Neutral Citation Number: [2011] EWHC 1669 (Pat)

Case No: HC09C04770

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 5 July 2011

Before :

THE HON MR JUSTICE ARNOLD

- -

Between :

MEDIMMUNE LIMITED	**Claimant**
- and -	
(1) NOVARTIS PHARMACEUTICALS UK LIMITED	**Defendants**
(2) MEDICAL RESEARCH COUNCIL	

- -

- -

Richard Meade QC, **Tom Mitcheson** and **James Whyte** (instructed by **Marks & Clerk Solicitors LLP**) for the **Claimant**
Simon Thorley QC, **Justin Turner QC** and **Joe Delaney** (instructed by **Allen & Overy LLP**) for the **First Defendant**
The **Second Defendant** did not appear and was not represented

Hearing dates: 10-13, 16-20, 24-27 May 2011

- -

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

.....

THE HON MR JUSTICE ARNOLD

MR. JUSTICE ARNOLD :

Contents

Introduction

1. The Claimant ("MedImmune", formerly known as Cambridge Antibody Technology Ltd ("CAT")) and the Second Defendant ("the MRC") (jointly, "the Patentees") are joint proprietors of European Patents (UK) Nos. 0 774 511 ("511") and 2 055 777 ("777") (together, "the Patents"). MedImmune is the exclusive licensee of the MRC's interest in the Patents. MedImmune alleges that the First Defendant ("Novartis") has infringed the Patents by sales of a pharmaceutical product whose international non-proprietary name is ranibizumab and which is sold under the trade mark Lucentis. Lucentis is approved for the treatment of an eye condition known as wet age-related macular degeneration, which can lead to loss of vision. Novartis disputes infringement and counterclaims for revocation of the Patents. The MRC has been joined to the claim so as to be bound by the result, but has not played an active part in the proceedings. Ranibizumab was developed by Genentech, Inc., which is not a party to the proceedings.

2. The Patents are members of a family of European patents and patent applications based on International Patent Application No. PCT/GB91/01134 filed on 10 July 1991 which was subsequently published as WO 92/01047 ("the Application"). Each of the patents in this family claims priority from five priority documents, namely:

    i) United Kingdom Patent Application No. 9015198 filed on 10 July 1990;

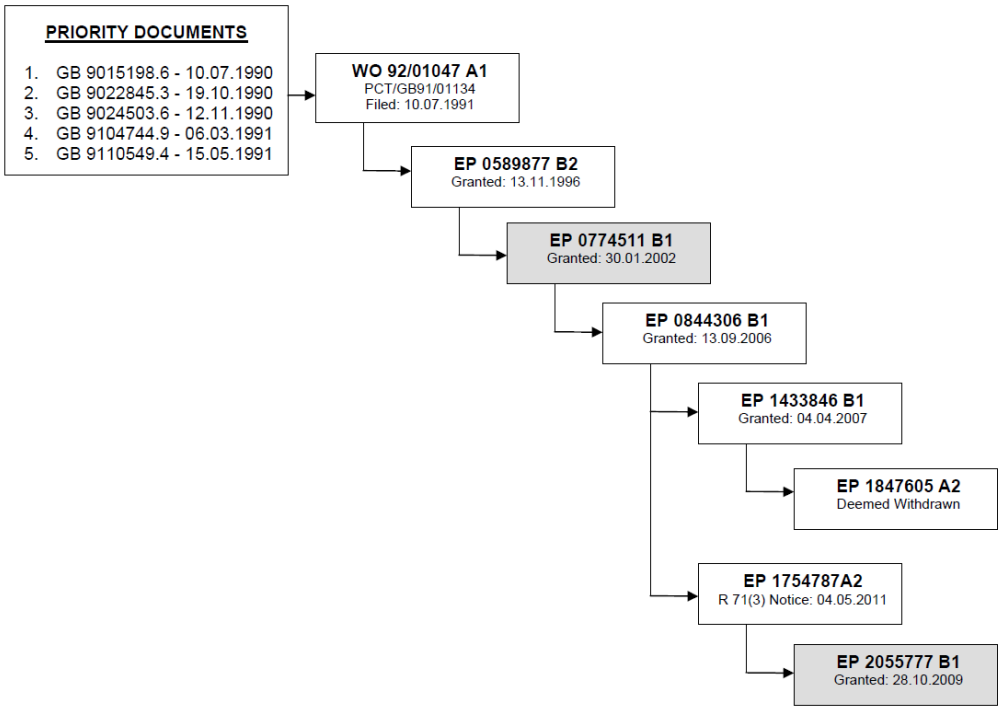
    ii) United Kingdom Patent Application No. 9022845 filed on 19 October 1990;

    iii) United Kingdom Patent Application No. 9024503 filed on 12 November 1990;

    iv) United Kingdom Patent Application No. 9104744 filed on 6 March 1991; and

    v) United Kingdom Patent Application No. 91110549 filed on 15 May 1991.

3. 511 is a divisional of the parent, European Patent No 0 589 877 ("877"), while 777 is a divisional of a divisional of a divisional of 511. The relationship between the Patents, the other members of the family, the Application and the priority documents is conveniently shown in the following diagram:



4. Novartis challenges the entitlement of the Patents to priority. Attention has focussed on the entitlement of the Patents to priority from the third of the priority documents listed above ("PD3") since (a) MedImmune accepts that the Patents are invalid if they are not entitled to priority from that document and (b) Novartis does not rely upon any prior art which was made available to the public in the interval between the filing dates of the first and third priority documents. Novartis disputes both that the claimed inventions are disclosed by PD3 and that the Patentees have the right to claim priority from PD3. It became clear at an early stage of the trial, however, that the parties were not ready to contest the latter issue. Accordingly, it was agreed that that issue will be tried separately at a later date.

5. Although MedImmune has not conceded that the Patents are invalid over any particular item of prior art if they are not entitled to priority from PD3, it is convenient to note at this point that some of the work described in the Patents was published on 6 December 1990 in a paper by McCafferty et al, "Phage antibodies displaying antibody variable domains", *Nature*, 348, 552-554 ("McCafferty"). The authors of McCafferty were a group of four scientists from CAT and the MRC Laboratory of Molecular Biology led by Dr (now Sir) Greg Winter. Those four together with eight others are the named inventors of the Patents.

6. Apart from the priority attack, Novartis' principal challenge to the validity of the claims of the Patents in issue is that they are obvious over Parmley and Smith, "Antibody-selectable filamentous fd phage vectors: affinity purification of target genes", *Gene*, 73, 305-318 (1988) ("Parmley & Smith") and a talk entitled "Filamentous phage as vectors for antibody libraries" given by Professor George Smith of the University of Missouri at a conference on "Vectors for Cloning the Immune Response" held at the Banbury Center, Cold Spring Harbor Laboratory, New York on 23-26 April 1990 ("the Banbury Conference"). In addition, Novartis contends that the Patents are invalid on the grounds of insufficiency and added matter.

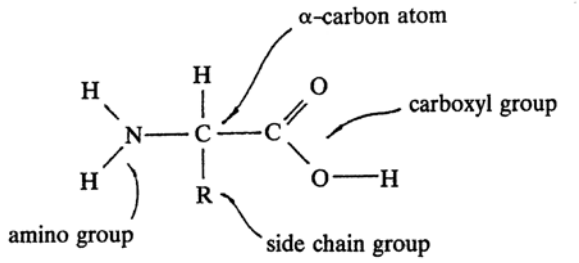
7. The claims in issue are claims 5-8 of 511 and claim 1 of 777. All of these claims are process claims. MedImmune alleges that Novartis has infringed these claims by virtue of section 60(1)(c) of the Patents Act 1977. Novartis disputes both that Lucentis was produced by a process which falls within the scope of the claims and that Lucentis is a product "obtained directly by means of" any of the claimed processes.

Technical background

8. The following account of the technical background to this dispute is largely based on the technical primer ("the Primer") which the parties sensibly agreed for use in these proceedings, supplemented to a minor extent from the expert evidence. The first part of the Primer was in turn based on the judgments of the Court of Appeal in *Genentech Inc's Patent* [1989] RPC 147 at [1.01]-[3.17] and of Laddie J in *Cambridge Antibody Technology Ltd v Abbott Biotechnology Ltd* [2004] EWHC 2974 (Pat), [2005] FSR 27 at [26]-[27], [30]-[33], [35]-[36], [39] and [46]-[48]. Unless otherwise attributed, the illustrations are taken from the Primer.

Amino acids

9. Amino acids are simple, small, naturally-occurring organic molecules sharing the same overall structure. They consist of an amino group (NH_2), a carboxylic acid group (COOH), a hydrogen atom (H) and a side chain group all attached to a central carbon atom (the alpha carbon):



10. There are 20 common naturally-occurring amino acids, each of which is referred to by a three-letter abbreviation or code and a one-letter code, as follows:

Amino Acid	1-Letter Code	3-Letter Code
Alanine	A	Ala
Cysteine	C	Cys
Aspartic acid	D	Asp
Glutamic acid	E	Glu
Phenylalanine	F	Phe
Glycine	G	Gly
Histidine	H	His
Isoleucine	I	Ile
Lysine	K	Lys
Leucine	L	Leu
Methionine	M	Met
Asparagine	N	Asn

Proline	P	Pro
Glutamine	Q	Gln
Arginine	R	Arg
Serine	S	Ser
Threonine	T	Thr
Valine	V	Val
Tryptophan	W	Trp
Tyrosine	Y	Tyr

11. It is in the nature of the side chain that amino acids differ one from another, and it is upon these side chains that the various properties of the amino acids depend. In the construction of proteins, each amino acid is joined to the next one by a peptide bond (CO-NH) formed by the reaction between amino group of one amino acid and the carboxylic acid group of the other amino acid and the loss of a water (H_2O) molecule. A short chain of amino acids is referred to as a "peptide" and a long chain as a "polypeptide".

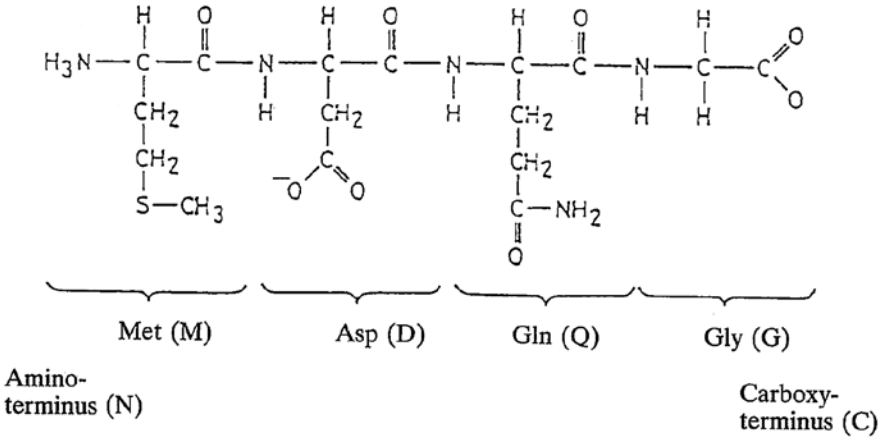
Proteins

12. Proteins are relatively large, complex, naturally-occurring organic molecules made of polypeptide chains. Most of the basic building blocks of cells, and many other important chemicals in nature, are proteins.

13. The structure of a protein can be considered at several levels. The primary structure is the linear sequence of amino acids. The secondary structure can be described as the physical appearance of individual sections (or segments) of the linear chain that arrange themselves in a particular way. These "arrangements" include so-called alpha helices (where the sequence forms a spiral formation in a given segment) or beta sheets (where the sequence forms into a series of hairpin loops in a given segment). These segments will be linked by intervening turns. These elements of secondary structure further fold upon themselves to create the tertiary structure which packs together the secondary structures and the amino acid side chains into stable structures known as domains. Essentially, a polypeptide chain folds down on itself to create as compact and as organised a structure as possible with the linear sequence of amino acids it contains (different amino acid residues favour different secondary structures and the side chain groups dictate the interactions that create the tertiary structure). Hence, the structure of a protein is largely dictated by its sequence of amino acids.

14. A protein may consist of a single domain or may have multiple domains packed together into the complete protein structure. A further level of structure, known as quaternary structure, concerns multimeric proteins. These have multiple polypeptide chains which may be identical (e.g. a homodimer has two identical polypeptides) or different (e.g. a heterodimer has two different polypeptides).

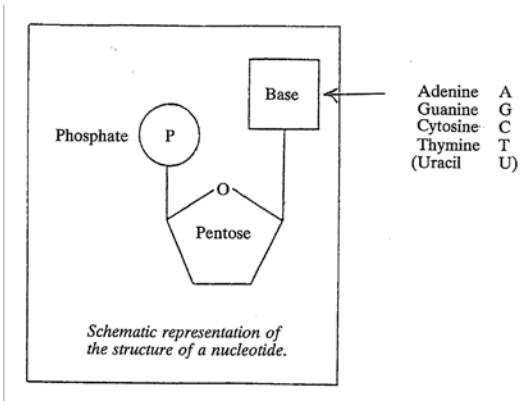
15. Proteins vary immensely in size and their polypeptide chain may contain anything between 50 and 2000 amino acids or more. However long they are, there will be an amino group at one end and a carboxylic group at the other (the "N terminus" and the "C terminus"), as shown in this illustration of a four amino acid peptide:



Nucleic acids

16. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are large, complex, naturally-occurring organic molecules. These encode the information which is contained in an organism's genes.

17. Like proteins, nucleic acids are polymers composed of smaller units. In the case of DNA and RNA, the component units are relatively small, simple naturally-occurring organic molecules called nucleotides. These consist of a pentose sugar, a phosphate group and a base:



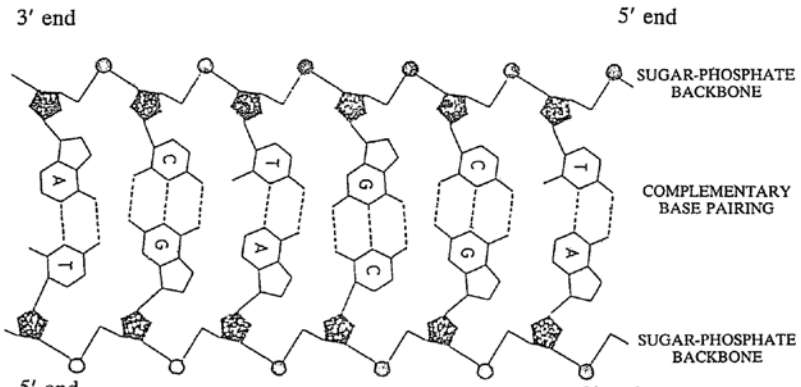
Schematic representation of the structure of a nucleotide.

18. Both DNA and RNA use combinations of only four bases each to perform their coding function. These are adenine, guanine, cytosine and thymine in the case of DNA. RNA also uses adenine, guanine and cytosine but in the place of thymine a chemically similar base called uracil is used. These bases are known respectively by their first letters, namely A, G, C, T and U. They have an important characteristic, namely that C forms hydrogen bonds ("pairs") with G, but not with A or T, and A pairs with T or (in the case of RNA) U, but not with G or C. This propensity to form paired structures ("base pairs") is an important feature underlying the function of nucleic acids.

19. Just as amino acids join together via peptide bonds to form chains, so too nucleotides join together, with the phosphate group of nucleotide reacting with the sugar of the next to form a "sugar-phosphate backbone". Just as a peptide chain has a N-terminus

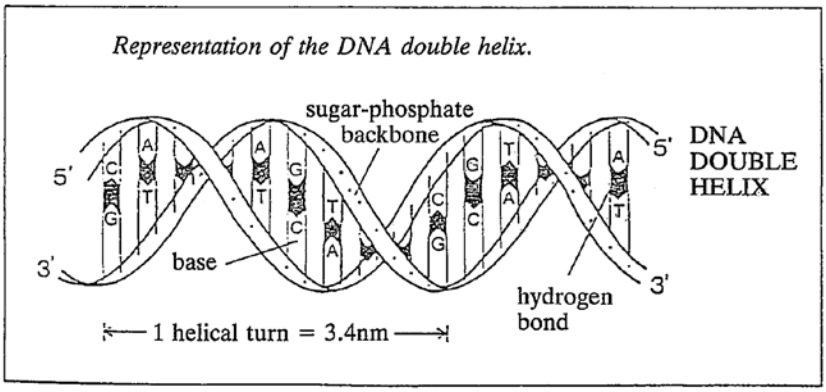
and a C-terminus, so too a nucleotide chain has a "3' end" and a "5' end".

20. In its normal state DNA consists of two complementary strands of nucleotides running in opposed directions. The two strands are held together by hydrogen bonds between the base pairs, referred to as "complementary base pairing":



COMPLEMENTARY BASE PAIRING

21. The two strands form a double helix in which the complementary base pairing holds the two helices together:



DNA DOUBLE HELIX

22. DNA molecules are relatively stable. RNA molecules are shorter-lived and exist in various forms which serve different functions. One form is messenger RNA (mRNA). Others forms include transfer RNA (tRNA) and ribosomal RNA (rRNA).

Genes

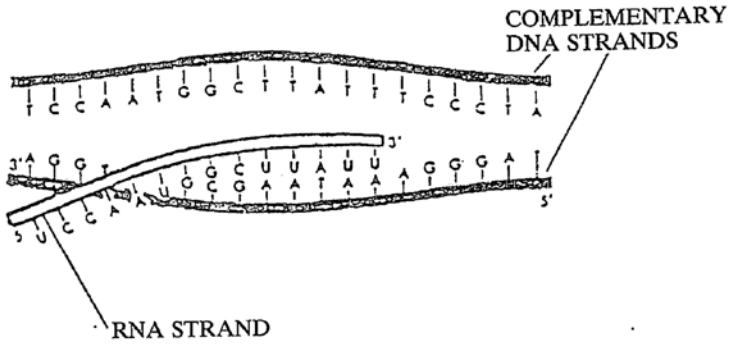
23. Genes are made of DNA and serve as the repository of instructional information governing the organism. They determine its composition and structure and to a large extent how it will grow as well as its behaviour and lifespan. In particular, they specify the structure of the proteins of the cell, by sending the instructional information in the form of a RNA copy to the protein-synthesising machinery of the cell.

24. When a cell replicates by division, the whole genetic complement of the cell must be

faithfully copied so that it is inherited by each daughter cell. In this process the double helix unwinds rupturing the hydrogen-bond pairing of the bases from the two strands and allowing each strand to expose the linear sequence of its unpaired bases. An enzyme (DNA polymerase) promotes the creation of a new strand complementary to each of the parent strands with the appropriate base being joined on the new opposite strand, namely C acquires a G, T an A, etc. In other processes, e.g. transcription (see below), the helix is similarly locally denatured to expose the bases.

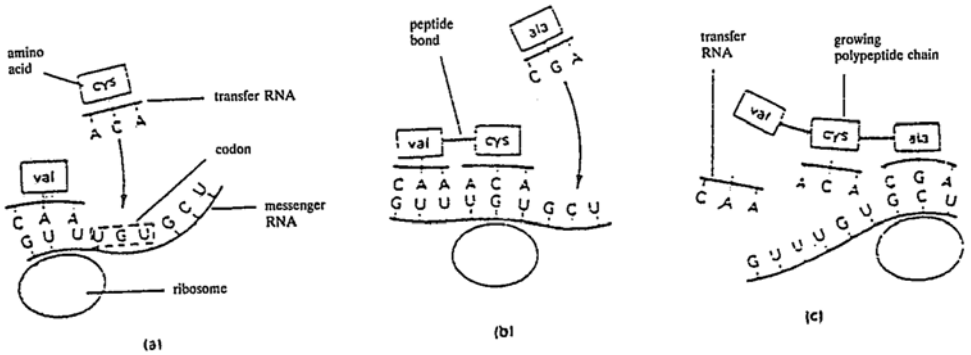
Transcription and translation

25. When DNA is expressed in a cell, the two strands are separated locally and an enzyme, RNA polymerase, copies or, as it is said, "transcribes" the sequence from one strand into a sequence of bases of mRNA. Within every cell there are, for each of the many different genes, varying numbers of mRNA copies. Each mRNA will reflect the nucleotide sequences of the DNA for which it is the messenger and will have a similar composition with the exception that it has only one strand:



SYNTHESIS OF RNA — TRANSCRIPTION

26. In the cell's function of creating a protein, the mRNA is then "translated" into a polypeptide chain. Thus, if the gene is a blueprint for a protein, its mRNA is a working copy. Ribosomes (components of cells which synthesise proteins from amino acids) bind to an initiation signal in the mRNA and the sequence is then decoded, three bases (a "triplet") at a time, by the transfer RNAs carrying in their amino acids in the correct reading frame. When a termination signal in the mRNA is reached, the ribosome will break off translation producing a completely free polypeptide chain:



The genetic code

27. The correspondence between the nucleotide sequence of the mRNA and the amino acid sequence of the polypeptide chain is given by the genetic code. The bases are read in groups of three, and each triplet, or codon, codes for one specific amino acid. Because there are 64 (4^3) triplets, but only 20 amino acids, in most cases more than one codon is used to code for any particular amino acid. The genetic code is conveniently shown in the form of the table below:

THE GENETIC CODE

First Position (5' end)	*Second Position*				*Third Position (3' end)*
	U	C	A	G	
	Phe	Ser	Tyr	Cys	U
U	Phe	Ser	Tyr	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
	Leu	Pro	His	Arg	U
C	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
	Ile	Thr	Asn	Ser	U
A	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
	Val	Ala	Asp	Gly	U
G	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

28. AUG is an initiation signal and also codes for methionine, while UAA, UAG and UGA do not code for any amino acid and are translation termination signals. While it is possible to translate a nucleotide sequence uniquely into an amino acid sequence, this cannot be done in the reverse direction. The redundancy or degeneracy of the code means that, with very few exceptions, it is possible to have several nucleotide sequences which correspond to a given amino acid sequence.

