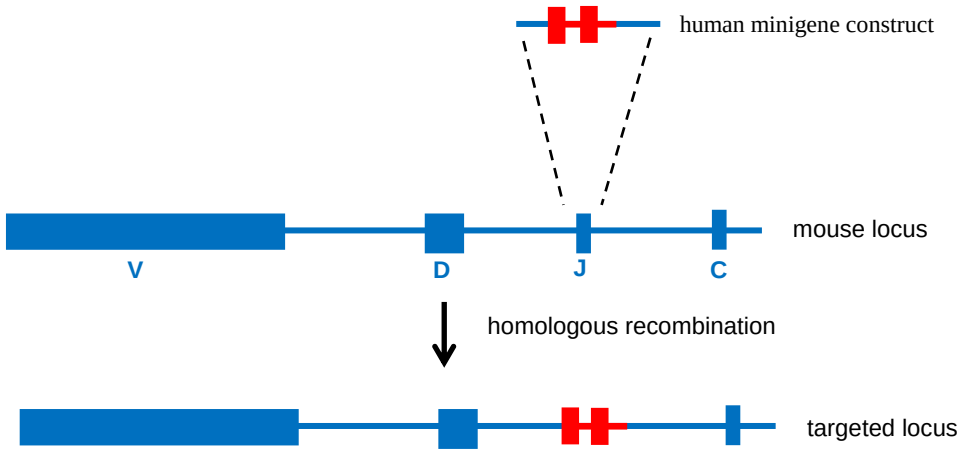
181. However, Professor Stewart then introduced at [195] of his first report the possibility of using minigenes:

> "The only way it would have been feasible to create a transgenic mouse in which part of the immunoglobulin variable region was replaced by part of the human immunoglobulin variable region at the priority date would be to use a small minigene construct up to approximately 20 kb in length containing a subset of the human immunoglobulin variable region gene segments."

182. Professor Stewart returned to this issue in his second report at [102]–[105]. Here he reiterated that a minigene construct of up to 20 kb in length could contain a subset of the human immunoglobulin variable region gene segments (V, D and J gene segments in the case of the heavy chain, and V and J gene segments in the case of the light chain). He understood from Professor Howard that the skilled immunologist would have wanted to replace the mouse J region with the 20 kb gene construct in such a way that the mouse J gene segments would be deleted and so prevent the formation of fully mouse antibodies. He continued at [103]:

> "103. This would involve the replacement of less than 5 kb of mouse sequence (spanning the J gene segments) with the 20 kb minigene construct. As I explained at paragraph 37 of my First Report, replacements of this size were technically feasible at the Priority Date. Furthermore, I believe that the targeting construct that would have been used by the Skilled Genetic Engineer would have contained homology arms of the length commonly used at the Priority Date (i.e. 1-5 kb), designed such that the human minigene construct would replace the J region of the mouse immunoglobulin variable region, …"

183. Professor Stewart illustrated this approach in this figure in which the mouse sequence is shown in blue, and the human in red:



184. Much the same point was made by Professor Howard in his first report in the context of Kucherlapati. He said at [128]-[129] that the skilled immunologist would have understood that a useful antibody repertoire could be achieved from a subset of variable region gene segments, and that the minimum size of a cloned genomic construct containing one human V, one D and one J segment (i.e. spanning from the beginning of the most proximal V segment to the end of the most distal J segment in the human heavy chain locus) would be approximately 75 kb in length. But, as an alternative, the skilled team could have used smaller minigene constructs (engineered to include rearranged V, D and J segments).

185. The use of minigenes was picked up by Professor Stewart again in considering Lonberg. This publication is referred to in Example 3 of the 287 patent at [0114] and, in discussing it in his first report, Professor Stewart asked himself what steps the skilled team would have taken at the priority date if tasked with making a transgenic mouse that expressed chimeric antibodies of the kind it describes. After considering and rejecting random transgenesis as an option, Professor Stewart addressed the possibility of using gene targeting. In that connection, he said this at [204]:

> "204. As I explained above in relation to Kucherlapati, although it would have been desirable to create a transgenic mouse containing the entire human immunoglobulin variable region, for the reasons already described, this would not have been technically feasible at the Priority Date. The Skilled

> Genetic Engineer would therefore have used a minigene construct containing a subset of the V, D and J segments, which would be inserted at the proximal end of the mouse immunoglobulin variable region in place of the J segments. Such minigene constructs are described in Lonberg in column 15, lines 37 to 63."

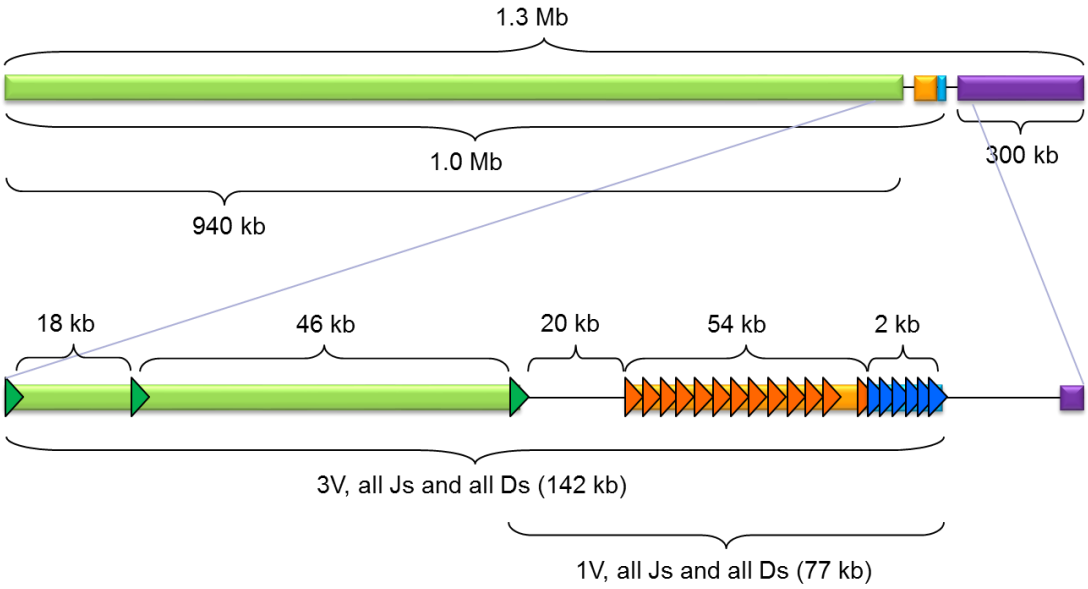
186. In the end the judge rejected the attack based upon Kucherlapati, not because he rejected the evidence of the experts concerning the use of minigenes but because aspects of its teaching were not clear and, more fundamentally, it did not disclose the reverse chimeric locus or, so far as claim 1 of the 287 patent was concerned, the use of LTVECs or the MOA assay. The attack based upon Lonberg was abandoned by Kymab during the course of Mr Tappin's closing speech on its behalf.

187. In our judgment it is clear from this evidence that, notwithstanding the judge's conclusion about the teaching of Kucherlapati, the concept of the minigene was common general knowledge at the priority date and we have no doubt that the skilled team seeking to implement the teaching of the patents would have appreciated that it was possible to create a transgenic mouse in which part of the mouse immunoglobulin variable region had been replaced by part of the human immunoglobulin variable region by using a small minigene construct of up to 20 kb in length containing a subset of the human V, D and J segments (in the case of the heavy chain) and a subset of the V and J segments (in the case of the light chain), and that this could have been achieved by homologous recombination and without undue effort.

188. That brings us to the alternative way of implementing the various aspects of the teaching, namely by the use of the techniques described in Example 3 (that is to say, LTVECs and the MOA assay) with obvious adjustments. Here, for the reasons we have given, we must consider the expert evidence given in cross-examination at the trial in rather more detail than is usually the case on an appeal.

189. Professor Stewart maintained in his oral evidence that Example 3, as described, would have presented a real challenge and would not have worked. He was then asked about possible modifications to the experimental protocols it contains. He explained that, faced with the failure of Example 3 and other deficiencies in the description, the skilled team might have become alarmed and uncertain as to what the patent was teaching, but that an obvious way forward would have been to make the strategy more realistic and reduce the size of the inserts to, say, 75 kb in length (see day 6, p.910, line 12 - p.912, line 2).