Genetic engineering

29. Manipulation of the nucleotide sequence in an organism's genes can alter the proteins that are produced by the nucleic acid. This is referred to as "genetic engineering". To enable such manipulation, small molecules known as vectors are used. A vector is a DNA molecule capable of directing its own replication in a host cell. Plasmids (double-stranded self-replicating DNA molecules) and bacteriophages (as to which, see below) are frequently used vectors. A vector can be used to "clone" DNA of interest by insertion of the DNA into the vector sequence. The insert is replicated and multiplied by the host cell as part of the vector. In this way the investigator can generate identical copies (clones) of the DNA on demand for further analysis and manipulation. Such DNA is often referred to as "recombinant" DNA.

30. It is commonly necessary in molecular biology to manipulate DNA *in vitro*. The cornerstone of molecular cloning techniques is the ability to cut DNA strands using so-called restriction enzymes, which are specific for defined nucleotide sequences,

and then rejoin them using ligase enzyme. Together, these enzymes allow the cutting of a vector and the ligation (i.e. joining) of an insert into the break created. Different restriction enzymes cut DNA strands in different places.

31. The most commonly used *in vitro* method to copy DNA is the polymerase chain reaction (PCR) which utilizes repeated rounds of synthesis to amplify a target sequence by the use of "oligonucleotide primers" (short DNA molecules of about 18-50 nucleotides) which specifically bind to the target and are extended by the polymerase. There is an exponential increase in the number of molecules on each synthesis cycle. Thus, where a DNA template is available (even in very small amounts), PCR can be used to create useful quantities for further manipulation. PCR can also be used to make changes to the DNA.

32. Protein coding sequences can also be obtained in the form of a particular type of DNA copy called complementary DNA (cDNA). This can be produced *in vitro* by isolating mRNA from the cell of interest and using reverse transcriptase, a polymerase that copies RNA into DNA, to produce a complementary DNA strand. Since the cDNA is generated from mRNA transcripts of genes and thus only includes coding regions of eukaryotic (higher organism) genes, and not the non-coding introns which break up the genomic sequence, it codes for the genes being expressed in that cell. Such copies provide the best source of sequences for cloning eukaryotic coding sequences. After reverse transcription into single-stranded DNA, the cDNA can be converted to double-stranded DNA if necessary and cloned into a vector for further analysis or manipulation.

33. A common type of DNA manipulation is so-called site-directed mutagenesis. This involves creating a specific mutation at a defined site in a DNA molecule. This is achieved by means of an oligonucleotide primer containing the desired base change. By means of site-directed mutagenesis, changes to the amino acid sequence, and hence the protein, encoded by the DNA can be introduced. An alternative technique is random mutagenesis, which involves making random changes.

Recombinant production of proteins

34. Proteins that result from the expression of recombinant DNA within living cells are termed "recombinant proteins". The production of a recombinant protein from its encoding DNA allows quantities of protein to be produced which are sufficient for use in laboratory studies or in large scale industrial production.

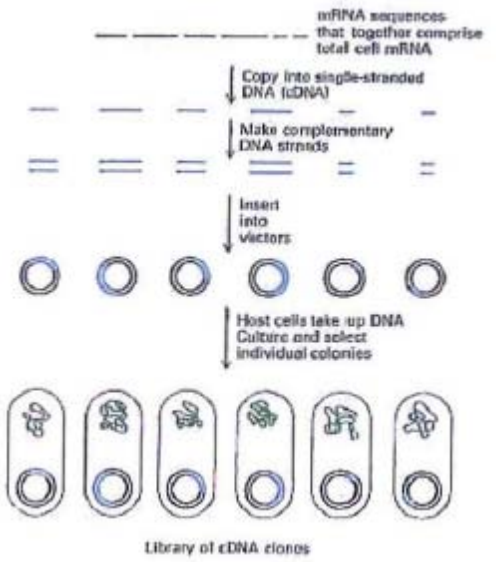
35. Recombinant protein expression requires the cloning of the corresponding DNA sequence into an expression vector containing components suitable for producing the protein in a host cell. The simplest systems are generally based on *Escherichia coli*. However, mammalian proteins may not always be successfully produced by the simple prokaryotic (bacterial) machinery in *E. coli*, and therefore eukaryotic systems are also used, including yeast and mammalian cell cultures. Large polypeptides of eukaryotic origin can be toxic when expressed in bacteria, due to their aggregation and/or precipitation in the cytoplasm of the bacteria. In addition, mammalian proteins often require post-translational modifications, such as the addition of sugar groups (glycosylation) or fatty acids, and can also require help to correctly fold. Thus, recombinant protein expression is often not a simple procedure, and the expression

systems have to be carefully selected and tested for a given protein before large scale production can be initiated.

36. Once the recombinant protein has been expressed by the host cell, it will often be necessary to purify it for further use. Purification requirements vary greatly. Depending on the cell type and the system, a protein may be simply secreted from the cell and can be collected in the growth medium. Alternatively, and frequently in *E. coli*, a protein may have to be released from the cell by lysis (bursting open of the cell). Once released from the cell, the protein may be in a functional form or can be refolded in controlled conditions. Depending on the protein features and the purity required, the mixture of proteins present in a crude cell lysate or growth medium may be subjected to multiple purification methods to remove the other contaminating cellular proteins.

Creation of cDNA libraries

37. For research purposes, in order to analyse which proteins are being expressed in a cell, the RNA coding for all the genes expressed in, for example, an immune cell can be isolated from those cells. The RNA can then be reverse transcribed back into cDNA using an enzyme called reverse transcriptase. This cDNA can be inserted into an expression vector for recombinant production in bacteria of all the proteins coded for by the RNA (i.e. all the protein being expressed in that cell at that time). The proteins in this library can then be analysed for size, activity or any other property of interest. The process for constructing a cDNA library is shown schematically below (source: Lodish *et al*., *Molecular Cell Biology* (2nd edition), Scientific American (1990)):



38. PCR can be used to isolate a gene of interest from a cDNA library if the sequence or part of the sequence is known, and then to amplify the DNA encoding the desired the protein. This could then be subjected to mutagenesis as described above.

Antibodies

39. Antibodies are molecules which are generated by an animal's immune system to assist in neutralising or destroying foreign matter, for example bacteria and viruses, which may have entered or be trying to enter the body. When a bacterium or virus enters, say, the blood stream of a human being, the immune system recognises it as foreign and will set about trying to destroy or neutralise it. Each bacterium or virus will have a number of proteins on its surface which are recognised as foreign and which can provoke an immune response from the host, in particular the production of antibodies. The foreign molecule is known as an antigen and the sites recognised by the antibody are called epitopes. An antibody is a molecule which the host immune system designs to lock onto an epitope. Since each epitope is different, different antibodies have to be made to lock on to each of them.

40. Once an antibody has been produced and it has attached to the antigen, it may interrupt some adverse behaviour of the protein, so that that behaviour is neutralised, or it may make the protein recognisable by the molecule-destroying systems in the host, with the result that the protein is destroyed. There will usually be a number of different antibodies which can attach to a single antigen. Some will attach faster than others and some will have greater neutralising power than others.

41. Antibodies are themselves proteins. They are manufactured in specialist cells called B lymphocytes (or B-cells). An individual B lymphocyte can only produce a single design of antibody. If, therefore, the host needs to make five different antibodies to combat a foreign protein, it will be necessary to stimulate five different B lymphocytes. Each of these B-cells will give rise to identical clones and each clone will produce its particular antibody.

Antibody diversity

42. The immune system is anticipatory, in that it attempts to generate antibodies in advance of challenge by an antigen, although it also reacts to the presence of an antigen. The key to the anticipatory response is the production of a large diversity of antibodies.

43. The primary repertoire of antibodies is generated by re-arrangement of the antibody-encoding DNA during B-cell development. An antibody, like other proteins, is encoded by genes. However, unlike most other proteins, the polypeptide chains of an antibody are encoded by multiple small genes (called mini-genes) that are rearranged in B-cells (and only in these cells), i.e. joined together to form the sequence encoding the full polypeptide. The exact sequences of the re-arranged genes vary from one antibody to another due to random selection of the mini-genes to be rearranged. In particular, this re-arrangement affects mini-genes that encode one of the complementary-determining regions or CDRs (as to which, see below) of antibodies, enabling a huge diversity in the sequences of these CDRs. The combination of different pairs of heavy and light chains (again, see below) also increases the diversity of the repertoire. This primary repertoire is expressed by the differentiated B-cells in which each B-cell encodes and produces one antibody. These antibodies circulate at a low level in a continual surveillance mode designed to detect foreign antigens.

44. A further level of antibody diversity is generated once the immune system has been challenged by an antigen which has already been detected by an antibody. The antibody may have only a low affinity (as to which, see below) for that antigen. The immune system operates to improve the antibody's ability to recognise and bind to antigen by further diversifying the B-cell clone that expresses the selected antibody. During this diversification the genes encoding the variable domains (see below) are mutated in many locations simultaneously (or "hyper-mutated") to produce a range of antibodies. The higher affinity antibody-producing clones are favoured. In this way the affinity of the antibody response to the antigen is increased in a process called "affinity maturation". The favoured B-cell is multiplied to increase the amount of antibody available.

Specificity and affinity

45. Two important properties of antibodies are their "specificity" and "affinity", both of which are defined by reference to particular antigens or epitopes. Antibodies with high specificity bind to one, or at most a few, known antigens or epitopes and do not bind to other known antigen epitopes. Specificity can be demonstrated by experiments where small changes in an antigen or epitope cause a significant loss in binding with respect to a particular antibody.

46. The affinity of an antibody, on the other hand, is the strength of the binding of the antibody to a particular antigen or epitope. Antibodies that combine tightly (or associate) with antigens and separate (or dissociate) slowly are said to have high affinity. Mathematically, the affinity of a particular antibody ("Ab") for an antigen ("Ag") can be defined as:

$$K_A = \frac{k_{ON}}{k_{OFF}} = \frac{[Ab \cdot Ag]}{[Ab] \bullet [Ag]}$$

47. In this equation, k_{ON} and k_{OFF} indicate the rate constants for the association and dissociation of the antibody-antigen complex respectively. The higher the affinity constant K_A for an antibody, the stronger its affinity for the antigen in question.

48. At a conceptual level, specificity is a qualitative concept in that an antibody is either specific for a particular antigen or it is not. Affinity, on the other hand, is a quantitative concept, since it can be measured.

49. One might think from the foregoing explanation that an antibody will not be able to bind to anything other than the particular antigen (or antigens) to which it is specific. In reality, however, binding molecules such as antibodies often also bind to other surfaces in a "non-specific" manner. Indeed, some surfaces can be very "sticky" to proteins (especially proteins that contain hydrophobic or fatty content on their surface). For example, nitrocellulose is so sticky that it can be used to immobilise proteins in assays.

50. In light of this, it is necessary to determine a threshold affinity constant above which an antibody can be said to be specific for a particular antigen. There is no set rule for this, but binding of the order of at least 10^5 M^{-1} would typically be regarded as

specific binding.

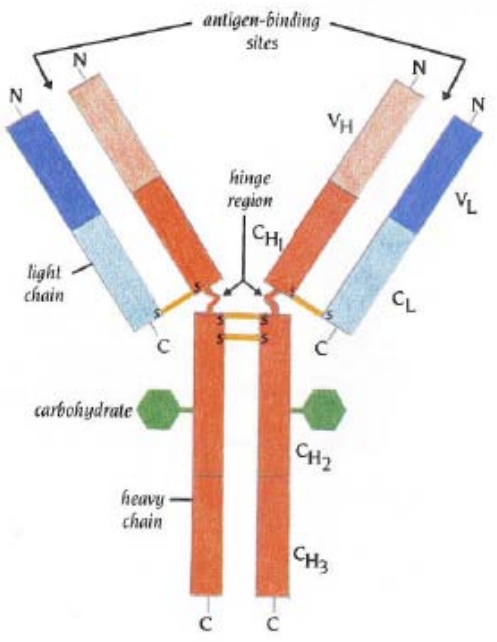
51. It should be appreciated that antibody-antigen binding is a stochastic process i.e. individual antibody molecules associate with and dissociate from individual antigen molecules randomly. The rate constants express the statistical result of this. It follows that the fact that a particular antibody molecule binds to a particular antigen molecule at a given time does not necessarily mean that those antibodies have a high affinity for those antigens.

Antibody structure and function

52. Antibodies form a group of proteins (strictly glycoproteins) known as immunoglobulins. There are a number of classes of immunoglobulins. The most prevalent is a class known as immunoglobulin-G ("IgG").

53. Because antibodies are proteins, they themselves can generate an immune response if they are put into an alien immune system. Thus a murine (mouse) antibody injected into a human being will generate an immune response in the human. This is important when it comes to designing antibodies for use as therapeutic agents in humans.

54. An IgG is made up of four chains of amino acids. There are two identical long chains, referred to as the heavy (H) chains, and two identical short chains, referred to as the light (L) chains. These are held together to create a symmetrical Y-shaped molecule which is illustrated diagrammatically below (source: Brandon and Tooze, *Introduction to Protein Structure*, Garland Publishing (1991)).



55. Each heavy chain (coloured red) consists of four domains or regions: three constant domains (C_H1, C_H2, C_H3) and one variable domain (V_H). Each light chain (coloured blue) consists of two domains: one constant domain (C_L) and one variable domain (V_L). The chains are joined by disulphide (SS) bonds (coloured orange), and also associate non-covalently. The four variable domains, which are located at the N-

terminal ends of the chains, form the antigen binding sites.

56. The domains are referred to as "variable" and "constant" to reflect the extent to which the amino acid sequence in them varies from antibody molecule to antibody molecule within the same animal. Thus, for example, a human being will have a large number of antibodies in his bloodstream, depending on the foreign materials (e.g. bacteria and viruses) which he has had to raise immune defences to. This will include many IgG molecules. The constant regions in one such molecule will be substantially identical to the constant regions in all the other IgG molecules his B lymphocytes produce. But the variable regions of the antibodies made to defend against, say, whooping cough will differ from the variable regions of the antibodies made to defend against, say, mumps. Indeed, because most foreign proteins have more than one epitope and the body's defence mechanism will make antibodies against most of them, and because that mechanism is likely to make a number of different antibodies against each antigen, there will be a number of antibodies for each foreign protein, and each of them will have variable domains which differ from the variable domains of the other antibodies. It is the ability of an immune system to make variations in the variable domains which contributes to its ability to create bespoke antibodies which lock onto single epitopes.

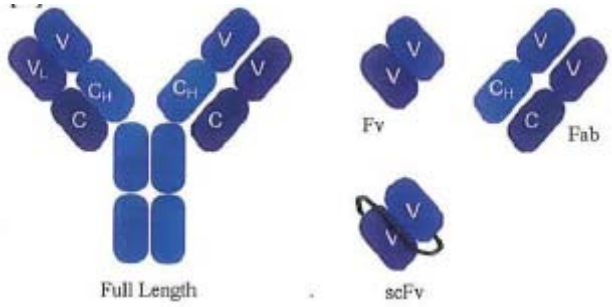
57. Each antigen binding site is formed by the juxtaposition of six segments of the variable domains referred to as complementarity-determining regions (CDRs). The CDRs are also referred to as the "hypervariable regions" or "hypervariable loops" of the antibody. They differ in amino acid sequence between antibodies against different epitopes, and in addition, certain of them vary in length from one antibody to another. There are three CDRs in each of the heavy and light chain variable domains. Each antibody can bind two epitopes at the same time, one on each arm.

58. The parts of the variable regions of both the heavy chains and light chains that are outside the CDRs are known as the framework regions. The framework regions of the variable domains are critical in forming the "scaffold" on which the CDRs sit, and consequently for correct display and presentation of the CDRs for binding to antigens.

59. Each different combination of amino acid residues in the CDRs, and to a lesser extent the framework regions, will produce an antigen binding site with a different shape which will have different binding properties.

Antibody fragments

60. It is possible to cut an IgG molecule into pieces or to manufacture pieces of it using recombinant methods. For example, it is possible to isolate each of the two arms. These are called "Fab" (Fragment antigen-binding) fragments. They will contain the variable domains (including the CDRs) and some of the constant domains. It is also possible to isolate the variable domains alone (i.e. the V_H and V_L domains): these are known as "Fv" (Fragment variable) fragments. The two variable domains in an Fv fragment can be linked together with a short chain of amino acid (called a peptide linker) to produce something which is called a "single-chain Fv" fragment or scFv (sometimes referred to as a "single-chain antibody" or SCA):



61. These types of fragment (Fab, Fv and scFv) possess some of the same properties as complete antibodies. In particular, they can bind to antigens, although they are monovalent, i.e. they only have a single binding site.

62. Another type of fragment consists of just heavy chain variable domains. These are referred to as dAb (domain Antibody) fragments.

Polyclonal and monoclonal antibodies

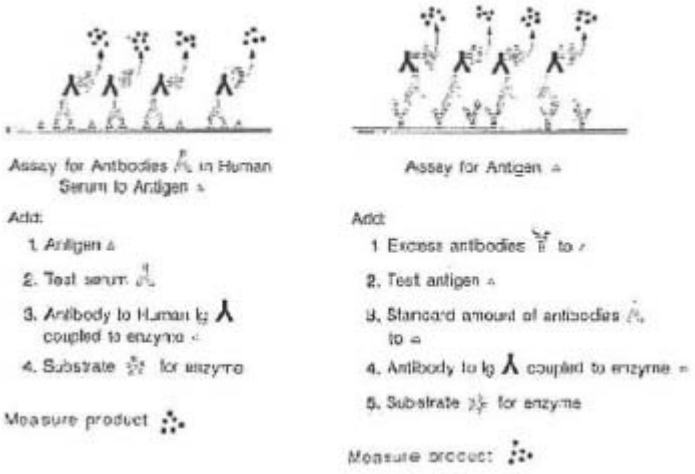
63. It has long been known that it is possible to obtain enriched preparations of antibodies for research purposes by inoculating a laboratory animal with an antigen of interest and purifying IgG from its serum once the animal has had the opportunity to produce an antibody response. Even though stimulated by a single antigen, these types of antibodies are "polyclonal" because they comprise mixtures of different antibodies, each of which binds to different epitopes on the same foreign antigen due to differences in their variable regions.

64. In 1975 Köhler and Milstein made an important breakthrough by devising a method of producing preparations of "monoclonal" antibodies, which were homogenous in structure and therefore shared the same binding properties (Köhler and Milstein, *Nature*, 256, 495-497 (1975)). Their technique involved the isolation of B-cells specialised in producing a particular antibody, stimulation of the B-cells with antigen so they produce antibodies specific for the desired antigen, and then fusion of the B-cells with "immortal" myeloma tumour cells (i.e. B-cells which proliferate indefinitely in culture) to make "hybridoma" cells. These hybridoma cells can then make monoclonal antibodies in substantial quantities.

Uses of antibodies

65. Apart from their obvious potential use in therapy, antibodies have a variety of laboratory uses, in particular in a variety of assays. A common type of assay is the Enzyme-Linked Immunosorbent Assay or ELISA first developed by Engvall and Perlman in 1971 (Engvall and Perlman, *Immunochemistry*, 8, 871-874 (1971)). In this method, antibodies raised to an antigen are used to detect antigen. The antibodies are bound to a plate and, after incubation with a sample containing the antigen, binding of the desired antigen to the antibody occurs. A second antibody that binds to the antigen and which is linked to a reporter enzyme is then added to report the binding and therefore the presence of antigen. Alternatively, ELISA can be used to detect antibodies, in which case the antigen of interest is bound to a plate. A sample containing antibody of interest is then added, the desired antibody binds to the fixed

antigen, and then a secondary reporter antibody is used to bind to and detect the presence of the first antibody. These possibilities are illustrated below (source: Rosen, Steiner and Unanue, *Macmillan Dictionary of Immunology*, Macmillan Press (1989)):



Making antibodies for human use

66. Köhler and Milstein's technique only works efficiently with murine hybridoma cells. Human cell-derived hybridomas are not as productive as the mouse equivalents and are unstable (meaning they will stop producing antibody after a period of time). In addition, it is difficult to select human antibodies against predefined antigens since it is not possible to immunise human volunteers with human-derived molecules in most cases.

67. Monoclonal antibodies derived from murine hybridoma cells are not suitable for pharmaceutical use, however, since humans will produce antibodies to mouse antibodies ("human anti-mouse antibody", HAMA). By 1990, a number of methods had been devised of obtaining murine monoclonal antibodies and then making them more compatible with the human immune system. The challenge was to do this without loss of specificity and affinity.

68. One approach was to fuse the antigen-binding variable region from a mouse antibody to a human constant region to create a "chimeric antibody". Since the entire variable region was retained, the antigen binding ability of the monoclonal antibody was almost entirely preserved. The addition of the human constant region reduced, but did not eliminate, the HAMA response.

69. Another approach was called "CDR grafting" or "humanisation". This involved taking the CDRs from a mouse antibody and inserting them into a homologous human antibody framework. The same result could be achieved by changing human antibody CDRs to the mouse sequences. It was found that, while this approach reduced the immune response, it also reduced the affinity of the antibodies.

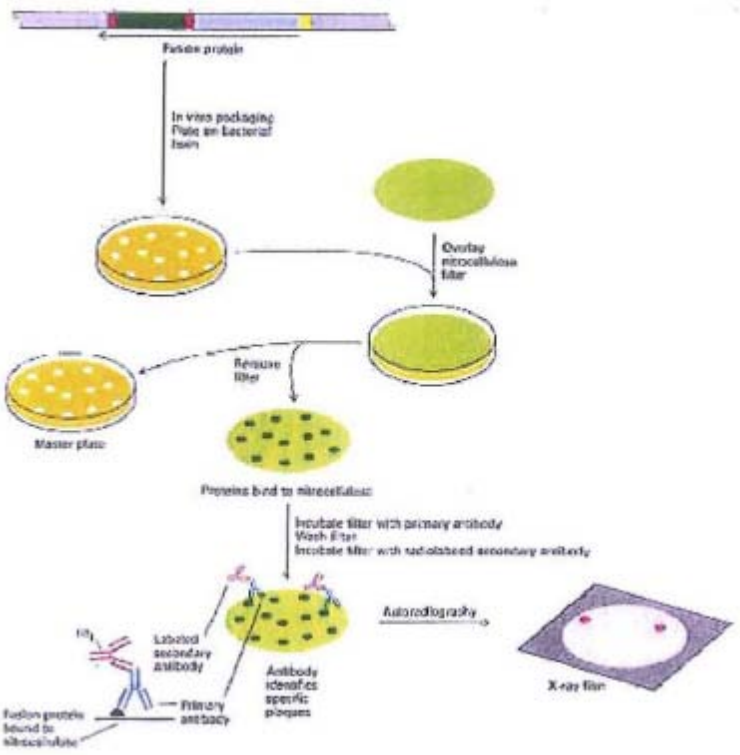
Creation of antibody libraries

70. There are a number of techniques for creating "libraries" of antibodies *in vitro*. First, a so-called "naïve" library can be extracted from a mammal (usually a mouse) and cloned into a suitable expression vector. This library would comprise all the antibodies extracted from the serum of the animal, whose products would be likely to show specificity for a wide range of antigens. The second option is to immunise the mouse first, and then extract the serum. This extracted serum would contain antibodies with a wide range of specificities, but there would tend to be a strong bias for antibodies specific for the particular antigen used for immunisation. Thirdly, a library can be created by *in vitro* diversification of the appropriate parts of the antibody genes, in particular those encoding the CDRs or other parts of the variable regions of the antibodies thought to play a role in antigen binding. To some extent, this process mimics the affinity maturation process of B-cells upon exposure to antigen.

Screening libraries by plaque lift

71. It will be appreciated from what has been said above that researchers often want to screen large libraries of antibodies or antigens for an antibody or antigen of interest. In 1990 an established technique for doing this was a method called "replica plate-lift". In this method, the vector containing DNA for each member of the library is inserted into bacteria, which are spread onto a plate containing an appropriate growth medium. The bacteria grow into colonies, each colony expressing that particular member of the library in large quantities. Once the colonies have grown, a nitrocellulose filter is overlaid and the proteins of interest in each colony stick to the nitrocellulose and then can be probed with antibody or antigen probes (depending on whether it was an antigen or antibody library). Bound molecules can be detected by autoradiography. Clones showing a positive signal can simply be cut out and re-plated to grow more colonies and amplify the clone (and also separate out the desired clone from any others that may have also been accidentally re-plated). A variant of this technique involves plating out the bacteria at sufficiently high dilution for a uniform lawn of bacteria to grow, which is then pockmocked with holes ("plaques") where the bacteria have been killed by bacteriophage (as to which, see below). This variant was known as "plaque lift".

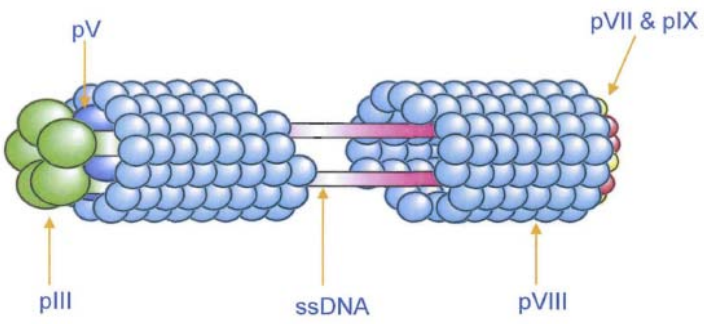
72. Plaque lift is illustrated schematically in the following diagram (source: Lodish *et al.*, *Molecular Cell Biology* (3rd edition), Scientific American (1995)):



Bacteriophages

73. Bacteriophages (or phage for short) are simple viruses which infect bacteria. They consist of a protein coat (capsid) encapsulating nucleic acid. Many types of phage have been identified, studied and used in the laboratory. Each class of phage has different properties making them useful for different purposes. Phage can have RNA or DNA genomes which may be in single- or double- stranded form. Two classes are used in particular: (a) the lytic phage such as lambda (a well-known example of which is λgt11) and T4, so called since they burst open ("lyse") the bacterial host cells following replication to release the phage particles into the environment for infection of new hosts; and (b) filamentous phage (which do not lyse their host cells and are filament-like in structure) such as fd (or Fd) and M13.

74. The defining characteristic of filamentous phage is their circular single-stranded DNA (ssDNA) genome packaged in a long flexible tube composed of a single major coat protein. The genome is relatively small (6408 nucleotides for fd). When encapsulated it forms a 6.5nm diameter tube 930nm long (in its native state):

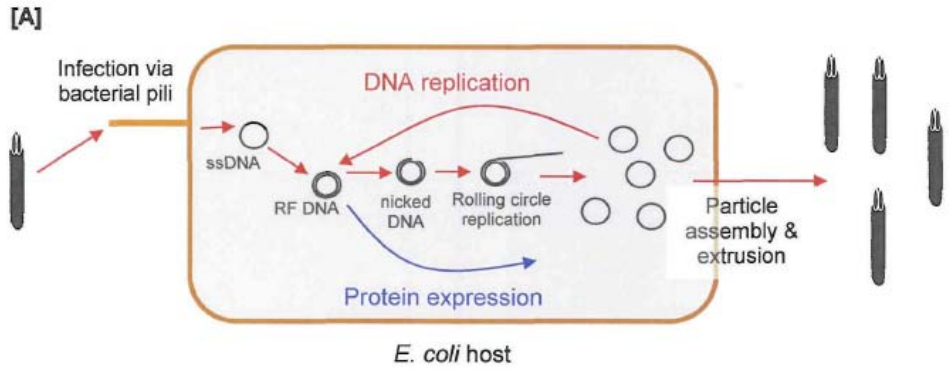


75. The filamentous phage coat contains five types of proteins. One end of the tubular particle consists of two proteins, pVII and pIX, which are present at around five copies each. The hollow tube surrounding and protecting the DNA consists of several thousand copies of the major coat protein, pVIII, in a helical repeat. The opposite end of the phage consists of about five copies each of two proteins, pIII and pVI. pIII consists of three domains: two N-terminal domains (N1 and N2) protrude from the phage surface while the C-terminal domain is buried in the particle. The N-terminal domains are involved in infection by binding to the bacterium, while the C-terminal domain is responsible for assembly termination.

76. The genes encoding for these proteins are referred to by the same numbers. Thus gene III encodes for pIII. Sometimes the proteins are referred to by reference by the gene e.g. "the gene III protein".

Phage lifecycle

77. Filamentous phage infect bacterial cells through the cell's pili (long slender proteinaceous appendages on the cell surface). The pilus is first bound by the N2 domain of pIII and then the pIII N1 domain binds to a bacterial surface protein, TolA. This is followed by the translocation (i.e. insertion) of the DNA into the bacterium's cytoplasm:



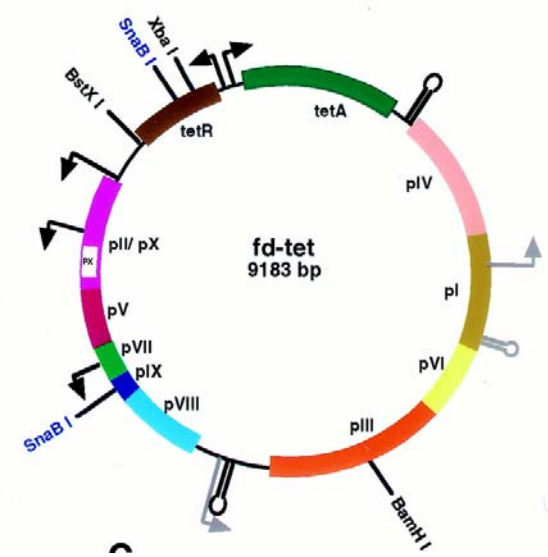
78. In the illustration above, the filamentous phage infect bacteria by injecting their ssDNA genome into the bacterial cytoplasm. ssDNA is converted to the double-stranded replicative form (RF). The RF DNA is used as a template for ssDNA production (and protein expression). ssDNA copies are either converted to further RF copies or undergo packaging to form progeny phage particles. DNA replication proceeds initially by generating further copies of the RF DNA by a rolling circle method generating ssDNA templates which are then converted to the RF DNA in the same manner as upon infection. When enough RF DNA and protein product has been generated, DNA replication switches to production of ssDNA copies.

79. Filamentous phage particles are produced in *E. coli* by a secretory process (i.e. they emerge by extrusion through the cell membrane). Assembly of the phage occurs in the cytoplasmic membrane of the bacterium where the coat proteins accumulate prior to assembly as part of the phage particle. Three phage-encoded proteins are involved in phage assembly, but do not form part of the coat. The non-coat proteins have a role in creating a channel for the passage of the phage out of the bacterial cell. The blunt

end proteins, pVII and pIX, interact with the ssDNA packaging signal and initiate the extrusion of the DNA packaged within pVIII, the major coat protein. Once the whole DNA molecule has been extruded the process is terminated by the incorporation of pIII and pVI into the capsid of the nascent phage which is subsequently released from the bacterial membrane.

Phage vectors

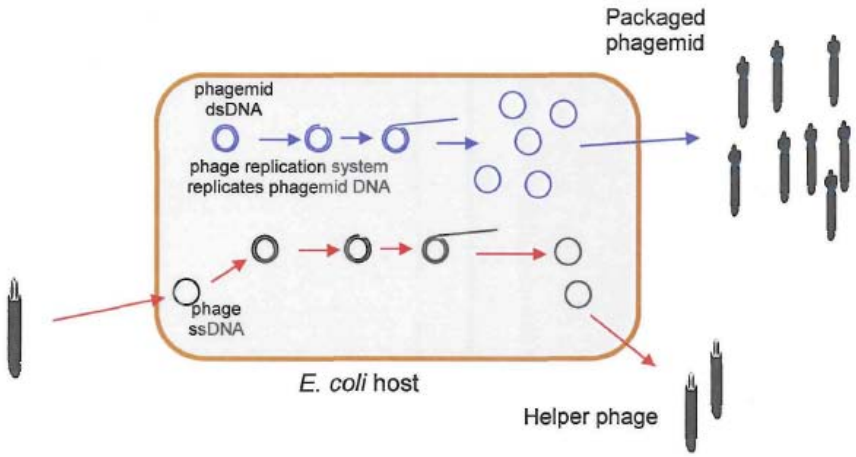
80. As noted above, phage are commonly used as vectors in genetic engineering. One such vector is fd tet. This is a version of fd phage which has all genes necessary to produce a complete phage particle, but in addition has been modified by the insertion of genes (tetA and tetR) for resistance to the tetracycline antibiotic. This enables bacteria to be selected for successful incorporation of this vector. The illustration below is a schematic diagram of fd tet, showing the arrangement of the genes for the constituent proteins of the fd phage, labelled pI to pX, and tetA and tetR:



Phagemids

81. Several vectors have been developed that combine desirable features of both plasmids and filamentous bacteriophages. In their simplest form, these vectors are plasmids with a double-strand origin of replication (e.g. ColE1) and a selectable marker for antibiotic resistance, which also carry a copy of the major intergenic region of a filamentous bacteriophage including the origin of replication for ssDNA. These are called "phagemid" vectors.

82. A phagemid is not a virus. When a phagemid vector is used, the vector itself does not contain all of the relevant genes to produce new phage particles (i.e. the full range of phage proteins to constitute a new particle cannot be produced). Accordingly, so-called "helper phage" is used simultaneously to infect the host in order to provide the remaining proteins. This helper phage is said to "rescue" the phagemid vector by providing the proteins required to activate ssDNA replication and packaging of the phagemid:



83. A well-known phagemid system, which was developed by Vieira and Messing in 1987, consists of pUC119 phagemid and M13K07 helper phage (Vieira and Messing, *J. Methods Enzymol.*, 153:3 (1987)). pUC119 is a phagemid version of a plasmid known as pUC19.

Phage display

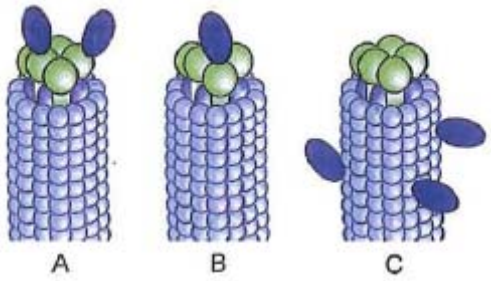
84. The Patents relate to a technique known as "phage display" which was originated by Professor Smith. Phage display essentially involves each of the protein encoding sequences in a DNA library being expressed on the surface of phage. Such phage can then be used to select the proteins that bind to the target of interest. To achieve this, some of the target is fixed to a solid support, and phage particles displaying the relevant proteins are allowed to run over its surface. Those phage expressing proteins that bind to the target will stick to the target molecules on the solid support, whereas others will not. This process is called "panning", and allows the phage (including the DNA sequences) of interest to be retained.

85. When first developed by Professor Smith, phage display involved display of antigen on the surface of the phage and panning using antibodies on the solid support ("antigen phage display"). The Patents concern phage display involving display of antibody (or, more specifically, antibody fragments) on the surface of the phage and panning used antigen on the solid support ("antibody phage display").

86. Phage display is based on the ability to engineer a filamentous phage to display a foreign amino acid sequence on its surface while also containing DNA encoding those amino acids in the phage genome. It is now known that phage can be used to display various molecules from small peptides to multimeric proteins (meaning the protein consists of more than one polypeptide chain). The display of the foreign peptide/protein on a phage is achieved by fusion to a coat protein (often referred to as the fusion protein). The most common fusion proteins are pIII and pVIII.

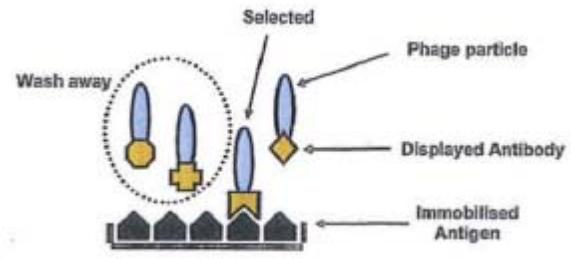
87. The illustration below shows phage with proteins (the dark blue ellipses) displayed on its surface fused to pIII (A and B), and pVIII (C). Phage display can result in multiple copies of a protein displayed on a given phage particle (as shown in A and C, referred to as "multivalent" display), a single copy (as shown in B, referred to as "monovalent" display), or no copies at all (not illustrated, referred to as "bald"

phage):



88. As I shall explain in more detail below, depending on the method chosen, wild type (i.e. unmodified) coat protein may be present in addition to fusion protein, or all the coat protein (e.g. pIII) may be the fusion form. In the former situation, by regulation of the level of wild type expression relative to fusion expression, the number of copies present on the average phage particle can be controlled. Monovalent display means that, statistically, of those phage expressing a fusion protein the majority only have a single copy present. In practice, if a population of phage is produced for monovalent display, about 10% of phage particles will display one copy of the fusion protein, a very small percentage will display two copies and the majority of particles will only have wild type coat protein (i.e. will be "bald" phage).

89. In this way antibody protein fragments can be displayed on the surface of phage. The display of the antibody on the phage surface means that the ability of the displayed antibody fragment to bind to a chosen antigen can be tested *in vitro*. Typically antigen is immobilised on a solid substrate and then presented with a library of potential binders (the phage antibody library). The desired antibodies, those that bind the antigen, will attach to the immobilised antigen while non-binders can be washed away. Once the non-binders have been washed away the selected phage antibody can be released from the antigen (this step is commonly referred to as elution), as shown below:



90. Phage display has two main advantages compared to plaque lift as a screening method. First, it makes it easier, and hence quicker, to screen large libraries. This is in large measure due to the fact that, unlike plaque lift, the whole exercise can be performed in solution. How much easier phage display is than plaque lift is a matter of dispute to which I must return later. Secondly, the antibody is physically associated with nucleic acid encoding its sequence which is contained within the phage upon which the antibody fragment is displayed (this is sometimes referred to as "preserving the genotype-phenotype link"). Having selected the phage antibody, the sequence of the antibody fragment polypeptide(s) can be easily elucidated by sequencing the DNA

of the phage display vector. This can then be used in subsequent recombinant processes.

The skilled team

91. A patent specification is addressed to those likely to have a practical interest in the subject matter of the invention, and such persons are those with practical knowledge and experience of the kind of work in which the invention is intended to be used. The addressee comes to a reading of the specification with the common general knowledge of persons skilled in the relevant art, and he or she reads it knowing that its purpose is to describe and demarcate an invention. He or she is unimaginative and has no inventive capacity. In some cases the patent is addressed to a team of persons with different skills.

92. In the present case there is a narrow, but nevertheless significant, dispute as to the identity of the skilled person or team to whom the Patents are addressed. MedImmune contend that the Patents are addressed to a team consisting of an immunologist and a molecular biologist, with the immunologist taking the lead, perhaps assisted by a biochemist. Novartis contend that the Patents are addressed to a team of scientists with differing backgrounds in areas such as immunology (in particular antibody structural biology), molecular biology and protein chemistry, but with a common interest in antibody engineering. The essential difference between the two formulations lies in the degree of specialisation of the team in the field of antibody engineering.