190. In this connection Professor Stewart also accepted that the skilled team would have known that another way of reducing the length of the inserts would have been to remove the intergenic regions by making a minigene. Here he was asked questions by reference to a diagram of the human immunoglobulin variable gene locus produced by Regeneron for the trial and identified as X12:



191. The following interchange then took place with Professor Stewart on day 6, p.911, line 20 – p.912, line 25):

> "Q. But if we can just take it in stages. My question to you is, if the skilled person was concerned that an insert, and I think you are alluding to an insert of 200 kb, was too big, an obvious option for the skilled person would be to say, I will put in a 75 kb insert. That would be an obvious ----
>
> MR. JUSTICE HENRY CARR: He has already said yes, I think.
>
> THE WITNESS: Yes.
>
> MR. TURNER: I do apologise, my Lord, if I missed that. I am sorry, professor. Let us then have a look at X12. Keep the patent out. Let us have a look at X12. This is the human locus and I am looking at the bottom strand. One can see there are -- I do not know if one calls them strictly intergenic regions or introns, but I am talking about the gaps between the D and the first V and the gap between the first V and the second V. Do you call them introns or intergenic regions in the context of this locus?
>
> A. This is not a normal gene. I do not know what immunologists would call these ----
>
> Q. Let us call them gaps. You could certainly take out sequence from those gaps, could you not? You could do that by recombineering? That would be one way of ----
>
> A. Reduce the distance between the two Vs?
>
> Q. For example, yes. If you wanted to put two Vs in, you could just say do some recombineering, delete out 30 ----

A. Yes, absolutely. In fact, I said that one way of doing this would be to make a minigene, and that is in my report.

Q. Yes, that is ----

A. The minigene would involve indeed reducing the distance between the coding regions, the V and the D and the J coding regions.

192. This minigene could then have been inserted at the 3' or proximal end of the mouse genome in LTVEC 1.

193. Mr Turner explored with Professor Stewart the position at the 5' or distal end and LTVEC 2 on day 6, p.913, line 22 – p.914, line 18:

"Q. If you could indulge me and let us just ignore what Regeneron did for a moment. Let us perhaps, first of all, look at the strategy that is suggested in this patent. Let us go back to page 40, figure 4B. The suggestion is to then put a second LTVEC in at the 5 prime region. Again, as a strategy, there is nothing wrong with that, is there?

A. You are talking about LTVEC2?

Q. Yes.

A. LTVEC2 suffers from the same improbabilities as LTVEC1.

Q. Right.

A. Again, the skilled genetic engineer and his team or her team would, you know, flounder around trying to do the described exercise and then come to the conclusion that it needed to be redesigned.

Q. Let us assume you are putting in your second insert at the 5 prime end and you decide to go with, let us say, 50 kb this time. You put in two or three Vs and a loxP site at the 5 prime end. There is nothing wrong with that, is there?

A. I believe you would be able to do something like that, yes. Make it a more realistic exercise and target the 5 prime end, yes."

194. Mr Turner returned to the same question a little later on the same day and, in another important passage of the evidence, explored with Professor Stewart whether an insertion into the mouse genome of a segment of human sequence of about 75 kb in length and a deletion from the mouse genome of a segment of about 17 kb in length could have been achieved (day 6, p.924, line 17 – p.926, line 2):

"Q. Now, yesterday we discussed the making of LTVEC and as I have said, I do not want to go over that again. I want you

to assume you have now made an LTVEC which contains, let us say, between 75 and 150, if we can take the range, human insert, which is going to go in at that locus we have been talking about and you have decided to make a small deletion of Js and maybe a D, so let us say 17 kb. So you are putting in 75 or a little more and you are taking out 17 kb. That is your intended experiment. The person skilled in the art in doing this has reduced the techniques to practise, has got them working well, has done his workup experiments or her workup experiments and is using of course long homology arms and the MOA assay. Provided that manipulation is performed diligently at a reasonable trial and error, that will work, will it not?

A. What, sorry?

Q. What you are trying to do is you are trying to put in 75 or perhaps a little more of Vs, Ds and Js.

A. Yes.

Q. We are back into the ES cell now.

A. Yes.

Q. And you are trying to make a deletion of about 17 kb. I am asking you to assume that. You have your LTVEC. Everything is working well. The ES cells are working well. The techniques are working well.

A. Good.

Q. And now you are going to do this manipulation. It is going to work, is it not?

A. If you had asked me that question in 2001, I would have said I have no idea. This is very ambitious. I have no idea if this is going to work. I hope it does, really, you know, I would like to see experiments like that work, but in 2001 I could not have given you an answer. In 2015 we know the answer.

Q. And the answer is?

A. Yes."

195. Basing himself on this evidence, Mr Turner submits that it would have been obvious to the skilled team seeking to implement the method of claim 1 of the 287 patent:

i) to use an LTVEC 1 containing human V, D and J segments of 50 to 75 kb in length;

ii) to use an LTVEC 2 containing human V segments of 50 to 75 kb in length;

iii) to delete the mouse V segments in the middle with SSR; and

iv) to insert by SSR in the place of the deleted mouse V segments around 10 kb of human V segment sequence.

196. Further, submits Mr Turner, this protocol would have worked and could have been implemented without undue effort, and the judge should have so held.

197. Mr Tappin counters that the skilled team could not have implemented Example 3 as described without undue effort and that, in these circumstances, the burden of proving that the claimed inventions could be implemented in some other way lay on Regeneron and it was a burden that it could not and did not discharge. The judge dealt with the suggestions for implementation put forward on behalf of Regeneron both at trial and after the judgment had been provided to the parties in draft, and he rejected each and every one of them.

198. Mr Tappin also submits that Professor Evans set out in his reports the various steps that he thought the skilled team would take to try and make Example 3 work. However, he did not at any point suggest the use of minigenes and so it was never properly explored in evidence. To the contrary, Mr Tappin continues, it was common ground that the minimum length of fragment required to implement the method of claim 1 of the 287 patent was 75 kb and the judge has made an express finding that the skilled team could not have inserted such a fragment into the mouse genome without undue effort. Here and elsewhere, says Mr Tappin, we are being asked to interfere with findings of fact made by the trial judge and that is something which we should not do.

199. We have carefully evaluated these submissions and the evidence to which we have referred and our conclusions are these.

200. First and by way of recap, we are satisfied, for the reasons we have given, that the use of minigenes was part of the common general knowledge. Further, it was Professor Stewart's evidence and we accept that it was technically feasible at the priority date to replace 5 kb of mouse sequence (spanning the J segments) with a 20 kb minigene construct containing a subset of the human immunoglobulin variable region segments (V, D and J gene segments in the case of the heavy chain, and V and J segments in the case of the light chain). In our judgment and given the idea of the reverse chimeric locus, it would have been obvious to the skilled team and technically feasible to produce a transgenic mouse that would produce hybrid antibodies containing human variable regions and mouse constant regions, and in which mouse V, D and J segments had been replaced with human V, D and J segments in the mouse immunoglobulin heavy chain gene locus, and mouse V and J segments had been replaced with human V and J segments in the immunoglobulin light chain gene locus.

201. Secondly, we have no doubt that it would also have been obvious to the skilled team, faced with what the judge described as the unprecedented insertions and deletions described in the Example 3, to make the insertions shorter. It would also have been perfectly apparent to the skilled team that any necessary deletions could be carried out in a separate step and that there were well known and effective ways of achieving this, including SSR.

202. Thirdly and as the judge found, a cloned genomic fragment of the human immunoglobulin heavy chain variable gene locus that contains one V segment and all of the D and J gene segments will be about 75 kb in length, including the intergenic

regions. But of course, deletion of some of the intergenic regions would make it considerably shorter. In that regard, we have already seen that it was common ground that a 20 kb fragment of the human immunoglobulin variable locus could contain V, D and J segments. But the point is also made good by the locus map identified at trial as X12 which was explored with Professor Stewart in cross-examination in the passage of his evidence we have cited above and is given further support by figure 31 of the Lonberg citation relied upon by Kymab to which we were taken by Mr Turner during the course of the hearing.

203. Fourthly, we have given anxious consideration to Mr Turner's submission that we should reverse the judge's finding concerning the feasibility of using LTVECs and the MOA assay to effect and detect the targeted insertion into the mouse endogenous immunoglobulin heavy (or light) chain locus of a cloned human gene fragment of 75kb and the deletion of 17 kb from that locus. We recognise the force of Mr Turner's submission in light of the evidence of Professor Stewart that we have cited at [191] and [193]-[194] above. The opinion that Professor Stewart expressed there was not, to our minds, dependent on any work that Regeneron had carried out after the priority date; nor was it dependent upon the use by Regeneron of a particular improvement called the 3hVH vector, as Kymab appears to have suggested. Nevertheless, as Lewison LJ explained in *Fage UK Ltd v Chobani UK Ltd* [2014] EWCA Civ 5, [2014] FSR 29 at [114], appellate courts have been repeatedly warned by decisions at the highest level not to interfere with findings of fact by trial judges unless compelled to do so and, in the circumstances of this case, where the judge has had the benefit of hearing the expert witnesses give their evidence, that warning is particularly apposite. We therefore reject Mr Turner's submission.