93. The correct approach to identifying the skilled person to whom a patent is addressed was recently considered in detail by Jacob LJ, with whom Sullivan and Waller LJJ agreed, in *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819, [2010] RPC 33 at [30]-[70]. The issue under discussion was whether the addressee is the same, and has the same common general knowledge, when considering both obviousness and insufficiency. In the course of that discussion, however, Jacob LJ drew at [42] the following conclusion from the decision of the Court of Appeal in *Dyson Appliances Ltd v Hoover Ltd* [2001] EWCA Civ 1440, [2002] RPC 22:

> "I think one can draw from this case that the Court, in considering the skills of the notional 'person skilled in the art' for the purposes of obviousness will have regard to the reality of the position at the time. What the combined skills (and mind-sets) of real research teams in the art is what matters when one is constructing the notional research team to whom the invention must be obvious if the Patent is to be found invalid on this ground."

94. In my judgment the evidence in the present case shows that real research teams in the field to which the Patents are directed were teams of the kind contended for by Novartis. "Antibody engineering" was the title of an address by Dr Winter to the Royal Society in 1989 in which he discussed the both current state of the art and future directions (*Phil. Trans. R. Soc. Lond.* B 324, 537-547 (1989)). He concluded with a section on "exploitation of antibody engineering" in which he described the

MRC's strategy of funding basic research for its own sake, but rapidly identifying and exploiting discoveries which could be applied by means of spin-off companies, patents and licensing, saying "the MRC is taking antibody engineering to the market place". The Banbury Conference in April 1990 was an early academic conference in the field, which was attended by some scientists whose interests extended beyond it; but the field was sufficiently well-established for the first commercial conference to be staged by IBC later that year. In 1990 the three leading teams in the field of antibody engineering were probably those led by Dr Winter at the MRC Laboratory of Molecular Biology/CAT, by Professor Richard Lerner at the Scripps Research Institute ("Scripps") and by Dr Andreas Plückthun at the Max-Planck-Institut für Biochemie, but there were others. Thus Professor Stefan Dübel (as to whom, see below) described himself as having "started research into antibody engineering and phage display" at the Deutsches Krebsforschungszentrum ("DKFZ") in 1989. There were also a number of commercial enterprises in the field, for example at Genentech, Genex Corporation ("Genex") and International Genetic Engineering, Inc. Furthermore, by July 1990 both SmithKline Beecham and Genetics Institute had placed advertisements in *Science* for "antibody engineers" and someone skilled in "antibody engineering/protein chemistry/cell biology" respectively. Indeed, it is noticeable that Dr Teillaud himself used the expression "antibody engineering" no less than three times when summarising "the antibody landscape as at July 1990" in his first report. Finally, I would add that in my view the specifications of the Patents are consistent with this characterisation of the skilled team.

95. The identification of the skilled team to which the Patents are addressed as corresponding in terms of its combined expertise with that of the actual teams in the field of antibody engineering leads on to a further point, as to which there is no real issue between the parties, but perhaps a difference of emphasis. As Novartis accepts, teams such as those at the MRC/CAT and Scripps included inventive people, but the notional skilled team from whose perspective the obviousness or otherwise of the Patents must be considered is deemed to lack inventive capacity.

96. In this connection counsel for MedImmune cited a long passage from *Case Law of the Boards of Appeal of the European Patent Office* (6th ed) at pages 182-184 headed "Definition of the person skilled in the art in the field of biotechnology". In my view this passage must be treated with a little care since, as counsel for MedImmune accepted, it mixes statements of principle with statements based on the facts of individual cases whose priority dates go back as far as 1978. By November 1990, the field of biotechnology was much more firmly established than it was in 1978. Nevertheless, I accept that the tenor of the Boards of Appeal's case law in this field is to distinguish between "routine experimental work" which does not require invention and "scientific research" which does, as can be seen from the following extract:

> "This case law was confirmed in T 500/91 – 'BIOGEN II'. The board ruled that the average skilled person - who might also be a team of specialists in the relevant field - operated at a practical level, and the technical development which might normally be expected of him did not include solving technical problems through scientific research.

> From the notional skilled person nothing more can be expected than the carrying out of experimental work by routine means within the framework of the normal practice of filling gaps in knowledge by the application of existing knowledge (T 886/91, T 223/92, T 530/95, T 791/96)."

97. In my judgment this approach is consistent with the long-standing approach of the courts of this country of treating the skilled person as being "an unimaginative man with no inventive capacity" (per Lord Reid in *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] RPC 346 at 355 and see also Jacob LJ in *Technip France SA's Patent* [2004] EWCA Civ 381, [2004] RPC 46 at [7]-[10]).

The expert witnesses

98. Each side called two expert witnesses. MedImmune called Professor William Brammar and Dr Jean-Luc Teillaud. Novartis had intended to call one expert, Dr William Huse, but in the event called Dr Ton Logtenberg as well for the reasons discussed below.

The preparation of experts' reports in patent cases

99. For reasons that will appear, I wish to say a few words about the preparation of experts' reports in patent cases. I must begin by setting out the legal framework.

100. CPR Part 35 includes the following rules:

> "**Experts—overriding duty to the court**
>
> 35.3(1) It is the duty of experts to help the court on matters within their expertise.
>
> (2) This duty overrides any obligation to the person from whom experts have received instructions or by whom they are paid.
>
> …
>
> **Contents of report**
>
> 35.10(1) An expert's report must comply with the requirements set out in Practice Direction 35.
>
> (2) At the end of an expert's report there must be a statement that the expert understands and has complied with their duty to the court.
>
> (3) The expert's report must state the substance of all material instructions, whether written or oral, on the basis of which the report was written.
>
> …"

101. Practice Direction 35 – Experts and Assessors, which supplements CPR Part 35, sets out general requirements for expert evidence which include the following:

> "2.1 Expert evidence should be the independent product of the expert uninfluenced by the pressures of litigation.
>
> 2.2 Experts should assist the court by providing objective, unbiased opinions on matters within their expertise, and should not assume the role of an advocate.
>
> 2.3 Experts should consider all material facts, including those which might detract from their opinions."

102. The Practice Direction also sets out the following requirements for the form and content of an expert's report:

> "3.1 An expert's report should be addressed to the court and not to the party from whom the expert has received instructions.
>
> 3.2 An expert's report must:
>
> (1) give details of the expert's qualifications;
>
> (2) give details of any literature or other material which has been relied on in making the report;
>
> (3) contain a statement setting out the substance of all facts and instructions which are material to the opinions expressed in the report or upon which those opinions are based;
>
> (4) make clear which of the facts stated in the report are within the expert's own knowledge;
>
> (5) say who carried out any examination, measurement, test or experiment which the expert has used for the report, give the qualifications of that person, and say whether or not the test or experiment has been carried out under the expert's supervision;
>
> (6) where there is a range of opinion on the matters dealt with in the report –
>
> (a) summarise the range of opinions; and
>
> (b) give reasons for the expert's own opinion;
>
> (7) contain a summary of the conclusions reached;
>
> (8) if the expert is not able to give an opinion without qualification, state the qualification; and

(9) contain a statement that the expert –

(a) understands their duty to the court, and has complied with that duty; and

(b) is aware of the requirements of Part 35, this practice direction and the Protocol for Instruction of Experts to give Evidence in Civil Claims.

3.3 An expert's report must be verified by a statement of truth in the following form –

'I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.'"

103. The Protocol for the Instruction of Experts to Give Evidence in Civil Claims includes the following paragraphs (emphasis added):

"**1. Introduction**

Expert witnesses perform a vital role in civil litigation. It is essential that *both those who instruct experts and* experts themselves are given clear guidance as to what they are expected to do in civil proceedings. The purpose of this Protocol is to provide such guidance….

2. Aims of Protocol

2.1 This Protocol offers guidance to experts *and to those instructing them* in the interpretation of and compliance with Part 35 of the Civil Procedure Rules (CPR 35) and its associated Practice Direction (PD 35) and to further the objectives of the Civil Procedure Rules in general. It is intended to assist in the interpretation of those provisions in the interests of good practice but it does not replace them. It sets out standards for the use of experts and the conduct of experts *and those who instruct them*. The existence of this Protocol does not remove the need for experts *and those who instruct them* to be familiar with CPR35 and PD35.

…

3. Application

…

3.3 Experts, *and those instructing them*, should be aware that some cases may be 'specialist proceedings' (CPR 49) where there are modifications to the Civil Procedure Rules. Proceedings may also be governed by other Protocols. Further, some courts have published their own Guides which supplement the Civil Procedure Rules for proceedings in those courts. They contain provisions affecting expert evidence. Expert witnesses *and those instructing them* should be familiar with them when they are relevant.

…

4. Duties of experts

4.1 Experts always owe a duty to exercise reasonable skill and care to those instructing them, and to comply with any relevant professional code of ethics. However when they are instructed to give or prepare evidence for the purpose of civil proceedings in England and Wales they have an overriding duty to help the court on matters within their expertise (CPR 35.3). This duty overrides any obligation to the person instructing or paying them. Experts must not serve the exclusive interest of those who retain them.

…

4.3 Experts should provide opinions which are independent, regardless of the pressures of litigation. In this context, a useful test of 'independence' is that the expert would express the same opinion if given the same instructions by an opposing party. Experts should not take it upon themselves to promote the point of view of the party instructing them or engage in the role of advocates.

…

8. Instructions

8.1 *Those instructing experts should ensure that they give clear instructions*, including the following:

…

(c) the purpose of requesting the advice or report, a description of the matter(s) to be investigated, the principal known issues and the identity of all parties;

…"

104. Long before the advent of CPR Part 35, Practice Direction 35 and the Protocol, Lord

Wilberforce (with whom Lord Fraser of Tullybelton expressly agreed on this point) said in *Whitehouse v Jordan* [1981] 1 WLR 246, a case of alleged medical negligence, at 256-257:

> "While some degree of consultation between experts and legal advisers is entirely proper, it [is] necessary that expert evidence presented to the court should be, and should be seen to be, the independent product of the expert, uninfluenced as to form or content by the exigencies of litigation."

105. In his well-known seven-point summary of the duties and responsibilities of expert witness in *The Ikarian Reefer* [1993] 2 Lloyds Rep 68 at 81-82, Cresswell J reproduced the part of this statement beginning with the words "expert evidence" as point 1. He thus omitted the first part of the statement.

106. Lord Wilberforce's statement has now been further condensed into paragraph 2.1 of Practice Direction 35. The requirement of independence imposed by that paragraph is, however, expanded upon by paragraph 4.3 of the Protocol. As that makes clear, what is required is that an expert witness should express an independent and impartial opinion which is unaffected by the identity of the party instructing him.

107. CPR rule 35.3 Practice Direction 35 and the Protocol emphasise the responsibilities of expert witnesses, but the parts of the Protocol that I have emphasised above make it clear that the lawyers who instruct expert witnesses have important responsibilities too. In short, it is the responsibility of the lawyers to ensure that the expert is properly instructed. A cardinal aspect of properly instructing the expert is to ensure that the expert is put in a position to express an independent and impartial opinion. This may involve more than simply telling the expert that that is his or her duty and providing the expert with copies of the Practice Direction and the Protocol.

108. As Lord Wilberforce said "some degree of consultation between experts and legal advisers is entirely proper". What degree of consultation is appropriate will depend on the nature of the claim, the expertise of the witness and other relevant circumstances of the case.

109. Expert witnesses in patent litigation stand in a rather unusual position. They are generally leading scientists or engineers in the field in question. Frequently they are academics. Sometimes they are consultants. In most cases, they will not have given expert evidence in patent litigation before, although there are exceptions to this. Not only that, but also they will generally have little experience of the patent system. Where do they have experience, it will generally be as inventors named on patents. As such, they may have had scientific input, but generally they will have learnt little about patent law in the process. In some fields, they may also be accustomed to using patents and patent applications as sources of technical information, but again without necessarily understanding much about patents themselves. When asked to prepare an expert report in a patent case, they will have to consider such questions as the identity and attributes of the person skilled in the art to whom the patent is addressed, the common general knowledge of the skilled person and whether something would or would not be obvious to that person in the light of particular prior art given the constraints imposed by the law of obviousness. Usually, this is not a task of which

they will have any previous experience.

110. For these reasons expert witnesses in patent actions require a high level of instruction by the lawyers. Furthermore, even if they are experienced authors, they need considerable assistance from the lawyers in drafting their report. In practice, most expert reports in patent cases are drafted by the lawyers on the basis of what the expert has told them and the draft is then amended by the expert. This, of course, requires the lawyers to understand what the expert is saying. It follows that the drafting of an expert's report in a patent action involves a steep learning curve for both the expert and the lawyers. The lawyers are learning the technology and the expert is learning enough of the law to understand the questions he must address. It follows that a high degree of consultation between the expert and the lawyers is required. Frequently, the preparation of the report will involve an iterative process through a number of drafts.

111. It is obvious that this process entails a risk of loss of objectivity on the part of the expert even if the expert is striving to remain independent and impartial. It is therefore crucial that the lawyers involved should keep the expert's need to remain objective at the forefront of their minds at all times. If they cause or allow the expert to lose his objectivity, they are doing both the expert and their client a disservice. They are doing the expert a disservice because he may be subject to criticism during cross-examination and in the court's judgment as a result. They are doing the client a disservice because partisan expert evidence is almost always exposed as such in cross-examination, which is likely to reduce, if not eliminate, the value of the evidence to the client's case.

112. I will illustrate this point by reference to two common traps for the unwary. The first lies in discussing the prior art. The expert will generally be asked by the party instructing him to express an opinion as to whether taking a particular step would or would not have been obvious to the skilled person at the relevant date in the light of certain prior art. Suppose the instructing party contends that the step would be obvious. The lawyers show the expert the prior art after having carefully explained to him the correct approach to this question, and ask him for his opinion. The expert expresses his genuine, independent and impartial opinion that taking the step would indeed have been obvious. Then the lawyers assist the expert to draft a report expressing that opinion. When drafting such a report, there is a natural tendency to focus on the parts of the prior art document which support the opinion which the expert holds. It is often the case, however, that there are parts of the document which point the other way or might be thought to point the other way or are equivocal. (Otherwise, it is unlikely that there will be a dispute.) It is important that the lawyers bring home to the expert the need to give a balanced account of the document in his report. The expert may think, for example, that such a passage is ambiguous and therefore best ignored; but if those instructing him allow him to pass over that passage in silence in his report, the inevitable consequence is that he will be confronted with that passage in cross-examination, asked why he did not mention in his report and accused of failing in his duty to the court.

113. The second example arises out of the fact that it is not uncommon for an expert witness to have some involvement with the invention in issue, or a similar invention,

in the past. For example, he may have published a paper commenting on the invention or have been a named inventor on a patent application claiming a similar invention filed before or after the one in suit or he may even have given evidence in some form (such as a declaration filed with a patent office). The lawyers who are instructing the expert should make sure that the expert discloses such contributions and, where appropriate, explains them in his report. I am not suggesting that it is incumbent on the expert to carry out a search for such documents, merely that the expert should reveal what he is aware of. It should be brought home to the expert that the lawyers for the opposing party are likely to comb through his published papers and other publicly accessible records (such as patent office files); and that, if they find something relevant that has not been disclosed by the expert in his report, then the expert may be accused in cross-examination of failing in his duty to the court if it appears to favour the opposing party. If this is not made clear to the expert by those instructing him, then the expert may find himself in an uncomfortable position even though he had thought he was complying with his duty to the court (e.g. because he thought at the time of preparing the report that the material was not significant).

114. The law reports are littered with cases, including some patent cases, in which judges have criticised expert witnesses for failing to be objective or in other ways. It is regrettably true that from time to time an expert witness does succumb to the temptation of giving partisan evidence, and that is clearly unacceptable. But I wish to emphasise that the lawyers who instruct expert witnesses bear a heavy responsibility for ensuring that an expert witness is not put in a position where he can be made to appear to have failed in his duty to the court even though he conscientiously believes that he has complied with that duty. It is also important that courts should be cautious about criticising an expert witness purely on the basis of omissions from his report unless it is clear that the fault lies with the expert rather than those instructing him, bearing in mind that the court will not usually be privy to the expert's full instructions (whatever may be the effect of CPR r. 35.10(4), which it is not necessary to go into for present purposes).

Professor Brammar

115. Professor Brammar obtained a first degree in biochemistry in 1961 and a PhD in microbial physiology in 1965 from University College, London. He was a lecturer in the Department of Molecular Biology at the University of Edinburgh from 1967 to 1977 before taking up the Chair of Biochemistry at the University of Leicester. He was Head of the Department of Biochemistry (1978-81, 1987-1992), Chairman of the School of Biological Sciences (1982-1986), Budget Centre Manager for Biological Sciences (1992-1998), Dean of the Faculty of Medicine & Biological Sciences (2000-2003) and Pro-Vice-Chancellor (Research) (2003-2007). He retired from his position as Professor of Biochemistry and Senior Pro-Vice-Chancellor (Research) at the University of Leicester in July 2007.

116. As counsel for Novartis rightly accepted, Professor Brammar was a model witness: he was very clear and careful in his evidence. At first blush, he might appear to be well qualified to act as an expert witness in the present case, since he had considerable experience at the material time with relevant techniques of molecular biology, and in the particular the use of phage vectors for DNA sequencing and *in vitro* mutagenesis.

As he made clear in his first report, however, he had no expertise in phage display. Furthermore, he could not recall having read most of the key papers in this case at the time they were published, and doubted that he would have. At an early point in his cross-examination, he was asked a question about the Bird paper discussed below. In the course of his answer, he said, "The novel teaching, as I understand it, looking in from the outside, is the linker…". I asked him to explain what he meant by saying that he was "looking in from the outside", and he replied:

> "I meant, my Lord, in the sense that I have never been an antibody engineer or a molecular immunologist. My role would be as part of a team, if you like, [a] hypothetical role, in working with the team to help them achieve the end of expressing and producing an antibody. As a molecular biologist who has no experience of doing just that with antibodies, though I have done it with other proteins, and who has no deep knowledge or real interest in antibody structure per se, then I can only look in from outside. I am not an expert in antibody structure, antibody function or antibody engineering. So I do not sit here as an expert in those topics. In that sense I am looking in from outside."

He went on to accept that he was unable to assist the court as to the common general knowledge of a molecular biologist interested in producing antibodies or as to the reaction of such a person to some of the key papers.

117. It follows that, while Professor Brammar's evidence was of considerable assistance to me in understanding the technical issues, it did not reflect the perspective of the skilled team, or even that of a member of the skilled team whose background was in molecular biology.

118. A separate point about Professor Brammar's evidence is that he testified in cross-examination that, when he was instructed in this matter, he was first asked to consider the prior art, then the priority documents and then the Patents. That was the correct way for those instructing him to proceed, since it was calculated to enable Professor Brammar to form and express his opinions on the prior art without knowledge of the invention and on the priority documents without knowledge of the Patents. It is unfortunate that his report was not drafted in a manner which reflected this. For example, the report contained a lengthy and detailed consideration of the Patents before turning to a relatively short consideration of the priority documents. Thus I was deprived of the full benefit of the manner in which Professor Brammar was instructed.

Dr Teillaud

119. Dr Teillaud obtained his first degree in immunology in 1980 from the Pasteur Institute, Paris 7 University. In 1981 he obtained a Doctorat de 3eme Cycle and in 1984 a Doctorat d'Etat ès Sciences from Paris 7 University, both for work on the Fc region of immunoglobulins. He joined the Institute National de la Santé et de la Recherche Médicale (INSERM) in 1984 and became a Director of Research in 1991. In 1993 he established the Laboratoire de Biotechnologie des Anticorps (LBA). In 2001, he joined the Centre de Recherches Biomédicales des Cordeliers, heading a molecular and cellular immunology group. In parallel, he was responsible for the development

of the program on therapeutic monoclonal antibodies of the Laboratoire Français du Fractionnement et des Biotechnologies (LFB). In 2005, he became INSERM's "1st Class Research Director". In 2007, he founded the newly created Cordeliers Research Center/INSERM Antibody Bio-Engineering Laboratory which he still heads.

120. Dr Teillaud was not involved in the field of antibody engineering in November 1990, although he had worked on various aspects of antibody structure and function. In about December 1990 he read McCafferty and was "extremely excited" by it. As a result he attended a workshop on "Expression of heterologous proteins in prokaryotic and eukaryotic cells" at INSERM in January 1992 which included a lecture by Dr Andrew Griffiths of the MRC/CAT team which published McCafferty. Following this, he attended a three week practical course at the MRC in September 1992, where he was intensively trained in generating scFv and in building a phage library for scFv. As a result of this experience, he "became convinced that the filamentous phage technique was a powerful and elegant technique for the selection of antibodies and antibody variants". Subsequently, he sent a post-doctoral student to work in Dr Winter's laboratory and organised a workshop at INSERM in March 1994, at which both Dr Winter and Dr Plückthun gave lectures.

121. It follows that, while Dr Teillaud does have relevant expertise in antibody engineering, and in particular phage display, his experience was gained after November 1990. Not only that, but in addition he was drawn into the field by reading McCafferty and acquired all his initial experience from or with the MRC/CAT team. As with Professor Brammar, therefore, while Dr Teillaud's evidence was of assistance to me in understanding the technical issues, it did not necessarily reflect the perspective of the skilled team, or even that of a member of the skilled team whose background was in immunology.

122. Dr Teillaud gave evidence in English. Although his English is fairly good, I did not always find him easy to follow either live or when reading the transcript. In assessing his evidence, I have made allowance for the fact that he was not giving evidence in his mother tongue and for my own difficulties in comprehension. Even making full allowance for those factors, however, I have to say that found him to have a tendency at times not to answer the questions put to him and to be slightly argumentative. Nevertheless, I am sure that he was doing his best to assist the court.

123. A final point to note about the evidence of Professor Brammar and Dr Teillaud is that Dr Teillaud opined in his first report, consistently with MedImmune's case, that the Patents were addressed to a team consisting of an immunologist interested in producing antibodies that bind to a target chosen by the investigator and a molecular biologist with expertise in phage, the team being led by the immunologist. Professor Brammar said in his first report that he agreed with this. Despite this, their reports did not really read as those of members of a team addressing separate areas of specialisation. Rather, each approached all the issues in the case from his own perspective with only occasional cross-references to what the other had to say.

Dr Huse

124. Dr Huse graduated from Massachusetts Institute of Technology in 1975 with a BSc in chemistry. In 1982 he completed a PhD in neuroscience at the Albert Einstein College

at Yeshiva University. From 1982 to 1984 he was a post-doctoral researcher in molecular neurobiology at Cold Spring Harbor Laboratory. From 1984 to 1986 he was an Assistant Professor at Yale University, where he was a founding member of the molecular neurobiology department. From 1984 to 1989 he was Head of Discovery and Research at Vector Cloning Systems, later called Stratagene Cloning Systems, Inc. ("Stratagene"). From 1989 to 1990 he worked as a consultant at Scripps.

125. In 1989 Dr Huse founded Ixsys, Inc., later called Advanced Molecular Evolution, Inc ("AME"). He was Chief Scientific Officer of AME from 1990-1999 and President and Chief Executive Officer from 1999-2004. In 2004 AME was acquired by Eli Lilly, and from 2004-2007 Dr Huse was a Vice-President of Eli Lily and President and Chief Medical Officer of AME. In 2007 he founded Advanced Molecular Design, Inc.

126. As discussed below, Dr Huse was one of the authors of two of the key papers in this case, which were both published in 1989. He also attended the Banbury Conference. Thus he was working in the field of antibody engineering in November 1990, although he was modest about the extent of his actual achievement by that date.

127. Of all the expert witnesses, I think that Dr Huse was the closest to being representative of the expertise of a member of the skilled team. On the other hand, it is clear that, as counsel for Novartis accepted, Dr Huse was of an inventive turn of mind, having a number of patents and patent applications to his name.

128. Unfortunately, Dr Huse became seriously ill shortly before finalising his first report. Despite this, he continued to act as an expert in this case. To accommodate Dr Huse's condition, Novartis instructed Dr Logtenberg, who took over certain areas of the case (particularly priority and infringement) from Dr Huse. At trial, Dr Huse gave evidence in the mornings, and Dr Logtenberg gave evidence in the afternoons. It is a tribute to Dr Huse's dedication that he gave evidence in these circumstances.

129. Counsel for MedImmune put it Dr Huse in cross-examination, and submitted in his closing submissions, that Dr Huse had failed to comply with his duty to the court in that he had failed to be impartial and objective since he had omitted certain matters from his first report that he should have mentioned because they were adverse to Novartis' case. Counsel for MedImmune also submitted that Dr Huse had compounded this failure by failing to mention these matters in his second report or in his oral evidence in chief. Counsel for Novartis riposted that in certain respects the cross-examination of Dr Huse had been unfair.

130. It is convenient to deal with the latter point first. The most important respect in which it was alleged that the cross-examination was unfair was that counsel for MedImmune cross-examined Dr Huse on the basis that Dr Huse had attended an interview with an examiner at the US Patent and Trademark Office ("USPTO") in connection with Ixsys' patent application (as to which, see below) in 2002, whereas in fact this turned out not to be the case. Furthermore, although MedImmune's team provided Dr Huse with no less than three bundles of documents which were proposed to be put to Dr Huse (on the evening of Sunday 16 May with Dr Huse beginning his oral evidence on Tuesday 17 May), the document which counsel was relying on was neither included

in these bundles, nor put to the witness in cross-examination. Still further, it should have been apparent from the document in question that Dr Huse had not attended the interview, it was another William. On the other hand, counsel for MedImmune himself spontaneously acknowledged the error at a later point in the cross-examination, and subsequently apologised unreservedly for it. In my view this error was avoidable and unfortunate, and I accept that it may have unsettled the witness and that due allowance must be made for this in assessing his evidence. I do not consider, however, that it meant that the cross-examination was unfair. Still less do I consider that the other matters relied on meant that the cross-examination was unfair. On the contrary, I consider that the cross-examination was conducted with courtesy and sensitivity and that the questions put to Dr Huse dealt with matters which it was counsel's duty to investigate.

131. Counsel for MedImmune submitted that Dr Huse had failed to mention in his first report five matters that he should have mentioned. I will concentrate on what I regard as the two main points.

132. The first matter was that, in his discussion of Parmley & Smith, Dr Huse had omitted reference to the crucial paragraph relied upon by MedImmune (as to which, see below) despite quoting the paragraphs before and after it. So far as this is concerned, Dr Huse accepted during cross-examination that he had failed in his duty in leaving this passage out. His explanation was that he regarded the paragraph in question as ambiguous, that he did not agree with the concerns which on one view were raised in it and that he had advised Novartis' representatives that Professor Smith should be asked about it. Counsel for MedImmune submitted that this explanation should be rejected as completely implausible, but when he put to this to Dr Huse in cross-examination Dr Huse stood by his explanation. I see no reason to believe that Dr Huse was lying about this. Counsel for Novartis submitted that, notwithstanding his admission in cross-examination, Dr Huse had not failed in his duty to the court, because he had in fact addressed the points which MedImmune rely on the passage as supporting elsewhere in his report (namely, in the context of discussing various comments made about Professor Smith's work in the Patents). Counsel for Novartis also submitted that the cross-examination was based, and Dr Huse's admission extracted, on an unfair premise given the evidence of Professor Brammar and Dr Teillaud about the passage in question during cross-examination. I do not accept the latter point, because Dr Huse signed his first report long before those witnesses gave evidence.

133. In my judgment, Dr Huse should have mentioned the passage in question in his first report, if only to say that he regarded it as ambiguous. I am unable to conclude, however, that Dr Huse was personally at fault in this respect. The fault may have lain with the lawyers who assisted him to draft his report or there may have been a misunderstanding between Dr Huse and the lawyers. Given that he regarded the passage as ambiguous, and had told Novartis' representatives of that opinion, Dr Huse may have received the impression that it was unnecessary for him to refer to the passage, and sufficient to deal with the substance of the points in the way in which he did.

134. The second matter relied upon by counsel for MedImmune is that, although Dr Huse

mentioned in his first report that he was a named inventor on a number of patents and patents applications, he failed to reveal that one of these patent families was for antibody phage display. The story which emerged in cross-examination was of some complexity, and I am not entirely confident that even now I have the whole picture. On any view, the fault for this cannot be laid wholly at the door of the witness: in addition to the error made by counsel to which I have referred above, the cross-examination was further marred by the fact that the granted patent which was put to Dr Huse was not included in the cross-examination bundles either and was only produced on the third morning of the cross-examination.

135. In summary, the position appears to be as follows. On 28 September 1990 (i.e. between the dates of the Patentees' first and second priority documents) Ixsys as assignee from Dr Huse filed US Patent Application 07/590,219 entitled "Surface expression libraries of heteromeric receptors". Using this application as the priority document, on 27 September 1991 Ixsys filed International Application No. PCT/US91/07149, which was subsequently published as WO 92/06204. The broadest claim of both the priority document and the PCT application, claim 1, was as follows:

> "A composition of matter comprising a plurality of cells containing diverse combinations of first and second DNA sequences encoding first and second polypeptides which form heteromeric receptors, one or both of said polypeptides being expressed as fusion proteins on the surface of a cell."

There were 64 other claims, one of which, claim 16, was as follows:

> "A cloning system for the coexpression of two or more DNA sequences encoding polypeptides which form a heteromeric receptor, comprising a set of first vectors having a diverse population of first DNA sequences and a set of second vectors having a diverse population [of] second DNA sequences, said first and second vectors having two pairs of restriction sites symmetrically oriented about a cloning site for containing said first and second populations of DNA sequences so as to allow only the operational combination of vector sequences containing said first and second DNA sequences."

136. Dr Huse's evidence was that the patent application was initially filed because of litigation between Stratagene on the one hand and Ixsys and himself on the other. Stratagene claimed that certain ideas that it believed Dr Huse had devised during his employment by Stratagene belonged to it, and consequently Dr Huse was advised by his attorneys to protect Stratagene's potential interest by making a patent application. This evidence is partially corroborated by extracts from a transcript of evidence given by Dr Huse at the trial of those proceedings in San Diego in September 1991, which show that Stratagene brought its claim in May 1990.

137. It was also Dr Huse's evidence that he did not believe that the phage display aspects of the application were patentable and that he had advised the investors in Ixsys of this. By contrast, he did believe that the aspect concerning the restriction sites (i.e. claim 16) was patentable. This evidence is corroborated by two pieces of evidence.

The first is a record of an interview with an examiner in the US Patent and Trademark Officer attended by Dr Huse on 29 September 1993 (not 2002), which records that "Applicant explained the central nature of the restriction cleavage site to the invention". The second is a declaration made by Dr Huse on 17 August 1999 in support of an opposition by Dyax Corporation to 877 in which he expressed the view that "the vectors of [Parmley & Smith] would have been viewed as an obvious choice to implement the display of ScFv on phage advocated by [European Patent Application No 0368684 published in May 1990]". It should be noted that this declaration is broadly consistent with the opinions Dr Huse expressed in his evidence in the present case. Dr Huse did not refer to it in his reports either. He explained that this was for the simple reason that he had forgotten about it.

138. Dr Huse was pressed in cross-examination with the fact that AME pursued prosecution of this patent family for a considerable period of time. This activity included filing continuations in the US, filing foreign applications, trying to persuade examiners of the patentability of the inventions and filing submissions in response to oppositions by four opponents (including CAT) to AME's European Patent No 0 550 645 in which it was argued that the combination of Parmley & Smith with Huse (as to which, see below) did not render antibody phage display obvious. Dr Huse's evidence was to the effect that this was a business decision on the part of AME and his only involvement was to provide scientific input when called upon to do so. He also said that, after AME had been taken over by Eli Lilly in 2004, the patents and applications were abandoned on his advice. When it was pointed out to Dr Huse that US Patent No 6,893,845 had been granted to AME in May 2005 with a broad claim 1 (corresponding to claim 1 of the original application but with two additional limitations, the main one being to expression of "a fusion protein with the protein product of gene VIII of a filamentous phage"), he expressed surprise. As he explained in re-examination, however, claim 8 of this patent (corresponding to claim 16 of the original application with some additional limitations) was directed to what he had always regarded as being inventive.

139. Counsel for Novartis submitted that there was no need for Dr Huse to mention this patent family in his report. I disagree. In my judgment Dr Huse should have mentioned it, since it was relevant to the opinions he was expressing. Again, however, I am unable to conclude that Dr Huse was personally at fault in this respect. He may not have appreciated from his instructions that this was something he ought to mention.

140. I do not propose to discuss the other three omissions relied upon by counsel for MedImmune. These relate to Professor Smith's talk about the Banbury Conference, a sentence from Bass et al., "Hormone Phage: An Enrichment Methods for Variant Proteins With Altered Binding Properties", *Proteins: Structure, Function and Genetics*, 8, 309-314 (1990) ("Bass", as to which see below) and a literature search about the use of phage display he had carried out. It suffices to say that in my judgment these are all more marginal matters than the two discussed above, and do not materially advance the objection made by MedImmune. The same goes for a point made about the way in which Dr Huse described the status of phage display in 1990.

141. Finally, what I consider to be most important is that, whatever imperfections there

may have been in his first report, in his oral evidence Dr Huse gave me the impression of a frank witness who was doing his best to assist the court in difficult circumstances. Indeed, I consider that, if anything, he was over-ready to admit fault on his own part.

142. For these reasons I do not accept the submission that Dr Huse failed to comply with his duty to the court.

143. Counsel for MedImmune also made six submissions about Dr Huse's evidence which do not reflect on his integrity. First, it was submitted that he was not representative of the notional skilled addressee. So far as Dr Huse's expertise is concerned, I do not accept this. On the contrary, as I have already said, I consider that he is more representative of the addressee than either Dr Teillaud or Professor Brammar. On the other hand, as I have also said, Dr Huse is inventive whereas the addressee is not.

144. Secondly, it was submitted that Dr Huse had assessed the question of obviousness from his own perspective and not that of the uninventive skilled person. Dr Huse disputed this when it was put to him in cross-examination, saying he had tried to put himself in the position of the skilled person. I accept that he did his best to do this. As I shall explain in more detail below, however, Dr Huse had arrived at the invention even before reading Parmley & Smith (let alone hearing Professor Smith's talk at the Banbury Conference). It inevitably follows that his perspective was different to that of the addressee, and I do not think he was entirely successful in distinguishing between the two. I have borne this in mind in assessing his evidence, but I do not accept that it renders Dr Huse's opinions worthless, as counsel for MedImmune submitted.

145. Thirdly, it was submitted that hindsight had crept into Dr Huse's reasoning. Hindsight is, of course, always a problem for experts (and courts) in patent cases. I do not consider that Dr Huse's evidence was particularly afflicted by it, however. On the contrary, as I have just said, Dr Huse's problem was the opposite one of having arrived at the invention before reading the cited prior art.

146. Fourthly, it was submitted that Dr Huse had applied a wrong test for common general knowledge. This is another common difficulty for expert witnesses in patent actions, but I do not consider that Dr Huse went far wrong. In any event the point is of little significance given that, as discussed below, there was little dispute between the parties as to the common general knowledge by the end of the trial.

147. Fifthly, it was submitted that Dr Huse had failed to give reasons for his opinions. No attempt was made to substantiate this submission, however. Instead, counsel argued that Dr Huse had changed his reasons for saying that the patented invention was obvious. That is a different point. I will consider Dr Huse's reasons for saying that the invention was obvious in due course.

148. Finally, it was submitted that Dr Huse had strayed beyond his expertise in giving one answer. Dr Huse accepted that this was so, but it was an isolated incident.

Dr Logtenberg

149. Dr Logtenberg obtained a first degree in medical biology in 1983 and a PhD in immunology in 1987, both from the University of Utrecht. From 1987 to 1989 he was

a post-doctoral researcher in the laboratory of Professor Frederick Alt at Columbia University. Professor Alt's group was prominent in using molecular biology to analyse and manipulate antibody genes, and one of Dr Logtenberg's colleagues at Columbia subsequently attended the Banbury Conference.

150. In late 1989, Dr Logtenberg became an Assistant Professor in immunology at the University of Utrecht. His work focussed on the analysis of the link between antibody specificities, recombination of antibody genes and further somatic hypermutation in the immune system. Thus he was in the field of antibody engineering in November 1990. Between 1993 and 1995, he successfully created a phage display library of human scFv antibody fragments that was shown to contain specific scFv fragments for many different antigens. Thus he has experience of phage display, albeit acquired after November 1990.

151. In 1996, Dr Logtenberg was appointed Professor of Immunobiotechnology at Utrecht University Hospital. At about the same time he founded U-Bisys, whic merged with Introgene to become Crucell NV in 2000. From 2000 to the end of 2002 Dr Logtenberg was Chief Scientific Officer of Crucell. In 2003 he founded Merus Biopharmaceuticals BV, of which he remains Chief Executive.

152. Dr Logtenberg gave evidence in fluent English. Counsel for MedImmune accepted that he was generally trying to assist the court, but suggested that he sometimes tried to avoid giving an answer that might be adverse to Novartis' case. The two examples relied on by counsel both concerned Dr Logtenberg's evidence as to the meaning of the word "derivative". In neither case do I consider that Dr Logtenberg was doing anything other trying to assist the court as to his understanding of the meaning of this term.

Common general knowledge

153. I reviewed the law as to common general knowledge in *KCI Licensing Inc v Smith & Nephew plc* [2010] EWHC 1487 (Pat), [2010] FSR 31 at [105]-[115]. That statement of the law was approved by the Court of Appeal [2010] EWCA Civ 1260, [2011] FSR 8 at [6].

154. Notwithstanding the difference between the parties as to the skilled team, by the end of the trial there was little dispute between them as to the skilled team's common general knowledge in November 1990. It is common ground that it would have included all the matters I have set out in the technical background section of this judgment other than the paragraphs describing phage display. In addition, MedImmune accepted in the light of the evidence that the following papers would also have been common general knowledge. This is of some importance because the evidence of Professor Brammar in his reports was that none of these papers was common general knowledge to the molecular biologist, while the evidence of Dr Teillaud in his reports was that the general principles exemplified by these papers were common general knowledge to the immunologist but not the details. Moreover, Dr Teillaud's and Professor Brammar's approach to the question of obviousness in their reports was predicated on that basis.

Better and Skerra & Plückthun

155. Better *et al.*, "*Escherichia coli* Secretion of an Active Chimeric Antibody Fragment", *Science*, 240, 1041-1043 (1988) ("Better") and Skerra and Plückthun, "Assembly of a functional immunoglobulin Fv fragment in *Escherichia coli*", *Science*, 240, 1038-1041 (1988) ("Skerra & Plückthun") were published in the same edition of *Science* in May 1988. The Plückthun group from the Max-Planck-Institut für Biochemie described production of a functional Fv fragment in *E. coli*, and the Better group from International Genetic Engineering, Inc. achieved the expression of a Fab fragment. It is common ground that the skilled team would have seen these as important papers.

156. Both groups had realised that a key step in the folding of antibodies was the formation of the disulphide bonds between the heavy and light chains. This required an oxidising environment such as the periplasmic space of bacteria (which is the region of bacteria between the inner and outer membrane). The principal solution arrived at by both groups was to direct the antibody fragment for secretion into the periplasmic space using a leader peptide from an enzyme called PelB. It was found that the antibody fragments expressed were fully functional and that the affinity of the recombinant antibody was essentially identical to that achieved by the native antibody.

Bird

157. Bird *et al.*, "Single-Chain Antibody-Binding Proteins", *Science*, 242, 423-426 (1988) ("Bird") was published by a group from Genex in October 1988. This reported the creation of what was then the new antibody fragment that became known as scFv.

Orlandi, Sastry and Ward

158. Orlandi *et al.*, "Cloning immunoglobulin variable domains for expression by the polymerase chain reaction", *Proc. Natl. Acad. Sci. USA*, 86, 3833-2837 (1989) ("Orlandi") was published by workers from the Institutio Nazionale per lo Studio e la Cura dei Tumori and the MRC Laboratory of Molecular Biology, including Dr Winter, in May 1989.

159. Sastry *et al.*, "Cloning of the immunological repertoire in Escherichia coli for generation of monoclonal catalytic antibodies: Construction of a heavy chain variable region-specific cDNA library", *Proc. Natl. Acad. Sci. USA*, 86, 5728-5732 (1989) ("Sastry") was published by collaborators from Scripps (including Dr Huse, although by then he was at Stratagene) and Pennsylvania State University in August 1989.

160. Ward *et al.*, "Binding activities of a repertoire of single immunoglobulin variable domains secreted from Escherichia coli", *Nature*, 341, 544-546 (1989) ("Ward") was published by a group from the MRC Laboratory of Molecular Biology, including Dr Winter, in October 1989.

161. Each of these papers demonstrated the ability to create diverse libraries of antibody fragments and variable domains using bacterial expression systems.