204. For like reasons we also decline to interfere with the judge's finding that the use by Regeneron of a reduced amount of DNA in the course of its development work would not have occurred to the skilled person seeking to implement the teaching of the specification.

205. Fifthly, that does not mean to say that the skilled team could not perform the method of claim 1 of the 287 patent, however, for that team would also have appreciated the possibility of using minigenes in that method, just as they would have appreciated the possibility of using minigenes to achieve targeted insertions of sequences of up to 20 kb in length using homologous recombination. Here we are not asked to reverse a finding of fact for the judge made no finding that this was not feasible and we have seen no effective answer to the submission by Mr Turner that Professor Stewart accepted that this was a viable approach in the course of his cross-examination on day 6 in the passages we have recited at [191] and [193]-[194] above, and that in this way a sequence of at least 50 kb could be inserted in one step using the LTVEC technology and detected using the MOA assay.

206. Sixthly, the judge rejected Regeneron's contentions (so far as they were made) that the skilled team could have implemented the teaching of Example 3 at the priority date using the techniques described in the Macdonald paper; by making repeated insertions using homologous recombination and so 'shunting up' the native mouse sequence; or by building up the desired sequence in the mouse immunoglobulin variable region gene locus by repeated BAC insertions. As we have explained, he also rejected Regeneron's submissions after circulation of the draft judgment as to the feasibility of making a targeted insertion of about 75 kb of the human sequence or

performing repeated small sequential insertions. But the judge did not reject as unworkable the teaching in Example 3 that there should be a targeted insertion at the proximal end of the mouse immunoglobulin variable region gene locus (using LTVEC 1), followed by a targeted insertion at the distal end of the locus (using LTVEC 2), followed by further steps in the middle to delete any unwanted mouse sequences (using SSR) and to insert a further human sequence of up to about 10 kb in length (using RMCE). In our judgment the evidence establishes that all of these steps would have been obvious and feasible and could have been performed without undue effort in light of the teaching of Example 3 and the common general knowledge.

207. In our judgment it follows that it would have been apparent to the skilled team in light of the teaching of the patents and the common general knowledge how to modify the endogenous immunoglobulin heavy chain variable region gene locus of an isolated mouse ES cell by an *in situ* replacement of V, D and J gene segments of the endogenous gene locus with orthologous human V, D and J segments to create a modified locus that produced hybrid antibodies containing human variable regions and mouse constant regions. It would also have been apparent to the skilled team that one way of achieving this would have been to use a cloned genomic fragment greater than 20 kb containing orthologous human V, D and J gene segments; to use bacterial homologous recombination to modify this cloned genomic fragment to create an LTVEC for use in a mouse ES cell; to introduce the LTVEC into a mouse ES cell to replace the V, D and J segments *in situ* with the orthologous human V, D and J segments; and to use the MOA assay to detect the mouse ES cells in which this replacement had occurred. In this way the skilled team could have made a reverse chimeric locus containing several V segments without undue effort.

The law

208. This appeal raises once again the issue of the permissible scope of a patent claim having regard to the ground for revocation in s.72(1)(c) of the Patents Act 1977 that the specification of the patent does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art. This provision corresponds to the ground of opposition in Article 100(b) of the European Patent Convention (the "EPC") and reflects the requirements of Article 83 EPC. We should also mention Article 84 EPC which provides that the claims must be clear and concise and supported by the description. This gives effect to the same legal principle that the patent monopoly should be justified by the technical contribution to the art that the disclosure of the invention has made.

209. Certain general principles of relevance to this appeal were not in dispute:

i) the sufficiency of the disclosure is to be assessed having regard to the specification as a whole, including the description and the claims;

ii) the disclosure is to be considered through the eyes of the skilled person or, as here, the skilled team to whom the patent is addressed; and

iii) the skilled person may use his or her common general knowledge to supplement the information contained in the specification.

The degree of enablement

210. It is now well established that the skilled team must be able to perform the invention without undue effort. The approach of the Boards of Appeal of the EPO was explained in T 226/85 *Stable bleaches/UNILEVER*:

> "8. Even though a reasonable amount of trial and error is permissible when it comes to the sufficiency of disclosure in an unexplored field or, – as in this case -, where there are many technical difficulties, there must then be available adequate instructions in the specification or on the basis of common general knowledge which would lead the skilled person necessarily and directly towards success through the evaluation of initial failures or through an acceptable statistical expectation rate in the case of random experiments."

211. The law has developed in this jurisdiction in the same way. In *Mentor Corp. v Hollister Inc.* [1991] FSR 557 Aldous J said this:

> "The section requires the skilled man to be able to perform the invention, but does not lay down the limits as to the time and energy that the skilled man must spend seeking to perform the invention before it is insufficient. Clearly there must be a limit. The sub-section, by using the words, clearly enough and completely enough, contemplates that patent specifications need not set out every detail necessary for performance, but can leave the skilled man to use his skill to perform the invention. In so doing he must seek success. He should not be required to carry out any prolonged research, enquiry or experiment. He may need to carry out the ordinary methods of trial and error, which involve no inventive step and generally are necessary in applying the particular discovery to produce a practical result. In each case, it is a question of fact, depending on the nature of the invention, as to whether the steps needed to perform the invention are ordinary steps of trial and error which a skilled man would realise would be necessary and normal to produce a practical result."

212. On appeal, Lloyd LJ (with whom Stuart-Smith and Scott LJJ agreed) approved that summary of the law: [1993] RPC 7 at 14. Lloyd LJ added this further guidance at 12-13:

> "In each case sufficiency will thus be a question of fact and degree, depending on the nature of the invention and the other circumstances of the case.
>
> But if a working definition is required then one cannot do better than that proposed by Buckley L.J. in giving the judgment of the Court of Appeal in *Valensi v British Radio Corporation* [1973] R.P.C. 337. After referring to a number of earlier authorities, including *Edison & Swan v Holland*, he said:
>
> 'We think that the effect of these cases as a whole is to show that the hypothetical addressee is not a person of exceptional

> skill and knowledge, that he is not to be expected to exercise any invention nor any prolonged research, inquiry or experiment. He must, however, be prepared to display a reasonable degree of skill and common knowledge of the art in making trials and to correct obvious errors in the specification if a means of correcting them can readily be found.'
>
> Then a little later:
>
> 'Further, we are of the opinion that it is not only inventive steps that cannot be required of the addressee. While the addressee must be taken as a person with a will to make the instructions work, he is not to be called upon to make a prolonged study of matters which present some initial difficulty: and, in particular, if there are actual errors in the specification—if the apparatus really will not work without departing from what is described—then, unless both the existence of the error and the way to correct it can quickly be discovered by an addressee of the degree of skill and knowledge which we envisage, the description is insufficient.'
>
> In that case there was a mistake in the specification. But Buckley L.J.'s language is equally apt to cover an omission. Aldous J said that the *Valensi* test is as apposite under the 1977 Act as it was under the 1949 Act. I agree."

213. Finally, we would emphasise that the sufficiency of the description is a matter which must be assessed having regard to the nature of the invention, the character of the technical field in which the invention is made, and the abilities of the skilled team: see, for example, *Halliburton v Smith International Inc* [2006] EWCA Civ 1715 at [13], [18]-[21].

Enablement across the scope of the claim

214. That brings us to the legal issue at the heart of this appeal, namely the extent to which and the manner in which an invention must be enabled across the whole scope of the claim. The answer to this question has been explored in a number of decisions of the Technical Boards of Appeal of the EPO to which we were taken in the course of the appeal hearing (and which, as is now well established, are of great persuasive authority in construing a provision such as s.72(1) of the 1977 Act which is so framed as to have, as nearly as practicable, the same effects in the United Kingdom as the corresponding provision of the EPC: see, for example, *Merrell Dow Pharmaceuticals Inc v H. N. Norton & Co Ltd* [1996] RPC 76 at 82). It is not necessary in this judgment to address each of those decisions, however, and we shall focus on those which illustrate the principles which are relevant to this appeal and upon which the parties particularly relied. It is convenient to take them in chronological order.

215. The first is T 0292/85 *Polypeptide expression/GENENTECH I*. Here the application disclosed a new method of transforming bacteria using plasmids which contained a homologous regulon in conjunction with a heterologous DNA insert encoding a

desired functional polypeptide or intermediate. The claims were cast in general functional language. Claim 1, directed to a recombinant plasmid, embraced, among other things, plasmids which might be developed in the future, regulons which had not yet been provided, and bacterial forms which were not yet known. The Examining Division found that in these circumstances the application failed to satisfy the requirements of Articles 83 and 84 EPC that all products and methods in the claims should be reproducible at will.