Huse

162. Huse *et al*., "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda", *Science*, 246, 1275-1281 (1989) ("Huse") was published by collaborators from the Scripps Research Institute, the Krebs Institute at the University of Sheffield, Pennsylvania State University and Stratagene in December 1989. This is a significant paper in that it describes the creation of a large antibody library which can be screened to identify antibody fragments of interest.

163. The approach described in Huse involved cDNA cloning using PCR. First, the authors created separate heavy chain and light chain libraries each comprising a diverse collection of genes. The use of two lambda vectors with "antisymmetric" cloning sites enabled the DNAs from the two libraries to be combined to create a Fab combinatorial library. Each member of that library encoded a particular combination of heavy and light chain with (potentially) particular binding properties. The technique employed by the authors for screening their combinatorial library was plaque lift.

164. At page 1279-1280 the authors discuss how their phage library compares with the *in vivo* antibody repertoire in terms of size, diversity and ease of access. In relation to size, they say:

> "The size of the mammalian antibody repertoire is difficult to judge, but a figure of the order of 10^6 to $l0^8$ different antigen specificities is often quoted. With some of the reservations discussed below, a phage library of this size or larger can readily be constructed by a modification of the method described. Once an initial combinatorial library has been constructed, heavy and light chains can be shuffled to obtain libraries of exceptionally large numbers."

165. In relation to diversity, the authors say:

> "In principle, the diversity, characteristics of the naive (unimmunized) in vivo repertoire and corresponding phage library are expected to be similar in that both involve a random combination of heavy and light chains. However, different factors act to restrict the diversity expressed by an in vivo repertoire and phage library."

They go on to discuss these differences, and changes which can be made to increase diversity in the phage library.

166. In relation to ease of access, the authors say:

> "In practical terms the phage library is much easier to access. The screening methods used have allowed one to survey the gene products of at least 50,000 clones per plate so that 10^6 to 10^7 antibodies can be readily examined in a day."

167. The paper concludes by saying that the authors' data "shows that it is now possible to construct and screen at least three orders of magnitude more clones with monospecificity than previously possible".

Phage display

168. I have briefly described phage display in the technical background section above. As stated there, phage display was initially developed by Professor Smith. During the period prior to the filing of PD3, he published three papers on the technique. At the beginning of the trial it was Novartis' position that Professor Smith's work on phage display, including the gist of at least the first two papers, was common general knowledge. MedImmune disputed this. In closing submissions, Novartis maintained that the basic concept of phage display at a high level would have been common general knowledge, but did not press the contention that any more than that was. MedImmune disputed that even the basic concept was common general knowledge. I agree with Novartis on this point for reasons I will explain later. I also agree with Novartis, however, that it does not matter if MedImmune is right. This is nevertheless a convenient juncture at which to introduce Professor Smith's work. I will have to return to this in more detail when describing the prior art relied on by Novartis and when discussing the case on obviousness.

Smith

169. Smith, "Filamentous Fusion Phage: Novel Expression Vectors That Display Cloned Antigens on the Virion Surface", *Science*, 288, 1315-1317 (1985) ("Smith") was published in June 1985. Smith is the seminal paper on phage display. The abstract reads as follows:

> "Foreign DNA fragments can be inserted into filamentous phage gene III to create a fusion protein with the foreign sequence in the middle. The fusion protein is incorporated into the virion, which retains infectivity and displays the foreign amino acids in immunologically accessible form. These 'fusion phage' can be enriched more than 1000-fold over ordinary phage by affinity for antibody directed against the foreign sequence. Fusion phage may provide a simple way of cloning a gene when an antibody against the product of that gene is available."

For present purposes the details of the work do not matter.

Parmley & Smith

170. This paper was published in December 1988. It is a key item of prior art and so I shall describe it in detail below. At this stage it is sufficient to quote the summary:

> "Foreign DNA fragments can be inserted into a minor coat protein gene of filamentous phage, creating a fusion protein that is incorporated into the virion; we call these particles 'fusion phage'. The foreign amino acids are displayed on the

> surface, allowing fusion phage bearing antigenic determinants from a target gene to be purified in infectious form by affinity to antibody directed against the gene product. Here we introduce fusion-phage vectors that accept foreign DNA inserts with little effect on phage function; and describe affinity purification of virions bearing a target determinant from a 10^8 fold excess of phage not bearing the determinant, using minute amounts of antibody. These 'antibody-selectable' vectors are a promising alternative to conventional expression systems for using antibodies to clone genes, though the ability to isolate rare clones from actual libraries remains to be demonstrated."

Scott & Smith

171. Scott & Smith, "Searching for Peptide Ligands with an Epitope Library", *Science*, 249, 386-390 ("Scott & Smith") was published in July 1990. Again, at this stage it sufficient to quote the abstract:

> "Tens of millions of short peptides can be easily surveyed for tight binding to an antibody, receptor or other binding protein using an 'epitope library.' The library is a vast mixture of filamentous phage clones, each displaying one peptide sequence on the virion surface. The survey is accomplished by using the binding protein to affinity purify phage that display tight-binding peptides and propagating the purified phage in *Escherichia coli*. The amino acid sequences of the peptides displayed on the phage are then determined by sequencing the corresponding coding region in the viral DNA's. Potential applications of the epitope library include investigation of the specificity of antibodies and discovery of mimetic drug candidates."

PD3

172. PD3 is quite a long document, albeit rather shorter than the Patents: including tables, but excluding the figures, the specification runs to 46 pages. There are no claims.

173. The specification is entitled "Binding substances". It begins (at page 1 lines 3-15) with the following paragraph:

> "The present invention relates to binding substances. The present invention also relates to methods for the production of binding substances eg binding molecules and to the biological binding molecules produced by these methods. The present invention also relates to: a) the production of antibodies, receptor molecules and fragments and derivatives of these antibodies and receptor molecules; b) viruses encoding the above identified molecules which viruses have the ability to present said molecules at their surfaces; c) packages comprising a virus and an above identified molecule presented at the viral

> surface; and d) screening techniques utilising the unique properties of these packages."

174. The specification then describes the background to the invention, beginning with short discussion of monoclonal antibodies and of antibody structure. It goes on to record that it has been shown that antibody fragments can perform the function of binding antigens, in particular the Fv fragment and the dAb fragment, and that scFvs have made by recombinant methods, citing Bird and another paper.

175. The specification then says (at page 2 lines 22-25):

> "Whilst monoclonal antibodies, their fragments and derivatives have been enormously advantageous, there are nevertheless a number of limitations associated with them."

176. Two limitations are identified. The first is that immortal antibody-producing human cell lines are very difficult to establish and give low yields of antibody. The second is described (at page 3 lines 3-19) as follows:

> "Secondly, a key aspect in the isolation of monoclonal antibodies is how many different antibody producing cells with different specificities, can be sampled compared to how many need to be sampled in order to isolate a cell producing antibody with the desired specificity characteristics (Milstein, C., Royal Soc. Croonian Lecture, Proc. R. Soc. London B. 239; 1-16, (1990)). For example, the number of different specificities expressed at anyone time by lymphocytes of the murine immune system is thought to be approximately 10^7 and this is only a small proportion of the potential repertoire of specificities. However, during the isolation of a typical antibody producing cell with a desired specificity, the investigator is only able to sample 10^3 to 10^4 individual specificities. The problem is worse in the human, where one has approximately 10^{12} lymphocyte specificities, with the limitation on sampling of 10^3 or 10^4 remaining."

177. The specification explains that this problem has been partly addressed by recombinant technology, and in particular by the use of PCR to isolate antibody producing sequences from cells, which enables amplified V_H and V_L genes to be cloned directly into vectors for expression in bacterial or mammalian cells. It goes on (at page 4 lines 15-30):

> "Conversely, some of these techniques can exacerbate the screening problems. For example, large separate heavy and light chain libraries have been produced from immunized mice and combined together in a random combinatorial manner prior to screening (Huse, W.D. et al., 1989, Science 246, 1275-1281). Crucially however, the information held within each cell, namely the specific combination of one light chain with one heavy chain, is lost. This loses most, if not all, of the

> advantage gained by using immunization protocols in the animal. Currently, only libraries derived from single heavy chain variable domains (dAbs; Ward, E.S., et a1., 1989, supra.) do not suffer this drawback, but because not all antibody heavy chain variable regions are capable of binding antigen, more have to be screened.
>
> In addition, the problem of directly screening many different specificities in prokaryotes remains to be solved."

178. The specification then says there is a need for a screening system which ameliorates one or more of these problems. It continues (at page 4 line 33 – page 5 line 3):

> "The ideal system would allow the sampling of very large numbers of specificities (eg of the order of 10^6 and higher) rapid sorting at each cloning round, and rapid transfer of genetic material coding for the binding molecule from one stage of the production process, to the next stage."

179. The specification states that the most attractive candidates for this type of screening would be prokaryotic organisms which express antibody on their surface. It goes on (at page 5 lines 8-16):

> "It has already been shown that antibody fragments can be secreted through bacterial membranes with the appropriate signal peptide (Skerra, A., and Pluckthun, A., 1988, Science 240, 1038-1040; Better, M. et al., 1988, Science 240, 1041-1043). However, it has not been shown how an antibody or antibody fragment can be held on the bacterial cell surface in a configuration which allows efficient sampling of its antigen binding properties."

180. The specification says that bacteriophage make attractive candidates, but that the practical problem of how to use bacteriophages in this manner has not been solved, reference being made to a prior application in the name of Genex proposing the use of lambda phage. It continues with the following statement of the problem addressed by the invention (at page 5 line 36 – page 6 line 8):

> "The problem of how to use bacteriophages is in fact a difficult one. The antibody molecule must be inserted into the phage in such a way that the integrity of the phage coat is not undermined, and the antibody itself should be biologically active. Thus the antibody should fold efficiently and correctly and be presented for antigen binding. However, solving the problem for antibody molecules and fragments would also provide a general method for the screening of many receptor molecules."

181. The invention is then introduced (at page 6 lines 9-22) as follows:

> "Surprisingly, the applicants have been able to construct a bacteriophage that expresses and presents on its surface large binding molecules (eg large biologically functional antibody molecules) and which remains intact and infectious. The applicants have called the structure which comprises a virus particle and a binding molecule presented at the viral surface a 'package'. Where the binding molecule is an antibody (or a fragment or derivative of an antibody), the applicants call the package a phage antibody. However, except where the context demands otherwise, where the term phage antibody is used generally it should also be interpreted as referring to any package comprising a virus particle and a binding molecule presented at the viral surface."

182. The specification then says that phage antibodies are likely to find a range of applications in screening antibody V-genes encoding antigen binding activities. It goes on to say that they may also allow the construction of entirely synthetic antibodies. It continues (at page 6 line 35 – page 7 line 3):

> "For example, V-gene repertoires could be made in vitro by combining unrearranged V genes, with D and J segments. Libraries of pAbs could then be selected by binding to antigen, hypermutated in the antigen-binding loops in vitro and subjected to further rounds of selection and mutagenesis."

183. There follows a discussion of the application of the technology in areas which are not of direct concern in these proceedings, including the identification of ligand receptors, targeted gene transfer and applications relating to enzymes. In this context reference is made (at page 9 line 34) to "design and selection of mutant enzymes".

184. There is then what amounts to a series of consistory clauses. These begin with the methods of the invention (at page 10 line 9 – page 11 line 30):

> "The present invention provides a method for producing a package which method comprises the steps of:
>
> a) inserting a nucleotide sequence encoding the binding molecule within a viral genome;
>
> b) culturing the virus containing said nucleotide sequence, so that said binding molecule is expressed by the virus presented at its surface.
>
> The present invention also provides a method for producing a binding molecule specific for a particular epitope which comprises producing a package as described above and the additional step of screening for said binding molecule by binding of said molecule to said epitope. The method may comprise one or more of the additional steps of: i) separating the package from the epitope; ii) recovering said package; and

> iii) using the inserted nucleotide sequence in a recombinant system to produce the binding molecule separate from the virus. The screening step may isolate the nucleotide sequence encoding the binding molecule of desired specificity, by virtue of said binding molecule being expressed in association with the surface of the virus.
>
> In the above methods, the binding molecule may be an antibody, or a fragment or derivative of an antibody. Alternatively, the binding molecule may be an enzyme or receptor and fragments/ derivatives of any such enzymes or receptors.
>
> In the above methods, the virus may be a filamentous F-specific bacteriophage. The filamentous F-specific bacteriophage may be fd. In particular, it may be a tetracycline resistant version of fd known as fd tet. The nucleotide sequence may be inserted within the gene III region of fd. The sequence may be inserted after the signal sequence of gene III, preferably after amino acid+1 of the mature protein. The site for insertion may be flanked by short sequences corresponding to sequences which occur at each end of the DNA to be inserted. …
>
> …
>
> In the above methods the nucleotide sequences inserted within the viral genome may be derived from eg mammalian spleen cells or peripheral blood lymphocytes. The mammal may be immunised or non-immunised. Alternatively, the nucleotide sequence may be derived by the in vitro mutagenesis of an existing antibody coding sequence. The phage particle presenting said binding molecule may remain intact and infectious."

185. The specification then turns to the products of the invention, and says (at page 11 line 31 - page 12 line 10):

> "As previously mentioned, the present invention also provides novel screening systems and assay formats. In these systems and formats the gene sequence encoding the binding molecule (eg the antibody) of desired specificity is separated from the general population having a range of specificities by the fact of its binding to a specific target (eg the antigen or epitope).
>
> Thus, the present invention provides a method of screening a population of phage antibodies (where the binding molecule is an antibody) for a phage antibody with a desired specificity, which comprises contacting said population of phage antibodies with a desired epitope and separating phage antibody which binds to said epitope, from said epitope. The means for separating any binding

> phage antibodies may be varied in order to obtain binding phage antibodies with different binding affinities for said epitope."

186. At page 12 lines 27-31 the specification says that the applicants have chosen the filamentous F-specific bacteriophages to provide a vehicle for the expression of antibodies, fragments and derivatives on their surface and facilitate subsequent screening and manipulation. After briefly describing F-specific phages, the specification goes on (at page 13 lines 11-27):

> "Although these phages do not kill their host during normal replication, disruption of some of their genes can lead to cell death (Kornberg, A., 1980 supra.) This places some restraint on their use. The applicants have recognized that gene III of phage fd is an attractive possibility for the insertion of biologically active foreign sequences. The protein itself is only a minor component of the phage coat and disruption of the gene does not lead to cell death (Smith, G. 1988, Virology 167: 156-165). Furthermore, it is possible to insert some foreign sequences (with no biological function) into various positions within this gene (Smith, G., 1985 Science 228: 1315-1317., Parmley, S.F. and Smith, G.P Gene: 73 (1988) p. 305-318., and de la Cruz, V.F., et al., 1988, J. Biol. Chem., 263: 4318-4322). In these cases, although the infectivity of the virion was disrupted, the inserted sequences could be detected on the phage surface."

187. Having described the different domains of the gene III protein, the specification acknowledges that Professor Smith had inserted short sequences derived from protein molecules in two places in the gene III protein, namely an inter-domain region and between amino acids 2 and 3 at the N-terminus. It says that the latter sites were "more successful in maintaining the structural integrity of the gene III protein and displaying the peptides on the surface of the phage" (page 14 lines 5-7).

188. The specification then says that it is difficult to retain the biological function of a molecule that is expressed in a different context to its natural state. It goes on to say that inserting biologically active antibody fragments into the gene III region of fd to create a large fusion protein makes onerous demands on the functionality of the fusion. These are described (at page 15 lines 2-6) as follows:

> "The insertion is large, 100-200 amino acids; the antibody derived domain must fold efficiently and correctly to retain antigen-binding; and most of the functions of gene III must be retained."

189. The specification states that the applicants' approach was designed to minimise the risk of disrupting these functions. The initial vector used was fd-tet, and the applicants chose to insert their sequences after amino acid 1 of the gene III protein (i.e. one amino acid further towards the N-terminus of gene III than in Professor Smith's work).

190. The following statement is then made (at page 15 lines 24-31):

> "Surprisingly, by manipulating gene III of bacteriophage fd, the present applicants have been able to construct a bacteriophage that expresses on its surface large biologically functional antibody molecules and which remains intact and infectious. Furthermore, the phages bearing antibodies of the correct specificity, can be selected from a background where the majority of phages do no [sic] show this specificity."

191. Later the specification says (at page 17 lines 5-19) that conventional screening techniques can be used to identify the phage antibody of interest. The example given is fixing an antigen to a solid surface and passing the phage antibody over the top, followed by washing (i.e. panning). It is pointed out that the bound phage antibody can be amplified using PCR. The benefits of this system are explained (at page 17 lines 20-30) as follows:

> "The efficiency of this screening procedure for phage antibodies and the ability to create very large libraries means that the immunisation techniques developed to increase the proportion of screened cells producing antibodies of interest will not be an absolute requirement. The technique allows the rapid isolation of antigen-binding specificities, including those that would be difficult or even unobtainable by conventional techniques, for example, catalytic or anti-idiotypic antibodies. Removal of the animal altogether is now possible once a complete library of the immune repertoire has been constructed."

192. The specification goes on (at page 17 line 31 – page 20 line 12) to describe a number of applications of the invention, including affinity maturation screening, signal amplification, physical detection and diagnostic assays. At the beginning of the description of affinity maturation screening, it is said that (page 17 line 32 – page 18 line 10):

> "The applicants have also devised a series of novel screening techniques that are practicable only because of the unique properties of phage antibodies. The general outline of some screening procedures is illustrated in figure 2.
>
> The population/library of phage antibodies to be screened could be generated from immunised or other animals; or be created in vitro by mutagenising pre-existing phage antibodies… This population can be screened in one or more of the formats described below with reference to figure 2, to derive those individual phage antibodies whose antigen binding properties are different from sample c."

Two methods of affinity maturation screening are then discussed, involving binding/elution and competition. In the context of the latter, reference is made to "a population of mutant phage antibody" (page 18 lines 22-23).

193. Specific embodiments of the invention are then described, beginning with a description of the 16 figures (at page 20 line 18 - page 22 line 19) and a short materials and methods section (at page 22 line 20 - page 23 line 18). These are followed by 15 examples.

Example 1

194. Example 1 is headed "Design of Insertion Point Linkers and Construction of Vectors". It describes the construction of the phage vector used in subsequent experiments. This involved modification of the fd-tet vector to remove its existing restriction sites and introduce two new ones which could be used to insert the DNA encoding V_H antibody fragments. First, the existing BstEII restriction sites were removed to produce a vector called FDTδBst. Then PstI and BstEII sites were introduced into FDTδBst to produce a vector called FDTPs/Bs to facilitate "cloning of antibody fragments downstream of the gene III signal peptide" (in fact, after the first amino acid of the gene III protein). In addition, PstI and XhoI sites were introduced into FDTPs/Bs to produce a second vector called FDTPs/Xh "to facilitate cloning of single chain Fv fragments".

195. At page 25 lines 4-14 the specification states:

> "Clearly, alternative constructions will be apparent to those skilled in the art. For example, M13 and/or its host bacteria could be modified such that its gene III could be disrupted without the onset of excessive cell death; the modified fd gene III, or other modified protein, could be incorporated into a plasmid containing a single stranded phage replication origin, such as pUC119, superinfection with modified phage such as K07 would then result in the encapsulation of the phage antibody genome in a coat partially derived from the helper phage and partly from the phage antibody gene III construct."

196. The meaning of this paragraph is heavily disputed, but at this stage it may be noted that it is common ground that (i) "a plasmid containing a single stranded phage replication origin" is a phagemid, (ii) pUC119 is a well-known example of a phagemid and (iii) "K07" (i.e. M13K07) is a well-known example of a helper phage.

Example 2

197. Example 2 is headed "Insertion of Immunoglobulin Fv Domain into Phage Antibody". Example 2 describes the display of a scFv antibody fragment on phage. The particular scFv antibody fragment used in the example is a single chain Fv version of antibody D1.3 to hen egg lysozyme which was already in the hands of the applicants. It was inserted into the nucleic acid of the FDTPs/Xh vector created in Example 1. This gave rise to a construct called FDTSCFVD1.3 encoding the gene III signal peptide and first amino acid fused to the complete scFv followed by the gene III protein from amino acid 2. The example reports that expression of a fusion protein of the expected size was demonstrated.