216. The Board of Appeal disagreed. It observed that, in appropriate cases, it is only possible to define the invention in a way which gives fair protection having regard to the nature of the invention described, by using functional terminology:

> "3.1. Components of the future
>
> 3.1.1 Recombinant plasmids embrace, as components, various regulons which have not yet been provided and may, one day, represent inventions on the basis of some merit of their own. The same applies to the basic plasmid, which has been modified to possess the characteristics of the claim. The original plasmid might have complex structures to be developed in the future. Bacteria transformed with the claimed plasmids embrace mutant or modified forms not yet known. According to the Examining Division this situation contradicts the suggested requirement that all embodiments within the claims should be reproducible at will by the skilled person without having to make an invention.
>
> 3.1.2 There is, however, in the opinion of the Board, no such requirement in the European Patent Convention, nor is such principle established in normal patent practice within the Contracting States. The suggested features in the claims are essentially functional terms in this particular context, in spite of structural connotations, and may cover an unlimited number of possibilities. It follows that the features may generically embrace the use of unknown or not yet envisaged possibilities, including specific variants which might be provided or invented in the future. … In appropriate cases, such as the present, it is only possible to define the invention (the matter for which protection is sought - Article 84 EPC) in a way which gives a fair protection having regard to the nature of the invention which has been described, by using functional terminology in the claims.
>
> 3.1.3 What is also important in the present case is the irrelevancy of the particular choice of a variant within the functional terms "bacteria", "regulon" or "plasmid". It is not just that some result within the range of polypeptides is obtained in each case but it is the same polypeptide which is expressed, independent of the choice of these means. A term of this kind must, of course, be clear and enable the skilled person to find suitable specimens without undue difficulty. In the

present application enough choice is available, although some vehicles and hosts are preferred for practical reasons."

217. Then the Board explained that the objection against the use of broad functional terminology such as "plasmid" and "bacteria" was, in the circumstances of this case, untenable, and, importantly, that the need for fair protection governed considerations of the scope of claims and the requirements for sufficient disclosure:

> "3.1.5 The above examples show that the need for a fair protection governs both the considerations of the scope of claims and of the requirements for sufficient disclosure. Unless variants of components are also embraced in the claims, which are, now or later on, equally suitable to achieve the same effect in a manner which could not have been envisaged without the invention, the protection provided by the patent would be ineffectual. Thus it is the view of the Board that an invention is sufficiently disclosed if at least one way is clearly indicated enabling the skilled person to carry out the invention. Consequently, any non-availability of some particular variants of a functionally defined component feature of the invention is immaterial to sufficiency as long as there are suitable variants known to the skilled person through the disclosure or common general knowledge, which provide the same effect for the invention. The disclosure need not include specific instructions as to how all possible component variants within the functional definition should be obtained.
>
> 3.1.6 The Examining Division's tentative suggestion that such terms should be restricted to those available in the art has no basis in existing law. Unless broad, yet proper terminology is allowable, subsequent investigations by third parties might be encouraged to concentrate on finding alternatives outside the claims instead of trying to pursue progress through dependent inventions. The lack of recognition of the full significance and the interdependency of technical contributions could adversely affect progress in the area of microbiology and biochemistry.
>
> 3.1.7 In view of the above, it is also irrelevant that some of the variants of bacterial strains or regulons might only exist in private collections or can only be found in locations or derived from sources which are inaccessible or were only transiently available to the public. As long as there are means available for performing the invention, such exceptional circumstances cannot counteract the possibility that the invention can be carried out."

218. The Board turned next to the possibility that it might not be possible to put the invention into effect with some components and held that this was immaterial provided that some suitable variants were known to the skilled person. Further, in considering the legitimate scope of the claims it emphasised the need to have regard to the character of the invention:

> "3.3.2 … The present application is, however, not concerned with the problem of obtaining a finite set of particular products, as in the cited decision. The character of the invention this time is one of general methodology which is fully applicable with any starting material, and is, as it was already stated, also independent from, the known, trivial, or inventive character of the end-products. The transformed bacteria, as well as the claimed plasmids are agents and genetic precursors in a process of transformation, expression and recovery leading to the programmed products, and as long as the system works reliably at every stage there is no obligation to exclude future starting materials."

219. The Board therefore rejected the argument that the claims were insufficient. It held that disclosure was adequate and sufficient in the circumstances and there was enough information to apply the subject matter of the invention for the stated purpose.

220. The next decision of the Board of Appeal is T 0409/91 *Fuel Oils/EXXON*. Here the claimed invention lay in the field of fuel oils and the need to ensure that the wax crystals which form at low temperatures are as small as possible. Claim 1 of the main request was directed to fuel oils in which those crystals had a particle size of less than 4000 nm. The Opposition Division rejected the main request for two reasons: first, there was no teaching how to obtain a fuel oil in which the wax crystal size would be less than 1000 nm; and secondly, the need to have the crystals as small as possible was already known in the art and any patentable invention could only lie in the choice of the superior additive which would produce the crystals of the desired size, but no such additive was specified in the claim.

221. On appeal, the Board had no difficulty rejecting the main request, for the claims related to fuel oils containing wax crystals smaller than 1000 nm but no way of obtaining such fuel oils was disclosed or could be found in the common general knowledge. In the words of the Board:

> "2 ….in order to fulfil the requirement of Article 83 EPC, the application as filed must contain sufficient information to allow a person skilled in the art, using his common general knowledge, to carry out the invention within the whole area that is claimed."

222. An auxiliary request which differed from claim 1 of the main request by introducing a lower limit of the particle size of 1000 nm was also rejected under both Articles 83 and 84 EPC. In addressing Article 84, the Board said this:

> "3.3 … In the Board's judgment, this requirement reflects the general legal principle that the extent of the patent monopoly, as defined by the claims, should correspond to the technical contribution to the art in order for it to be supported, or justified (see T 133/85, OJ EPO 1988, 441). This means that the definitions in the claims should essentially correspond to the scope of the invention as disclosed in the description. In other words, as was stated in Decision T 26/81 (OJ EPO 1982, 211, point 4 of the reasons), the claims should not extend to subject-

> matter which, after reading the description, would still not be at the disposal of the person skilled in the art."

223. Then, in addressing Article 83, The Board continued:

> "3.5 …. In the Board's judgment, the disclosure of one way of performing the invention is only sufficient within the meaning of Art. 83 EPC if it allows the person skilled in the art to perform the invention in the whole range that is claimed, as was already stated in point 2 above."

224. The insuperable problem facing the applicant, however, was that the claims extended to the use of any additives but no information was given which would enable the skilled person to perform the invention with additives other that those described in the specification. Accordingly, the claimed monopoly was not justified by the applicant's contribution to the art. It did not allow the skilled person to perform the invention over the whole range of the claim, and having regard to the technical contribution, this deficiency was fatal to the validity of the claim.

225. The third decision of the Board of Appeal is T 0435/91 *Detergents/UNILEVER*, another case in which the claim in issue extended to products, here additives defined by function, but where the specification failed to disclose a concept fit for generalisation which would enable the skilled person to find other additives across its the scope. The Board explained:

> "2.2.1. … In the Board's judgment the criteria for determining the sufficiency of the disclosure are the same for all inventions, irrespective of the way in which they are defined, be it by way of structural terms of their technical features or by their function. In both cases the requirement of sufficient disclosure can only mean that the whole subject-matter that is defined in the claims, and not only a part of it, must be capable of being carried out by the skilled person without the burden of an undue amount of experimentation or the application of inventive ingenuity.
>
> The peculiarity of the "functional" definition of a component of a composition of matter resides in the fact that this component is not characterised in structural terms, but by means of its effect. Thus this mode of definition does not relate to a tangible component or group of components, but comprises an indefinite and abstract host of possible alternatives, which may have quite different chemical compositions, as long as they achieve the desired result. Consequently, they must all be available to the skilled person if the definition, and the claim of which it forms a part, is to meet the requirements of Article 83 or 100(b) EPC. This approach is based on the general legal principle that the protection covered by a patent should correspond to the technical contribution to the art made by the disclosure of the invention described therein, which excludes that the patent monopoly be extended to subject-matter which,

> after reading the patent specification, would still not be at the disposal of the skilled person …
>
> There cannot, of course, be a clear-cut answer to the question of how many details in a specification are required in order to allow its reduction to practice within the comprehensive whole ambit of the claim, since this question can only be decided on the basis of the facts of each individual case. Nevertheless, it is clear that the available information must enable the skilled person to achieve the envisaged result within the whole ambit of the claim containing the respective "functional" definition without undue difficulty, and that therefore the description with or without the relevant common general knowledge must provide a fully self-sufficient technical concept as to how this result is to be achieved."