Example 3

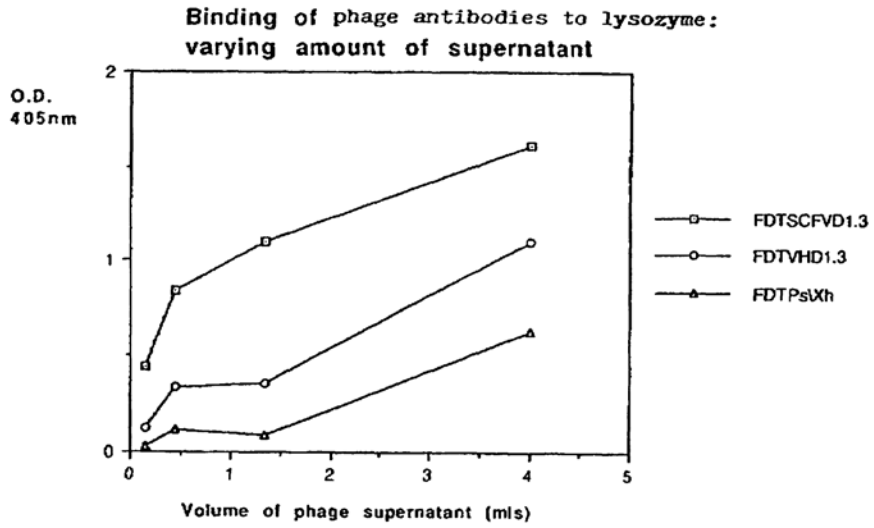
198. Example 3 is headed "Insertion of Immunoglobulin V_H Domain into Phage Antibody". It describes the display of a D1.3 V_H antibody fragment on phage. The method is the same as in Example 2 except that the FDTPs/Bs vector created in Example 1 is used. The construct is called FDTVHD1.3. Again it is reported that expression of a fusion protein of the expected size was demonstrated.

Example 4

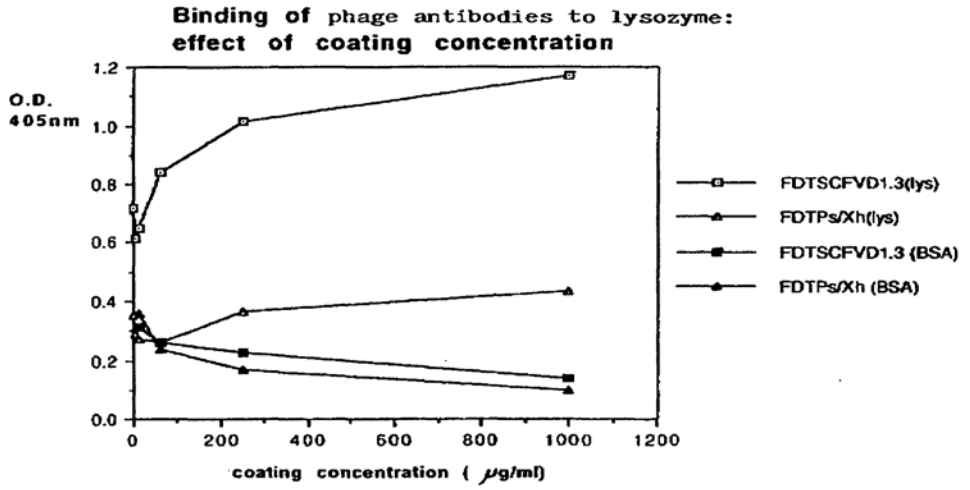
199. Example 4 is headed "Analysis of Binding Specificity of Phage Antibodies". It involves various assays, which are aimed at demonstrating that the D1.3 scFv and V_H antibody fragments that had been displayed on phage in Examples 2 and 3 retained their specificity for lysozyme.

200. ELISA was used to detect the presence of bound phage. The ELISA plate was coated with lysozyme, and the relevant phage antibody particles added. The intention of this was that, if the displayed antibody fragments retained their specificity, they would stick to the bound antigen. The plates were then washed (to remove unbound phage) and a sheep anti-phage antibody added (which should stick if the phage has stuck to the antigen). This is followed with a biotinylated anti-sheep antibody (which should stick to the sheep anti-phage antibody which in turn is bound to the antigen on the plate). Finally, a streptavidin/horseradish peroxidase complex is added (which should bind to biotinylated antibody through the streptavidin). After washing away unbound enzyme, the amount of bound phage is measured by looking at the increase in optical density of the plate upon incubation with a chromogenic substrate of peroxidase, which is proportional to the activity of the enzyme.

201. The specificity of the displayed fragments was tested in two ways. First, the applicants sought to vary the amount of phage antibody applied to the antigen-coated plates. The results of these tests are shown in Figure 6, which I reproduce below:



202. Secondly, the applicants varied the concentrations of lysozyme on the plate while keeping the concentration of phage antibody culture constant. The results of this are shown in Figure 7, which I reproduce below:



203. In this figure, FDTSCFVD1.3(lys) shows the binding of the phage which putatively expressed scFv to lysozyme, and FDTPs/Xh(lys) is blank phage. Two further negative controls were also included, which had bovine serum albumin (BSA) on the plates at varying concentrations rather than lysozyme. These plates were panned with both blank phage (FDTPs/Xh(BSA)) and the phage expressing the scFv for lysozyme (FDTSCFVD1.3(BSA)). The specification states that the results demonstrate that the binding detected is specific for lysozyme as the antigen.

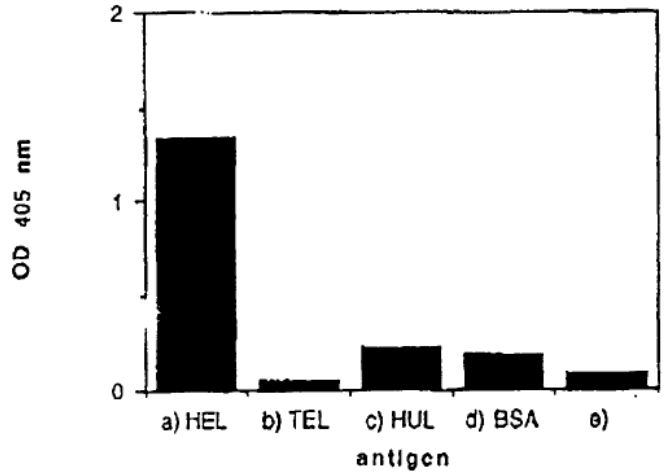
Example 5

204. Example 5 is headed "Construction of fdCat 2". It describes the creation of a vector called fdCAT2 from the FDTPs/Xh vector from Example 1 by *in vitro* mutagenesis. fdCAT2 has different restriction sites.

Example 6

205. Example 6 is headed "Specific Binding of Phage-antibody (pAb) to Antigen". It describes ELISA experiments similar to Example 4. Like Example 4, it uses the phage-scFv fusion particles generated from the FDTSCFVD1.3 construct. In this example, however, the binding of the displayed scFv fragments to hen egg-white lysozyme (HEL) is compared with their binding to turkey egg-white lysozyme (TEL). In addition, human lysozyme (HUL) and BSA are included as controls. The results are shown in Figure 9, which I reproduce below:

Figure 9 Binding of pAb(D1.3) to lysozymes



206. The specification states (at page 30 line 31 – page 31 line 2):

> "The results … show that the antibody bearing-phage had the same pattern of reactivity as the original D1.3 antibody … , and bound to hen egg-white lysozyme, but not to turkey egg-white lysozyme, human lysozyme or bovine serum albumin. The specificity of the phage is particularly illustrated by the lack of binding to the turkey egg-white lysozyme that differs from hen egg-white lysozyme by only 7 amino acids."

Example 7

207. Example 7 is headed "Expression of Fab D1.3 in fdCAT2". It describes the construction of a phage antibody that expresses a Fab fragment on its surface and shows that it binds specifically to its antigen. The genes for the heavy chain of the fragment are inserted into the phage antibody nucleic acid. The genes for the light chain are not inserted in the phage antibody, but are co-expressed in the bacterial cell. Thus the V_H and C_H1 regions of anti-lysozyme antibody D1.3 were cloned in fdCAT2 (from Example 5), and the corresponding light chain cloned into a separate plasmid pUC19. The heavy chain is therefore expressed as a gene III fusion. The light chain is expressed independently, but associates with the heavy chain gene III fusion in the periplasm.

208. An alternative possibility is mentioned at page 31 lines 21-27:

> "It is possible to express the light chain from within the pAb genome by, for example, cloning an expression cassette into a suitable place in the phage genome. Such a suitable place would be the intergenic region which houses the multicloning sites engineered into derivative [sic] of the related phage M13 (see, for example, Yanisch-Perron, C. et al., Gene 33, p103-119, (1985))."

209. The applicants tested whether their displayed Fab fragment would bind to lysozyme by the same techniques as in Example 6. The specification states (at page 32 line 37 – page 33 line 7):

> "The results (Figure 11) showed that when the heavy and light chain Fab derivatives from the original antibody D1.3 were present, the pAb bound to lysozyme. pAb expressing the fd VHCH1 fragment did not bind to lysozyme unless grown in cells also expressing the light chain. This shows that a functional Fab fragment was produced by an association of the free light chain with the VHCHl fragment fused to gene III and expressed on the surface of the pAb."

Example 8

210. Example 8 is headed "Isolation of Specific, Desired Phage from a Mixture of Vector Phage". In this example the applicants mixed FDTSCFVD1.3 phage-scFv fusion particles produced in Example 2 with normal (wild-type) fd phage in ratio of 1:4 million. The mixture was then passed over a column coated in lysozyme. The phage which bound to the column were found to have been enriched a thousand fold with the phage-scFv particles. By growing the enriched phage and passing it down the column again, enrichment of up to a million fold was achieved.

Example 9

211. Example 9 is headed "Construction of pAb Expressing Anti-hapten Activity". It involves the production of alternative scFv-fusion phage. In this case, the starting raw material is an anti-oxazolone antibody, NQ11. From a plasmid containing the V_H and V_L genes of NQ11, an scFv version of the antibody was first produced. This was then cloned into the FDTPs/Xh vector from Example 1. To assess the binding of the resulting construct pAb NQ11, the method of Example 6 was once again adopted. The results (shown in Figure 14) appear to show the binding of pAb NQ11 to its target antigen.

Example 10

212. Example 10 is headed "Enrichment of pAb D1.3 from Mixtures of Other pAb by Affinity Purification". It involves a similar separation experiment to that in Example 8. In Example 10, however, a mixture of phage-scFv specific for lysozyme (from Example 2) and phage-scFv specific for oxazolone (from Example 9) is used. The results are set out in Table 2. Enrichment is shown of the order of a thousand-fold after one round of purification from a $1:2.5 \times 10^5$ mixture of anti-lysozyme to anti-oxazolone scFv and of the order of a million-fold after two rounds of purification from a $1:2.5 \times 10^6$ mixture. It should be noted that this experiment involves selection of one binding specificity from a population of two. Furthermore, the experiment did not work if the frequency of the clone of interest dropped below $1:10^5$ (one round) or $1:10^6$ (two rounds).

Examples 11-14

213. These examples do not appear to be relevant for present purposes. They do not appear in either of the Patents.

Example 15

214. Example 15 (which is renumbered as example 11 in the Patents) is headed "Insertion of Binding Molecules into Alternative Sites in the Phage". As this suggests, it involves alternative insertion sites within gene III to those used in the previous examples. One site tried was a natural BamHI site of gene III, but it was found that this was not suitable for expression of functional scFv since no binding activity was detected.

Matters not disclosed in PD3

215. It is convenient at this point to mention certain matters that are not disclosed in PD3. First, there is no example of the use of a phagemid. Indeed, the only reference in the document to use of a phagemid is in the disputed paragraph at page 25 lines 4-14 (quoted in paragraph 195 above). Secondly, there is no example of the use of Fab where both the heavy and light chains are inserted into a phage (as opposed to co-expression). Thirdly, and as follows from the first two points, there is no example of the use of a phagemid incorporating the heavy and light chain genes of a Fab fragment. Fourthly, there is no example in which phage display has been used to select a binding molecule, such as an scFv, from a population of binding molecules having a range of binding specificities.

511

216. There are considerable differences between 511 and PD3. The differences mainly consist of additions to the text, but there are also some deletions and some amended passages. The specification has 535 numbered paragraphs. Including tables, but excluding the claims and the figures, it runs to 78 pages. Allowing for differences in typography, I estimate that it is roughly twice as long as PD3. In the following account, I shall focus on what is different in the specification of 511 compared to PD3, and in particular on the additions.

217. The first major addition, from [0017] at page 5 line 3 to [0024], consists of additional acknowledgements of prior art. This includes the following passage in [0017] at page 5 lines 4-15:

> "Bass et al., in December 1990 (after the earliest priority date for the 5 present application) describe deleting part of gene III of the filamentous bacteriophage M13 and inserting the coding sequence for human growth hormone (hGH) into the N-terminal site of the gene. The growth hormone displayed by M13 was shown to be functional. (Bass, S., et al. Proteins, Structure, Function and Genetics (1990) 8: 309-314). A functional copy of gene III was always present in addition, when this fusion was expressed. A Protein Engineering

> Corporation patent application W090/02809 proposes the insertion of the coding sequence for bovine pancreatic trypsin inhibitor (BPTI) into gene VIII of M13. However, the proposal was not shown to be operative. For example, there is no demonstration of the expression of BPTI sequences as fusions with protein VIII and display on the surface of M13. Furthermore this document teaches that when a fusion is made with gene Ill, it is necessary to use a second synthetic copy of gene Ill, so that some unaltered gene III protein will be present. The embodiments of the present application do not do this. In embodiments where phagemid is rescued with M13K07 gene III deletion phage, there is no unaltered gene III present."

218. The second major addition, at paragraphs [0028]-[0039], [0041] and [0043]-[0045], describes various aspects of the invention. This includes the following passage concerning gene III deletion helper phage:

> "[0038] Phagemids have been mentioned above. The applicants have realised and demonstrated that in many cases phagemids will be preferred to phage for cloning antibodies because it is easier to use them to generate more comprehensive libraries of the immune repertoire. This is because the phagemid DNA is approximately 100 times more efficient than bacteriophage DNA in transforming bacteria (see example 15). Also, the use of phagemids gives the ability to vary the number of gene III binding molecule fusion proteins displayed on the surface of the bacteriophage (see example 13). For example, in a system comprising a bacterial cell containing a phagemid encoding a gene III fusion protein and infected with a helper phage, induction of expression of the gene III fusion protein to different extents, will determine the number of gene III fusion proteins present in the space defined between the inner and outer bacterial membranes following superinfection. This will determine the ratio of gene III fusion protein to native gene III protein displayed by the assembled phage.
>
> [0039] Expressing a single fusion protein per virion may aid selection of antibody specificities on the basis of affinity by avoiding the 'avidity' effect where a phage expressing two copies of a low affinity antibody would have the same apparent affinity as a phage expressing one copy of a higher affinity antibody. In some cases however, it will be important to display all the gene III molecules derived by superinfection of cells containing phagemids to have fusions (e.g. for selecting low affinity binding molecules or improving sensitivity on ELlSA). One way to do this is to superinfect with a bacteriophage which contains a defective gene Ill. The applicants have therefore developed and used a phage which is deleted in gene Ill. This is completely novel."

I shall explain the technology being described here below when dealing with an issue of construction.

219. The third major addition, at [0051]-[0083], is of a series of definitions. These include the following:

"Specific Binding Pair

[0052] This describes a pair of molecules (each being a member of a specific binding pair) which are naturally derived or synthetically produced, One of the pair of molecules, has an area on its surface, or a cavity which specifically binds to, and is therefore defined as complementary with a particular spatial and polar organisation of the other molecule, so that the pair have the property of binding specifically to each other. Examples of types of specific binding pairs are antigen-antibody, biotin-avidin, hormone-hormone receptor, receptor-ligand, enzyme-substrate, IgG-protein A.

…

Library

[0078] A collection of nucleotide eg DNA, sequences within clones.

…

Derivative

[0083] This is a substance which derived from a polypeptide which is encoded by the DNA within a selected bacteriophage particle. The derivative polypeptide may differ from the encoded polypeptide by the addition, deletion, substitution or insertion of amino acids, or by the linkage of other molecules to the encoded polypeptide. These changes may be made at the nucleotide or protein level. For example the encoded polypeptide may be a Fab fragment which is then linked to an Fc tail from another source. Alternatively markers such as enzymes, flouresceins [sic] etc may be linked to eg Fab, scFv fragments."

220. The fourth major addition, at [0091]-[0107], again describes various aspects of the invention. This includes some passages adapted from PD3, including [0093] which has been adapted and expanded from the paragraph at page 11 lines 31-37 in PD3 quoted in paragraph 185 above:

> "In a method for producing a binding molecule as defined above, the gene sequence encoding the binding molecule of desired specificity is separated from a general population of filamentous bacteriophage particle having a range of specifies

> [sic], by the fact of its binding to a specific target (eg the antigen or epitope). Thus the filamentous bacteriophage particle formed by said expression may be selected or screened to provide an individual sbp member or a selected mixed population of said sbp members associated in their respective particles with nucleic acid encoding said sbp member or a polypeptide chain thereof. The particles may be selected by affinity with a member complementary to said sbp member."

"Sbp" stands for "specific binding pair".

221. Paragraph [0111] contains an addition to the discussion of Professor Smith's work contained in PD3 between the passages at page 13 lines 11-24 and page 13 line 25 – page 14 line 12 as follows:

> "Smith et al described the display of peptides on the outer surface of phage but they did not describe the display of protein domains. Peptides can adopt a range of structures which can be different when in free solution, than when bound to, for example, an antibody, or when forming part of a protein (Stanfield, R.1. et al., (1990) Science 248, p712-719). Proteins in general have a well defined tertiary structure and perform their biological function only when adopting this structure. For example, the structure of the antibody D1.3 has been solved in the free form and when bound to antigen (Bhat, T.N. et al., (1990) Nature 347, p483-485). The gross structure of the protein is identical in each instance with only minor variations around the binding site for the antigen. Other proteins have more substantial conformation changes on binding of ligand, for instance the enzymes hexokinase and pyruvate dehydrogenase during their catalytic cycle, but they still retain their overall pattern of folding. This structural integrity is not confined to whole proteins, but is exhibited by protein domains. This leads to the concept of a folded unit which is part of a protein, often a domain, which has a well defined primary, secondary and tertiary structure and which retains the same overall folding pattern whether binding to a binding partner or not. The only gene sequence that Smith et al., described that was of sufficient size to encode a domain a minimum of perhaps 50 amino acids) was a 335bp fragment of a β-galactosidase corresponding to nucleotides 861-1195 in the β-galactosidase gene sequence (Parmley, S. Smith, G.P. 1988 supra. This would encode 112 amino acids of a much larger 380 amino acid domain. Therefore, prior to the present application, no substantially complete domain or folded unit had been displayed on phage."

222. The fifth major addition, at [0133]-[0139], expands the description of affinity maturation.

223. The specific embodiments are described beginning at [0144]. A new paragraph at [0145] states:

> "In all embodiments of the invention filamentous bacteriophage particles containing a phagemid genome are employed. Display at the surface of particles containing a phage genome is not part of the invention and mention of this in this document, including the experimental examples, is for the purpose of illustration."

224. The sixth major addition, at [0160]-[0189], introduces Figures 16 to 43 which were not included in PD3.

225. The seventh major addition, at [0194]-[0230], consists of a so-called "index" (actually a short summary of each) of the examples.

226. The final major addition, at [0283]-[0534], is of Examples 12-38, none of which were included in PD3, followed by two paragraphs of "conclusions". Of the new examples, the most significant for present purposes are the following.

Example 13

227. Example 13 is headed "Construction of Phagemid Containing Gene III fused with the Coding Sequence for a Binding Molecule". This describes for the first time the creation of a pUC119 phagemid construct encoding an scFv fragment with specificity for HEL, referred to as pCAT-3 scFv D1.3.

Example 14

228. Example 14 is headed "Rescue of Anti-Lysozyme Antibody Specificity from pCAT-3 scFv D1.3 by M13KO7". This describes rescue of the phagemid construct created in Example 13 with M13K07 helper phage. It is shown that the phagemid particles are infective and present in the rescued phage population at a 100-fold excess over the helper phage. After this, ELISA is used to test for binding specificity for lysozyme. The results (in Figure 19) confirm that antibody specificity can be rescued efficiently.