226. The fourth decision of the Board of Appeal is T 0694/92 *Modifying plant cells/MYCOGEN* which once again emphasised the need to be sensitive to the nature of the invention and the contribution it has made to the art in assessing the sufficiency of the disclosure. Here the claims were directed to a general way of genetically modifying a plant cell by inserting a plant gene comprising a plant promoter and a plant structural gene into T-DNA in a particular configuration and then transferring that combination into a plant cell so that the cell would express the protein encoded for by the gene. The question for the Board was how to find the appropriate balance between, on the one hand, the technical contribution to the art made by the disclosure of the invention and, on the other hand, the wording of the claims so that the scope of protection was fair and adequate. It reasoned as follows:

> "5 … In certain cases a description of one way of performing the claimed invention may be sufficient to support broad claims with functionally defined features, for example where the disclosure of a new technique constitutes the essence of the invention and the description of one way of carrying it out enables the skilled person to obtain without undue burden the same effect of the invention in a broad area by use of suitable variants of the component features … . In other cases, more technical details and more than one example may be necessary in order to support claims of a broad scope, for example where the achievement of a given technical effect by known techniques in different areas of application constitutes the essence of the invention and serious doubts exist as to whether the said effect can readily be obtained for the whole range of applications claimed …. However, in all these cases, the guiding principle is always that the skilled person should, after reading of the description, be able to readily perform the invention over the whole area claimed without undue burden and without needing inventive skill …. On the other hand, the objection of lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts …." (Citations omitted).

227. The Board answered this question later in the decision. It held that the actual contribution to the state of the art by the disclosure of the patent lay in providing experimental support for the transfer into and expression in plant cells of a DNA encoding a particular protein, phaseolin, under the control of its own promoter. It was in effect the successful completion of an experiment anticipated by an oral disclosure made before the priority date, and the disclosure of the patent did not enable the skilled person to achieve the expression of other genes under the control of their own promoters in different plant cells. The claims were therefore insufficient.

228. The decision of the Board of Appeal in T 0636/97 *Erythropoetin II/KIRIN AMGEN* is also of some interest. This decision concerned the patent the subject of the Board's own earlier decision T 412/93 and the decision of the House of Lords in *Kirin-Amgen Inc v Hoechst Marion Roussel* [2004] UKHL 46, [2005] RPC 9, to which we will come. For present purposes, we need refer only to the discussion by the Board of the balance to be drawn between the need for fair protection and the requirement imposed by Article 83 EPC that the disclosure must be sufficient to enable the claimed invention to be performed across its scope:

> "4.5. For the board it is a fundamental principle of patent law that a claim can validly cover broad subject matter, even though the description of the relevant patent does not enable every method of arriving at that subject matter to be carried out. Otherwise no dominant patent could exist, and each developer of a new method of arriving at that subject matter would be free of earlier patents. In many cases in the field of biotechnology, patent protection would then become illusory. This is not to say that some claims might not be too broad in scope and not be enabled over their whole scope for the purpose of Article 83 EPC (see for example decisions T 409/91-3.3.1 (OJ EPO 1994, 653), but this was not considered to be the case in respect of Claim 1 by this board in T 412/93 on the evidence before the board and this is res judicata. The boards have considered this question of allowability of a broad claim versus the requirements of Article 83 EPC, strictly on a case by case basis, influenced by the extent to which the information in the patent could be used to develop further embodiments without a major conceptual leap."

229. The final decision of the Board of Appeal to which we must refer is T 1743/06 *Amorphous silica/INEOS*. Here the claim was directed to amorphous silica characterised by a series of parameters. The term amorphous silica comprised a host of chemical compounds which might or might not satisfy the requirements in the claims. The Board held the relevant claims were not sufficient because the lack of guidance as to how to find amorphous silicas which satisfied the parameter requirements of the claims across their scope meant the skilled person would be faced with a research program:

> "1.9 The skilled person is thus confronted with the uncontested fact that he has a lot of process variables affecting the claimed parameters, but once he has encountered failure in one parameter value, there is no clear guidance enabling him to

> adjust the multitude of process steps in order to arrive with certitude at silicas meeting the parameter requirements defined in claim 1 of both requests at issue.
>
> Even though a reasonable amount of trial and error is permissible when it comes to assessing sufficiency of disclosure, there must still be adequate instructions in the specification, or on the basis of common general knowledge, leading the skilled person necessarily and directly towards success, through evaluation of initial failures. This is not the case here, since the preparation of the amorphous silicas claimed is made dependent on the adjustment of different process parameters for which no guidance is given in the patent in suit, so that the broad definition of an amorphous silica as presently claimed is no more than an invitation to perform a research program in order to find a suitable way of preparing the amorphous silicas over the whole area claimed."

230. The decisions of the Boards of Appeal in *Detergents/UNILEVER*, *Modifying plant cells/MYCOGEN* and *Amorphous silica/INEOS* were considered by the Court of Appeal in *Novartis AG and anor v Johnson & Johnson Medical Ltd and ors* [2010] EWCA Civ 1039. Jacob LJ (with whom Patten and Ward LJJ agreed) explained that the heart of the test is: "Can the skilled person readily perform the invention over the whole area claimed without undue burden and without needing inventive skill". That is of course true. But in our judgment it is apparent from these decisions and the decisions of the Boards of Appeal in *Polypeptide expression/GENENTECH I*, *Fuel oils/EXXON* and *Erythropoetin II/KIRIN AMGEN* that, in assessing whether the skilled person can adequately perform the invention across the scope of the claim, the following points are also important.

231. First, it is not the law that a specification must necessarily enable the skilled person to make or perform all of the embodiments of a claimed invention. Were it otherwise, claims would be insufficient if they covered inventive improvements. But, as the decision in *Polypeptide expression/Genentech I* makes clear, in appropriate cases, a claim may embrace variants which may be provided or invented in the future and which achieve the same effect in a manner which could not have been envisaged without the invention.

232. Secondly, the assessment of insufficiency must be sensitive to the nature of the invention and the facts of the particular case. If the character of the invention is one of general methodology or is such that the invention is of general application then it may be permissible to claim it in general terms, even though the specification does not enable every way of arriving at its subject matter. Otherwise, as the Board explained in *Modifying plant cells/MYCOGEN*, no dominant patent could ever exist and each developer of a new method of arriving at that subject matter would be free of earlier patents. In many cases in the field of biotechnology, patent protection would then become illusory.

233. Thirdly, it is a general principle that the protection afforded by the claims must correspond to the technical contribution to the art made by the disclosure of the

invention. The patentee is entitled to fair protection having regard to the nature and character of the invention he has described.

234. That brings us to the leading authorities in this jurisdiction. Here we must start with the decision of the House of Lords in *Biogen v Medeva* [1997] RPC 1. It is helpful to have the relevant facts in mind. It was known at the priority date that the only available source of DNA for the hepatitis B virus (HBV) was the infective particle, the Dane particle. Professor Murray, the inventor, purified some DNA from Dane particles and cut it into fragments which were as large as possible. He then made a particular form of recombinant plasmid which he used to transform *E. coli*. He found that the bacteria expressed polypeptides with HBV antigen specificity. The inventive concept (for what he had done was indeed inventive) was the notion that the creation of large genomic fragments of eukaryotic DNA inserted into a particular plasmid and introduced into *E. coli* would work or, put another way, he had the idea of trying to express unsequenced eukaryotic DNA in a prokaryotic host. However, the claimed monopoly extended rather wider. It was, in effect, a product-by-process claim and encompassed any recombinant DNA molecule which expressed the genes of any HBV antigen in any host cell, and any way of making a DNA molecule which would achieve the necessary expression. This was significant because, once the DNA sequence of the Dane particle became known, no one would choose to proceed in the way Professor Murray did. A person skilled in the art would instead choose enzymes to digest the sites closest to the gene which expressed an antigenic fragment of the polypeptide; and, once they became available, that person would also use vectors for mammalian cells.

235. Against this background, Lord Hoffmann came to consider the concept of an enabling disclosure. He said this at 47-49:

> "What has been less clear is what the concept of an enabling disclosure means. Part of the difficulty has been caused by a misinterpretation of what the Technical Board of Appeal of the E.P.O. said in *Genentech I/Polypeptide expression* (T 292/85) [1989] O.J. E.P.O. 275. This was a patent for a plasmid suitable for transforming a bacterial host which included an expression control sequence or "regulon" which could enable the expression of foreign DNA as a recoverable polypeptide. The Examining Division was willing to grant a patent only in respect of the plasmids, bacteria and polypeptides known at the date of application. The Technical Board of Appeal allowed the appeal, saying that the Examining Division had taken too narrow a view of the requirement of enabling disclosure:
>
> > "What is also important in the present case is the irrelevancy of the particular choice of a variant within the functional terms `bacteria', `regulon' or `plasmid'. It is not just that some result within the range of polypeptides is obtained in each case but it is the same polypeptide which is expressed, independent of the choice of these means.… Unless variants of components are also embraced in the claims, which are, now or later on, equally suitable to achieve the same effect in a manner which could not have been envisaged without

> the invention, the protection provided by the patent would be ineffectual … The character of the invention this time is one of general methodology which is fully applicable with any starting material, and is, as it was already stated, also independent from the known, trivial, or inventive character of the end-products." [references omitted]

In other words, the applicants had invented a general principle for enabling plasmids to control the expression of polypeptides in bacteria and there was no reason to believe that it would not work equally well with any plasmid, bacterium or polypeptide. The patent was therefore granted in general terms.

In *Mölnlycke AB v. Procter & Gamble Ltd.* [1992] F.S.R. 549, however, Morritt J. interpreted this decision to mean that it was a general rule of European patent law that an invention was sufficiently disclosed if the skilled man could make a single embodiment. This interpretation was followed by Aldous J. in *Chiron Corporation v. Organon Teknika Ltd.* [1994] F.S.R. 202, although I think I detect in his judgment some surprise that the E.P.O. should have adopted such a mechanistic and impoverished approach to the concept of enabling disclosure. As we shall see, he applied the same rule in the present case.

In fact the Board in Genentech I/Polypeptide expression was doing no more than apply a principle of patent law which has long been established in the United Kingdom, namely, that the specification must enable the invention to be performed to the full extent of the monopoly claimed. If the invention discloses a principle capable of general application, the claims may be in correspondingly general terms. The patentee need not show that he has proved its application in every individual instance. On the other hand, if the claims include a number of discrete methods or products, the patentee must enable the invention to be performed in respect of each of them.

Thus if the patentee has hit upon a new product which has a beneficial effect but cannot demonstrate that there is a common principle by which that effect will be shared by other products of the same class, he will be entitled to a patent for that product but not for the class, even though some may subsequently turn out to have the same beneficial effect: see *May & Baker Ltd. v. Boots Pure Drug Co. Ltd*. (1950) 67 R.P.C. 23, 50. On the other hand, if he has disclosed a beneficial property which is common to the class, he will be entitled to a patent for all products of that class (assuming them to be new) even though he has not himself made more than one or two of them.

Since *Genentech I/Polypeptide expression* the E.P.O. has several times reasserted the well established principles for what amounts to sufficiency of disclosure. In particular, in

> *Exxon/Fuel Oils* (T 409/91) [1994] O.J. E.P.O. 653, paragraph 3.3 , the Technical Board of Appeal said of the provision in the European Patent Convention equivalent to section 14(5)(c) of the Act:
>
> > "Furthermore, Article 84 EPC also requires that the claims must be supported by the description, in other words, it is the definition of the invention in the claims that needs support. In the Board's judgment, this requirement reflects the general legal principle that the extent of the patent monopoly, as defined by the claims, should correspond to the *technical contribution to the art* in order for it to be supported, or justified.""

236. A little later, in considering whether the disclosure of the priority document contained an enabling disclosure which supported the claims, Lord Hoffmann held that the trial judge's findings that Professor's Murray's invention worked was one that was open to him and should be respected. But that was not the end of the matter because the question here was not whether the claimed invention could deliver the goods, but whether the claim covered other ways in which they might be delivered which owed nothing to the teaching of the patent or any principle it disclosed. In that connection, he explained at 50-51:

> > "It will be remembered that in *Genentech I/Polypeptide expression* the Technical Board spoke of the need for the patent to give protection against other ways of achieving the same effect "in a manner which could not have been envisaged without the invention". This shows that there is more than one way in which the breadth of a claim may exceed the technical contribution to the art embodied in the invention. The patent may claim results which it does not enable, such as making a wide class of products when it enables only one of those products and discloses no principle which would enable others to be made. Or it may claim every way of achieving a result when it enables only one way and it is possible to envisage other ways of achieving that result which make no use of the invention."

237. This was such a case for Professor Murray's contribution consisted in showing that, despite the uncertainties which then existed over the DNA of the Dane particle, known recombinant techniques could be used to make the antigens in a prokaryotic host cell. But this contribution did not justify a claim to a monopoly of any recombinant method of making the antigens. It was too broad, not because of an inability to achieve all the promised results, but because the same results could be produced by different means.

238. We draw the following points from this decision:

i) The extent of the patent monopoly, as defined by the claims, must correspond to the technical contribution to the art its disclosure has made in order for it to be justified.

ii) The specification must enable the invention to be performed to the full extent of the monopoly claimed. But if the invention discloses a principle capable of general application, the claims may be in correspondingly general terms.

iii) If the patentee has found a new product which has a beneficial effect but cannot demonstrate there is a common principle by which that effect will be shared by other products of the same class, he will be entitled to a patent for that product but not for the class. But if he has disclosed a beneficial property which is common to the class, he will be entitled to a patent for all the products of that class even though he has not himself made more than one or two of them.

iv) There is more than one way in which the breadth of the claim may exceed the technical contribution to the art embodied in the invention. The patent may claim results which it does not enable, such as making a wide class of products when it enables only one of those products and discloses no principle which would enable others to be made. Or it may claim every way of achieving a result when it enables only one way and it is possible to envisage other ways of achieving that result which make no use of the invention.

239. Lord Hoffmann provided further guidance in *Kirin-Amgen Inc v Hoechst Marion Roussel* [2004] UKHL 46, [2005] RPC 9. A team from Amgen was the first to clone and sequence the gene for erythropoetin ("EPO"). Once that sequence had been discovered it was possible to make the polypeptide by conventional methods of recombinant DNA technology. Amgen was in due course granted a patent with claims to a DNA sequence for use in securing expression in a prokaryotic or eukaryotic host cell of EPO, and to the recombinant polypeptide itself. The question arose as to whether these claims were sufficiently broad to encompass EPO made by any form of recombinant technology, so including a process used by Transkaryotic Therapies Inc ("TKT") which made EPO by introducing exogenous DNA into a cell and in that way activating the endogenous EPO gene, and if they were, whether they were insufficient.

240. The House of Lords held the relevant claims were not infringed so it was not necessary to determine this allegation of insufficiency. In the circumstances, Lord Hoffmann did not express a concluded view but nevertheless considered whether the sequence information that Amgen had disclosed in the patent and which TKT needed to perform its process constituted a principle of general application, as the trial judge had held. Having earlier reiterated the principle that the disclosure of a specification must enable the invention to be performed to the full extent of the monopoly claimed, and that whether a specification is sufficient or not is highly sensitive to the nature of the invention, Lord Hoffmann elucidated what was meant by the phrase "a principle of general application":

> "112 This gave rise to a good deal of argument about what amounted to a "principle of general application". In my opinion there is nothing difficult or mysterious about it. It simply means an element of the claim which is stated in general terms. Such a claim is sufficiently enabled if one can reasonably expect the invention to work with anything which falls within the general term. For example, in *Genentech I/Polypeptide expression* (T

> 292/85) [1989] O.J. EPO 275, the patentee claimed in general terms a plasmid suitable for transforming a bacterial host which included an expression control sequence to enable the expression of exogenous DNA as a recoverable polypeptide. The patentee had obviously not tried the invention on every plasmid, every bacterial host or every sequence of exogenous DNA. But the Technical Board of Appeal found that the invention was fully enabled because it could reasonably be expected to work with any of them.
>
> 113 This is an example of an invention of striking breadth and originality. But the notion of a "principle of general application" applies to any element of the claim, however humble, which is stated in general terms. A reference to a requirement of "connecting means" is enabled if the invention can reasonably be expected to work with any means of connection. The patentee does not have to have experimented with all of them."

241. Lord Hoffmann was of the view that the facts of the case did not support the application of this principle because the specification did not disclose a way of making EPO in sufficiently general terms to include the TKT process. It disclosed only how to make EPO by introducing exogenous DNA coding for EPO into a host cell. The TKT method was not a version of Amgen's method which could reasonably be expected to work just as well. It was different. Further, an invention was not enabled by the disclosure in the specification simply because it could not be worked without that disclosure. The disclosure must not only be necessary, it must be sufficient.

242. Lord Hoffmann then addressed a point made by the Court of Appeal, namely that the law contemplates that patents will not lack sufficiency, even though the claims cover inventive improvements, and said that:

> "117 … it is of course correct so far as it goes. The choice of a particular form of an integer falling within the terms of the claim may improve the way the invention works and be in itself an inventive step. The specification is not insufficient merely because it does not enable the person skilled in the art to make such an invention. The use of the improvement is still a way of working the original invention. But TKT does not rely upon the fact that the use by TKT of an endogenous EPO gene was inventive. Their objection is that it is not a way of making EPO which is disclosed, even in the most general terms, by the specification. As the point does not arise, I do not propose to express a concluded view. But, unlike the Court of Appeal, I think that the breadth of claim objection may well have been a good one."

243. *H Lundbeck A/S v Generics (UK) Ltd* [2008] EWCA Civ 311, [2008] RPC 19 concerned a claim to the (+) enantiomer of a well-known racemate called citalopram. The patentee, Lundbeck, found a way to separate the enantiomers and found that the

(+) enantiomer was the effective one. The trial judge, Kitchin J (as he then was), held, in light of the decision of the House of Lords in *Biogen*, that claim 1 of the patent, which was directed to the (+) enantiomer, was insufficient on the basis that the extent of the patent monopoly exceeded the technical contribution that Lundbeck had made, which was simply to find one way of making that enantiomer; and this contribution did not justify a claim to that enantiomer however made. The Court of Appeal disagreed. Lord Hoffmann, with whom Smith and Jacob LJJ agreed, held that the decision in *Biogen* was limited to the form of claim which the House of Lords was there considering, a product-by-process claim, and could not be extended to an ordinary product claim in which the product was not defined by a class of processes of manufacture. The technical contribution to the art here was the product and not the process by which it was made, even if that process constituted the only inventive step. In the course of his reasoning, Lord Hoffmann said this about the circumstances of and decision in Biogen:

> "34 Thus, as a matter of construction, the House of Lords interpreted the claim as being to a class of products which satisfied the specified conditions, one of which was that the molecule had been made by recombinant technology. That expression obviously includes a wide variety of possible processes. But the law of sufficiency, both in the United Kingdom and in the EPO, is that a class of products is enabled only if the skilled man can work the invention in respect of all members of the class. The specification might show that this has been empirically demonstrated or it might disclose a principle which can reasonably be expected to apply across the class: see T 292/85 *Polypeptide expression/GENENTECH* [1989] O.J. E.P.O. 275; T409/91 *Fuel Oils/EXXON* [1994] O.J. E.P.O. 653; *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2005] R.P.C. 9, [112]. But the specification in *Biogen* described only one method of making the molecule by recombinant technology and disclosed no general principle. It was easy to contemplate other methods about which the specification said nothing and which would owe nothing to the matter disclosed."

244. A further appeal to the House of Lords was dismissed: [2009] UKHL 12, [2009] RPC 13. The House agreed with the Court of Appeal. Lord Neuberger explained that, in the context of a simple product claim such as that in issue, the technical contribution, at least in the absence of special factors, was the product itself.

245. We believe the following further points of relevance to this appeal can be taken from the decision of the House of Lords in *Kirin-Amgen* and the decisions of the Court of Appeal and the House of Lords in *Lundbeck*:

    i) a principle of general application is simply an element of a claim which is stated in general terms;

    ii) a claim containing such an element is sufficiently enabled if the skilled person can reasonably expect the invention to work with anything which falls within the general term; and

iii) a particular form of an element of a claim may improve the way the invention works and be inventive. However, the patent is not insufficient simply because the specification does not enable that improvement. It is still a way (albeit an improved way) of working the original invention.

246. Finally we should mention the decision of the Court of Appeal in *Regeneron Pharmaceuticals Inc v Genentech Inc* [2013] EWCA Civ 93, [2013] RPC 28, to which the judge referred. This appeal concerned a patent claim directed to the use of a human vascular endothelial growth factor ("hVEGF") antagonist, such as an isolated hVEGF receptor, in the preparation of a medicament for the treatment of a non-cancerous disease characterised by excessive blood vessel growth. Genentech, the owner of the patent, claimed it was infringed by the use of a product developed by Regeneron called VEGF-Trap, a chimeric molecule containing two monomers linked together. Regeneron denied its molecule fell within the scope of the claims and argued that the patent was insufficient because the monopoly claimed was far too broad and encompassed the use of a vast number of antagonists which it did not enable. It contended, among other things, that it was not possible at the filing date to make a reasonable prediction based upon the teaching in the patent and the general knowledge that hVEGF antagonists would be useful in the treatment of all diseases of the kinds contemplated and that it would involve undue effort to find which antagonists were effective against which diseases. It also argued that if the claims were broad enough to cover VEGF-Trap, they covered products they did not enable.

247. In discussing the general legal principles applicable to the insufficiency attack, Kitchin LJ (with whom Longmore and Moses LJJ agreed) said this at [100]-[101]:

> "100 It must therefore be possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim or, put another way, the assertion that the invention will work across the scope of the claim must be plausible or credible. The products and methods within the claim are then tied together by a unifying characteristic or a common principle. If it is possible to make such a prediction then it cannot be said the claim is insufficient simply because the patentee has not demonstrated the invention works in every case.
>
> 101 On the other hand, if it is not possible to make such a prediction or if it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within the scope of the claim then the scope of the monopoly will exceed the technical contribution the patentee has made to the art and the claim will be insufficient. It may also be invalid for obviousness, there being no invention in simply providing a class of products or methods which have no technically useful properties or purpose."

248. Applying these principles, the court found no reason to interfere with the judge's findings rejecting the broad insufficiency attacks. The court then turned to the infringement - insufficiency squeeze, upheld the judge's finding that VEGF-Trap fell

within the scope of the claims and rejected the contention that this rendered the claims insufficient:

> "173 This does not, however, mean the patent is insufficient. A claim for an invention of broad application may properly encompass embodiments which may be provided or invented in the future and which have particularly advantageous properties, provided such embodiments embody the technical contribution made by the invention. VEGF-Trap does indeed embody the technical contribution made by the patent; it has a therapeutic effect in patients suffering from ARMD by treating the angiogenesis associated with that condition, and it does so by binding to VEGF and inhibiting its biological activity. VEGF-Trap is therefore one of those improvements which Lord Hoffmann had in mind in *Kirin-Amgen* [2004] UKHL 46, [2005] R.P.C. 9 at [117]."

249. This exposition is, we believe, entirely consistent with the principles we have identified. A claim is not insufficient simply because it encompasses inventive improvements provided they embody the technical contribution the disclosure of the invention has made to the art.

The application of the law

250. We summarised the arguments developed by Mr Turner on behalf of Regeneron earlier in this judgment. They have at their heart the contention that the judge failed properly to appreciate the nature and extent of the contribution to the art that the disclosure of the invention has made; fell into error in deciding what the disclosure of the patent in fact enabled; and ought to have found that, having regard to the principles we have explained, the specification of each of the patents did disclose the claimed invention clearly enough and completely enough for it to be performed by a person skilled in the art.

251. Mr Tappin, for Kymab, argues that each of Regeneron's submissions is flawed. He submits that the claims are to classes of products (claim 1 of the 163 patent and claims 5 and 6 of the 287 patent) or classes of processes (claim 1 of the 287 patent). As for the claims to classes of products, they include genetically modified cells and mice in which the entire mouse immunoglobulin variable region loci have been replaced with the orthologous human loci. Such cells and mice were specifically envisaged by the patents, and the patents assert that the skilled person could make them by using their teaching. However, on the judge's findings of fact, the patents do not enable such cells or mice or many other types of genetically modified products falling within the scope of the claims. As for claim 1 of the 287 patent, this encompasses the replacement, by homologous recombination, of at least the mouse D and J gene segments at the proximal end of the locus with several orthologous human V segments and the human D and J gene segments which involves the replacement of at least about 100 kb of mouse sequence with about 200 to 300 kb of human sequence. But again, the specification does not enable such replacement. Indeed, says Mr Tappin, vast swathes of the claims are not enabled. The law requires these claims to be enabled across their breadth, and they are not.

252. Mr Tappin also submits that the patents do not disclose any principle of general application and certainly not any principle which enables the skilled person to make products or carry out methods across the scope of the claims. Achievement of the replacement of the entire murine loci with the orthologous human loci cannot be regarded as an improvement invention; and the deficiencies in the specification cannot be excused on the basis that it might be possible to make something falling within a small corner of the claims. The judge directed himself properly as to the law and arrived at an overall conclusion which was, on the basis of his findings of fact, inevitable.

Discussion

253. The judge considered that all of the product claims were of broader scope than claim 1 of the 287 patent and so, in considering the parties' submissions, we shall start with claim 1 of the 163 patent. The following points are, we think, particularly material in light of the findings we have made and the principles we have sought to explain. We can at this stage express them quite shortly.

254. As we have seen, this claim is drawn in general language and is of broad scope. But each of the mice it encompasses has the reverse chimeric locus, that is to say, it is a mouse which produces hybrid antibodies containing human variable regions and mouse constant regions, and in which mouse V, D and J segments have been replaced with human V, D and J segments at a chromosomal immunoglobulin heavy chain locus, and mouse V and J segments have been replaced with human V and J segments at a chromosomal immunoglobulin light chain locus.

255. The disclosure of the reverse chimeric locus was, as we have described, a major contribution to the art for it provided the answer to a significant problem which those working in the field had faced, namely that transgenic mice produced by conventional methods were immunologically sick. Transgenic mice with the reverse chimeric locus do not suffer from this deficiency.

256. The character of this invention is therefore such that any transgenic mouse which falls within the scope of the claim and so produces hybrid antibodies containing the human variable regions and mouse constant regions will benefit from the technical contribution the disclosure of the 163 patent has made to the art, and will do so irrespective of the antigen which is used to challenge the mouse. In our judgment it is properly described as a principle of general application.

257. As for the ability of the skilled team seeking to implement the teaching of the 163 patent at the priority date, we are satisfied for the reasons that we have given that the skilled team, equipped with the common general knowledge, could have produced without undue effort a transgenic mouse falling within the scope of the claim by making a minigene construct of up to 20 kb in length containing a subset of the human V, D and J segments (in the case of the heavy chain) and a subset of the V and J segments (in the case of the light chain), and that this could have been achieved by conventional techniques of homologous recombination.

258. We are also satisfied that the skilled team seeking to implement the teaching of the 163 patent and equipped with the common general knowledge could have produced without undue effort a transgenic mouse falling within the scope of the claim by using LTVECs and the MOA assay in the manner we have described.

259. It is true to say that the transgenic mice produced by either of the methods described in the immediately foregoing paragraphs would have had only a subset of the human V gene segments. We also recognise that there was a perception at the priority date that the greater the number of human V gene segments that had been inserted into the transloci, the more varied the human antibody expression was likely to be. Nevertheless, as we have also seen, a transgenic mouse of this kind with only a few human V gene segments would have had an immunological response which was close to that of wild type mice.

260. These points, taken together, strongly suggest to us that the 163 patent does disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art. The character of the invention is one of general application. It applies to any mouse challenged with any antigen and the benefit it confers will be shared by every mouse falling within the scope of the claim. The skilled team would reasonably expect the invention to work across the scope of the claim and that expectation would be correct. What is more, there is nothing in the claim which could have been envisaged without the invention and, were protection to be limited to only those embodiments which could have been made at the priority date without undue effort, the protection provided by the patent would have rapidly become ineffectual.

261. Is the patent nevertheless insufficient because it was not possible at the priority date to perform Example 3 as described, or because it was not possible to delete 100 kb of mouse sequence and insert 200-300 kb of human sequence as illustrated in Figure 4 in a single step, or because it was not possible to delete 150 kb of mouse sequence and insert 75 kb of human sequence in one step? We do not believe it is. The following further matters are particularly relevant in this regard.

262. First and as we have shown, it is well-established that the skilled person is not bound to carry out the invention precisely as described and can use the common general knowledge to perform the invention and make any obvious changes that may be necessary, provided of course that any work involved is not undue.

263. Secondly, the evidence established that the skilled team would have regarded the implementation of Example 3 as extremely challenging and in these circumstances the obvious thing to have done would have been to shorten the inserts. The team would also have understood that there was no need to carry out deletions in the same step as insertions, and that any necessary deletions could be effected without undue difficulty in a later and separate step.

264. Thirdly and for the reasons we have given, we are satisfied that the skilled team could have produced transgenic mice within the scope of the claim without undue effort at the priority date and that such mice would have had a near wild type response.

265. Fourthly, the law does not require a patentee to enable each and every embodiment of a claimed invention. As the authorities recognise, a claim may encompass inventive improvements of what is described and a specification is not insufficient merely because it does not enable the person skilled in the art to make every such invention. It is important, however, that any such improvement is still a way of working the original invention. In this case we have no doubt that this is the case: there is no mouse falling within the scope of claim 1 of the 163 patent which does not embody the reverse chimeric locus and enjoy the benefits it brings.

266. Fifthly, if the claim of a patent is adequately enabled across its breadth and its scope is commensurate with the technical contribution the disclosure of the invention has made to the art, the patent does not cease to be sufficient simply because the specification promises too much. As we have explained, the skilled team would have recognised that Example 3, as described, presented a real challenge, and that the example would not have worked. But they would also have appreciated that an obvious way forward was to reduce the size of the inserts, and by proceeding in this way and in the manner we have described could have implemented the claimed invention without undue effort.

267. For all of these reasons, we have come to the conclusion that claim 1 of the 163 patent does not exceed the contribution to the art which the disclosure of its specification has made. We are satisfied that the extent of the patent monopoly, as defined by claim 1, does correspond to that technical contribution to the art and that it is adequately enabled across its scope.

268. We come next to claim 1 of the 287 patent and in our judgment very similar considerations apply. It is a claim to a method which is drawn in broad terms but each of the individual methods which it encompasses is a method of making a reverse chimeric locus in an isolated mouse ES cell by the replacement of V, D and J gene segments of the endogenous immunoglobulin heavy chain variable gene locus with orthologous human V, D and J segments. Further, each of the methods uses LTVECs to bring about the necessary modification of the endogenous chromosomal locus of interest and the MOA assay to detect those ES cells which have been modified successfully. It is, in short, a claim to a particular way of producing the reverse chimeric locus.

269. The methods of claim 1 therefore incorporate both aspects of the invention that we have described. They are all methods of producing within ES cells a reverse chimeric locus in the heavy chain variable region such that the cells will produce hybrid antibodies containing human variable regions and mouse constant regions. But they are also methods which involve the use of the MOA assay which was itself a significant technical contribution to the art for, in the words of the patent, it empowered the use of LTVECs as targeting vectors and reduced the time for identifying correctly modified eukaryotic cells from several days to a few hours.

270. In our judgment the character of the invention of claim 1 is such that any person carrying out a method falling within the scope of the claim will benefit from the technical contribution the disclosure of the specification has made to the art in both respects. The product of the method is an ES cell containing the reverse chimeric locus of the invention, and the method itself allows the skilled person to use LTVECs to carry out the modification, with all the benefits that attend the use of these large targeting vectors.

271. That said, the other points that we have made in connection with the enablement of claim 1 of the 163 patent are equally apposite here. We accept that the skilled person could not have carried out the large deletions and insertions described in Example 3 without inventive improvements but the skilled team would have appreciated that the obvious thing to do was to shorten the inserts and to carry out any necessary deletions in a separate step, and the result would have been the production of ES cells that had a near wild type response.

272. More fundamentally, the invention is not a way of achieving insertions and deletions of any particular length but rather a methodology of making the reverse chimeric locus in which successful integrations using LTVECs are detected by using the MOA assay. The character of the invention is one of general application. The method is applicable to any ES cell and the MOA assay will detect those cells in which the successful recombination event has occurred, whatever the length of the insert.

273. Just as in the case of claim 1 of the 163 patent, we have come to the conclusion that claim 1 of the 287 patent is adequately enabled across its breadth. There is nothing in the claim which could have been envisaged without the disclosure of the invention, and, having regard to the nature and extent of the contribution the disclosure of the invention has made to the art, the scope of the claim is no more than necessary to confer fair protection on Regeneron.

274. Claims 5 and 6 of the 287 patent raise no separate issues. It necessarily follows from our findings in relation to claim 1 that they too are adequately enabled across their scope.

275. We are conscious that in so deciding we are arriving at a conclusion which is different from that of an experienced patent judge. However, we have had the benefit of hearing fully developed argument upon aspects of the evidence which did not receive the same degree of attention at trial; we have come to the conclusion that the judge erred in his approach to the interpretation of claim 1 of the 287 patent; and we are satisfied that, in assessing the sufficiency of the disclosure of the patents, he did not attach sufficient weight to the character of the invention as claimed in each of the claims in issue, the contribution that its disclosure has made to the art and the need to confer a fair degree of protection on the patentee.

Conclusion on insufficiency

276. For all of these reasons we are satisfied that the specifications of the patents do disclose the claimed inventions clearly enough and completely enough for them to be performed by a person skilled in the art. We note the Board of Appeal reached the same conclusion in the case of the 287 patent (T 2220/14 of 9 November 2015). We have recently been notified that on 7 February 2018 the Opposition Division upheld the validity of the 163 patent on the basis of the claims as granted. The written decision is not yet available.

Overall conclusion

277. For the reasons we have given:

i) Kymab's appeal is dismissed.

ii) Regeneron's appeal is allowed.