229. The specification goes on:

> "[0323] It is considered a truism of bacterial genetics that when mutant and wild-type proteins are co-expressed in the same cell, the wild-type protein is used preferentially. This is analogous to the above situation wherein mutant (i. e. antibody fusion) and wild-type gene III proteins (from M13K07) are competing for assembly as part of the pUC119 phagemid particle. It is therefore envisaged that the majority of the resulting pUC 119 phage particles will have fewer gene III-antibody fusion molecules on their surface than is the case for purely phage system described for instance in example 2. Such phagemid antibodies are therefore likely to bind antigen with a lower avidity than fd phage antibodies with three or more copies of the antibody fusion on their surfaces (there is no wild-type

> gene III, in the system described, for instance, in example 2), and provide a route to production of phage particles with different numbers of the same binding molecule (and hence different acidities [sic] for the ligand/antigen) or multiple different binding specificities on their surface, by using helper phage such as M13K07 to rescue cells expressing two or more gene III-antibody fusions.
>
> [0324] It is also possible to derive helper phage that do not encode a functional gene III in their genomes (by for example deleting the gene III sequence or a portion of it or by incorporating an amber mutation within the gene). These defective phages will only grow on appropriate cells (for example that provide functional gene III in trans, or contain an amber supressor [sic] gene), but when used to rescue phage antibodies, will only incorporate the gene III antibody fusion encoded by the phagemid into the released phage particle."

Again, I will explain this below.

Example 15

230. Example 15 is headed "Transformation Efficiency of pCAT-3 and pCAT-3 scFv D1.3 phagemids". It shows that transformation of the phagemid vector is approximately 100 times more efficient than the parental fdCAT-2 vector despite the presence of an scFv fragment. The specification comments in [0326]:

> "This improvement in transformation efficiency is practically useful in the generation of phage antibodies libraries that have large repertoires of different binding specificities."

Example 16

231. Example 16 is headed "PCR Assembly of a Single Chain Fv library from an Immunised Mouse". This describes for the first time the construction of a library of different phage and antibody particles. The specification explains at [0327] that:

> "To demonstrate the utility of phage for the selection of antibodies from repertoires, the first requirement is to be able to prepare a diverse, representative library of the antibody repertoire of an animal and display this repertoire on the surface of bacteriophage fd."

To this end, mice were immunised with 2-phenyl-5-oxazolone (phOX), and an scFv library constructed from genes being expressed in spleen cells of immunised mice.

232. At the end of the example the specification states at [0330]:

> "Thus the ability to select antibody provided by the use of phage antibodies (as in example 17) is essential to readily

> isolate antibodies with antigen binding activity from randomly combined VH and VL domains. Very extensive screening would be required to isolate antigen binding fragments if the random combinatorial approach of Huse et al. 1989 (supra) were used."

Example 17

233. Example 17 is headed "Selection of Antibodies Specific for 2-phenyl-5-oxazolone from a Repertoire Derived from an Immunised Mouse". This is the first example to involve the selection of antibody fragments from a diverse library of different phage and antibody particles. The specification explains at [0331]:

> "The library prepared in example 16 was used to demonstrate that ability of the phage system to select antibodies on the basis of their antibody specificity."

234. Screening was carried out by displaying the scFv fragments on phage, passing the phage over an affinity column in contact with antigen, elution of the phage, amplification of the eluted phage and then use of the ELISA assay to determine binding. The specification concludes in [0340] that the example shows that "antigen specificities can be isolated from libraries derived from immunised mice".

Example 19

235. Example 19 is headed "Selection of Antibodies Displayed on Bacteriophage with Different Affinities for 2-phenyl-5-oxazolone using Affinity Chromatography". In this example phage particles (obtained using the phagemid/helper phage system) expressing either high or a low-affinity phOX-binders are mixed at a ratio of 20 low binders to 1 high binder, and it is shown that phOX-Sepharose affinity chromatography permits the preferential selection of the high affinity antibodies. The specification comments in [0347]:

> "Therefore phage antibodies can be selected on the basis of the antigen affinity displayed."

Example 21

236. Example 21 is headed "Display of Single Chain Fv and Fab Fragments Derived from the Anti-Oxazolone Antibody NQ10.12.5 on Bacteriophage fd using pHEN1 and fdCAT2". This is the first worked example involving the expression of Fab antibody fragments on the surface of bacteriophage particles using a phagemid vector. Unlike the only previous example involving the expression of a Fab fragment (Example 7) from two vectors, in this example both the heavy and light chains of the Fab are expressed from the same vector.

Example 27

237. Example 27 is headed "Construction of a Gene III Deficient Helper Phage". The description of this example begins with the following explanation:

> "[0386] To fully realise the potential of the phagemid cloning system, a helper phage lacking gene III is desirable. Rescue of gene III fusions with such a helper phage would result in all the progeny phagemids having a gene III fusion on their capsid, since there would be no competition with the wild type molecule.
>
> [0387] Control over the number of fusion molecules contained on each phage will provide particularly useful. For example, a gene III deficient helper phage can be used to rescue low affinity antibodies from a naive repertoire, in which high avidity will be necessary to isolate those phage bearing the correct antibody specificity. The unmutated helper phage can then be used when higher affinity versions are constructed, thereby reducing the avidity component, and permitting selection purely on the basis of affinity. This will prove a surprisingly successful strategy for isolation and affinity maturation of antibodies from naive libraries."

238. The specification goes on to describe the construction of a gene III-deficient helper phage referred to as M13KO7 gIII Δ No 3. This phage is used in two subsequent examples.

Example 28

239. Example 28 is headed "Selection of bacteriophage expressing scFv fragments directed against lysozyme from mixtures according to affinity using a panning procedure". The example is explained at [0396] as follows:

> "For isolation of an antibody with a desired high affinity, it is necessary to be able to select an antibody with only a few fold higher affinity than the remainder of the population. This will be particularly important when an antibody with insufficient affinity has been isolated, for example, from a repertoire derived from an immunised animal, and random mutagenesis is used to prepare derivatives with potentially increased affinity. In this example, mixtures of phage expressing antibodies of different affinities directed against hen egg lysozyme were subjected to a panning procedure. It is demonstrated that phage antibodies give the ability to select for an antibody with a K_d of 2nM against one with a K_d of 13nM."

Example 29

240. Example 29 is headed "Generation and Selection of Mutants of an Anti-4-hydroxy-3-nitrophenylacetic acid (NP) Antibody expressed on Phage using Mutator strains". This example is introduced as follows at [0424]:

> "It will sometimes be desirable to increase the diversity of a pool of genes cloned in phage, for example a pool of antibody

> genes, or to produce a large number of variants of a single cloned gene. There are many suitable in vitro mutagenesis methods. However, an attractive method, particularly for making a more diverse population of a library of antibody gene, is to use mutator strains. This has the advantage of generating very large numbers of mutants, essentially limited only be the number of phage that can be handled. The phage display system allows full advantage to be takeoff this number to isolate improved or altered clones."

241. Having described the use of a number of mutator strains, the specification concludes at [0438]:

> "Hence, the use of mutator strains generates a diverse range of mutants in phage antibodies when they are used as hosts for clones for gene III fusions. In this case some of the clones exhibit higher ELISA signals probably due to increased stability to proteolytic attack. The mutator strains can therefore be used to introduce into a clone or population of clones. This diversity should generate clones with desirable characteristics such as higher affinity or specificity. Such clones may then be selected following display of the proteins on phage."

Example 35

242. Example 35 is headed "Alteration of fine specificity of scFv D1.3 displayed on phage by mutagenesis and selection on immobilised turkey lysozyme". This is another example involving HEL and TEL (as in Example 6). As the specification explains, the D1.3 antibody binds to them with different affinities, higher in the case of HEL than in the case of TEL. As the reader will recall from Example 6, the difference in affinity means that D1.3 is specific to HEL but not TEL. Mutagenesis of particular candidate positions of the scFv D1.3 sequence inserted in the pCAT-3 scFv D1.3 phagemid vector was performed using randomised oligonucleotides. Previous studies had defined these positions as playing a major role in the differences of affinity of the D1.3 antibody for HEL and TEL. Three phage libraries differing by the number of mutated residues and/or their positions were prepared, mixed, and affinity-purified using TEL-Sepharose. Second and third rounds of adsorption/elution were performed and colonies derived from the last round tested by ELlSA for TEL and HEL binders. Clones exhibiting the same binding to HEL, but an increased binding to TEL, as well as clones exhibiting a lower binding to HEL, but a higher binding to TEL, as compared to the original clone, were recovered.

The claims

243. Claim 5 of 511 is as follows (broken down into integers):

> "[1] A method for producing a filamentous bacteriophage particle displaying at its surface a binding molecule specific for a particular target epitope or antigen, which method comprises the steps of:

[2] producing a population of filamentous bacteriophage particles displaying at their surface a population of binding molecules having a range of binding specificities,

[3] wherein the binding molecules are Fab antibody molecules able to bind target epitope or antigen,

[4] and wherein each filamentous bacteriophage particle contains a phagemid genome comprising nucleic acid with a nucleotide sequence encoding the binding molecule expressed from the nucleic acid and displayed by the particle at its surface;

[5] selecting for a filamentous bacteriophage particle displaying a binding molecule with a desired specificity by contacting the population of filamentous bacteriophage particles with a target epitope or antigen

[6] so that individual binding molecules displayed on filamentous bacteriophage particles with the desired specificity bind to said target epitope or antigen."

244. Claim 6 is as follows:

> "A method according to claim 5 additionally comprising separating bound filamentous bacteriophage particles from the target epitope or antigen"

245. Claim 7 is as follows:

> "A method according to claim 6 additionally comprising recovering separated filamentous bacteriophage particles displaying a binding molecule with the desired specificity"

246. Claim 8 is as follows (again broken down into integers):

"[1] A method for producing a binding molecule specific for a particular target epitope or antigen, which method comprises:

[2] performing the method according to claim 7;

[3] isolating from separated filamentous bacteriophage particles recovered according to the method of claim 7 nucleic acid encoding the binding molecule;

[4] inserting nucleic acid encoding the binding molecule, or a fragment or derivative thereof with binding specificity for the target epitope or antigen, in a recombinant system; and

[5] producing the binding molecule, or fragment or derivative thereof with binding specificity for the target epitope or antigen, in the recombinant system separate from filamentous

bacteriophage particles."

777

247. The specification of 777 is similar to that of 511. Although there are certain differences, it is not necessary to identify them.

248. Claim 1 is as follows (again broken down into integers):

"[1] A method for producing a molecule with binding specificity for a particular target, which method comprises:

[2] producing a population of filamentous bacteriophage particles displaying at their surface a population of binding molecules having a range of binding properties,

[3] wherein the binding molecules comprise antibody antigen binding domains for complementary specific binding pair members,

[4] wherein the binding molecules are displayed at the surface of the filamentous bacteriophage particles by fusion with a gene III protein of the filamentous bacteriophage particles,

[5] and wherein each filamentous bacteriophage particle contains nucleic acid encoding the binding molecule expressed from the nucleic acid and displayed by the particle at its surface;

[6] selecting for a filamentous bacteriophage particle displaying a binding molecule with a desired binding property by contacting the population of filamentous bacteriophage particles with a particular target

[7] so that individual binding molecules displayed on filamentous bacteriophage particles with the desired binding property bind to said target;

[8] separating bound filamentous bacteriophage particles from the target;

[9] recovering separated filamentous bacteriophage particles displaying a binding molecule with the desired binding property;

[10] isolating nucleic acid encoding the binding molecule from separated filamentous bacteriophage particles;

[11] inserting nucleic acid encoding the binding molecule, or a fragment or derivative thereof with binding specificity for the target, in a recombinant system; and

> [12] producing in the recombinant system separate from filamentous bacteriophage particles a molecule with binding specificity for the target,
>
> [13] wherein the molecule is said binding molecule or a fragment or derivative thereof with binding specificity for the target."

Construction: the law

249. In *Virgin Atlantic Airways Ltd v Premium Aircraft Interiors UK Ltd* [2009] EWCA Civ 1062, [2010] RPC 8 at [5] the Court of Appeal summarised the general principles applicable to the construction of patent claims as follows:

> "One might have thought there was nothing more to say on this topic after *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2005] RPC 9. The judge accurately set out the position, save that he used the old language of Art.69 EPC rather than that of the EPC 2000, a Convention now in force. The new language omits 'the terms of' from Art.69. No one suggested the amendment changes the meaning. We set out what the judge said, but using the language of the EPC 2000:
>
> [182] The task for the court is to determine what the person skilled in the art would have understood the patentee to have been using the language of the claim to mean. The principles were summarised by Jacob LJ in *Mayne Pharma Pty Ltd v Pharmacia Italia SpA* [2005] EWCA Civ 137 and refined by Pumfrey J in *Halliburton Energy Services Inc v Smith International (North Sea) Ltd* [2005] EWHC 1623 (Pat) following their general approval by the House of Lords in *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2005] RPC 9. An abbreviated version of them is as follows:
>
> (i) The first overarching principle is that contained in Article 69 of the European Patent Convention.
>
> (ii) Article 69 says that the extent of protection is determined by the claims. It goes on to say that the description and drawings shall be used to interpret the claims. In short the claims are to be construed in context.
>
> (iii) It follows that the claims are to be construed purposively - the inventor's purpose being ascertained from the description and drawings.
>
> (iv) It further follows that the claims must not be construed as if they stood alone - the drawings

and description only being used to resolve any ambiguity. Purpose is vital to the construction of claims.

(v) When ascertaining the inventor's purpose, it must be remembered that he may have several purposes depending on the level of generality of his invention. Typically, for instance, an inventor may have one, generally more than one, specific embodiment as well as a generalised concept. But there is no presumption that the patentee necessarily intended the widest possible meaning consistent with his purpose be given to the words that he used: purpose and meaning are different.

(vi) Thus purpose is not the be-all and end-all. One is still at the end of the day concerned with the meaning of the language used. Hence the other extreme of the Protocol - a mere guideline - is also ruled out by Article 69 itself. It is the terms of the claims which delineate the patentee's territory.

(vii) It follows that if the patentee has included what is obviously a deliberate limitation in his claims, it must have a meaning. One cannot disregard obviously intentional elements.

(viii) It also follows that where a patentee has used a word or phrase which, acontextually, might have a particular meaning (narrow or wide) it does not necessarily have that meaning in context.

(ix) It further follows that there is no general 'doctrine of equivalents.'

(x) On the other hand purposive construction can lead to the conclusion that a technically trivial or minor difference between an element of a claim and the corresponding element of the alleged infringement nonetheless falls within the meaning of the element when read purposively. This is not because there is a doctrine of equivalents: it is because that is the fair way to read the claim in context.

(xi) Finally purposive construction leads one to eschew the kind of meticulous verbal analysis

> which lawyers are too often tempted by their training to indulge."

250. The Court of Appeal went on at [6]-[22] to hold that the skilled reader is to be taken to know the purpose of (i) including reference numerals in patent claims, (ii) dividing claims into pre-characterising and characterising portions and (iii) filing of divisional applications, and to bring that knowledge to bear when he considers the scope of the claim.

Construction of claim 5 of 511

251. There are two issues of construction of claim 5 of 511. Before turning to the issues, two points which are common ground should be noted. The first is that the claim is limited to use of phagemids (see integer [4] and [0145] of the specification). The second is that the claim covers the case where the range of binding specificities from which a desired specificity is selected consists of two binding specificities.

"A range of binding specificities"

252. Integer [2] of claim 5 of 511 requires that the first step of the method should consist of "producing a population of filamentous bacteriophage particles displaying at their surface a population of binding molecules having a range of binding specificities". The issue is as to the meaning of the words "a range of binding specificities". Novartis contends that the skilled reader would understand the words "a range of binding specificities" to mean a range of specificities to different antigens, but not to cover a range of affinities for a single antigen. By contrast, MedImmune contends that the skilled reader would understand the words to encompass a range of affinities to a single antigen. It should be noted that this issue does not arise in relation to claim 1 of 777, since that contains the words "a range of binding properties", and it is common ground that "a range of binding properties" includes a range of affinities to a single antigen.

253. In my judgment Novartis' construction is the correct one for the following reasons. First, "specificity" is a term of art with a clear meaning in this field as I have explained above. So too is "affinity". The skilled team would approach the Patents with those meanings firmly established in their minds as part of their common general knowledge. The skilled team would note that the specification of 511 uses the words "specificity" and "affinity" a large number of times and that on each occasion the words appear to be used in accordance with their conventional meanings. Indeed, the very first use of the word "specificity" in paragraph [0002] of 511 refers to the "high specificity to a given antigen" of monoclonal antibodies.

254. Secondly, the skilled team would be well aware that "specificity" and "affinity" are different properties of an antibody. Counsel for MedImmune pointed out that the two properties are closely related to each other. That is true, but nevertheless they are conceptually and practically distinct. The skilled team would note that the specification is clearly intending to distinguish between these two properties when it refers sometimes to "specificity" and sometimes to "affinity". In these circumstances the skilled team would consider that the Patentees' choice of the word "specificities" in claim 5 was deliberate and intended to reflect this distinction.

255. Thirdly, the skilled team would note that the specification twice refers to "different specificities" when describing the problems with the prior art which the invention aims to address. The first time is in paragraph [0009] (corresponding to the passage at page 3 lines 3-19 of PD3 quoted in paragraph 176 above). This paragraph is clearly referring to the problem of isolating a "desired specificity" from a repertoire of "different specificities". The second time is in the last sentence of paragraph [0013] (corresponding to the passage at page 4 lines 29-30 of the PD3, which is the last sentence quoted in paragraph 177 above). This clearly refers to the problem of screening "many different specificities". The same point is repeated in paragraph [0014]. There is nothing in these passages of the specification to suggest that the Patentees are using the words "different specificities" as meaning anything other than specificities to different antigens. Again, this would confirm the skilled team in their understanding as to the reason for the use of the word "specificities" in the claim.

256. Fourthly, the skilled team would note that the specification says in paragraph [0025] that, if the problem of inserting a protein into a phage in such a way that the protein retains its biological activity can be solved for antibody molecules and fragments, it should provide a general method for "any biomolecule which is a member of a specific binding pair". This is defined in [0052] as a pair that "have the property of binding specifically to each other". Thus in generalising beyond antibodies, the Patentees use the same language and the same concept.

257. Fifthly, the skilled team would appreciate from reading the specification that a central aspect of the invention consists of selecting phage particles displaying an antibody fragment of desired specificity to a particular antigen from amongst particles displaying antibody fragments with specificities to a large number of antigens. This is reflected in a number of passages in the specification, among which I will mention four in particular. The first is in paragraph [0034], where, after describing two ways of creating a library having 10^{14} combinations of heavy and light chains, the specification states:

> "The 10^{14} combinations are then subjected to selection (see later for selection formats) as disclosed by the present invention. This selection will then produce a population of phages displaying a particular combination of H and L chains having the desired specificity."

The second is at paragraph [0039] quoted in paragraph 218 above. The third is at paragraph [0093] quoted in paragraph 220 above. This is particularly significant in my view, since it uses the same phraseology (allowing for an obvious typographical error) of "a range of specificities". The fourth is at paragraph [0140] corresponding to the passage at page 17 lines 20-30 of PD3 quoted in paragraph 193 above. Thus the skilled team would expect the claim to reflect this.

258. Sixthly, the structure and wording of claim 5 as a whole reinforces the understanding that the skilled team would derive from the body of the specification as to the way in which the Patentees are using the term "specificity". Thus it begins in integer [1] by saying that the method is for producing a phage displaying "a binding molecule specific for a particular target epitope or antigen". It then says the method consists of

two steps. The first involves producing a population of phage displaying "binding molecules having a range of binding specificities". The second involves selecting a phage displaying a "binding molecule with a desired specificity" (integer [5]) by contacting the population with a target epitope or antigen so that particles with "the desired specificity" bind to that target. The skilled team would clearly understand from this that the words "specificity" and "specificities" were being used consistently to refer to binding to particular epitopes or antigens.

259. Seventhly, the skilled team would appreciate that, if the Patentees were not intending to distinguish between specificity and affinity, then the claim could easily have referred to "a range of binding properties". "Binding properties" is an expression which is used in the specification, in particular at [0126]. As noted above, it is common ground that it would be understood as covering both specificity and affinity.

260. Finally, there is no difficulty with the word "range". One can have a range of binding specificities in the same way as one has a range of products in a shop. Although at earlier stages of the proceedings MedImmune suggested that the word "range" supported its construction, this suggestion had disappeared by the time of closing submissions.

261. MedImmune's argument to the contrary starts from the proposition that antibody phage display works purely on the basis of binding to the antigen that is being used to pan the library. Furthermore, when screening a library for binding to an antigen of interest, there is no interest in antibody specificities other than binding to that antigen of interest. This is true whether the library is created *in vitro* by mutagenesis or created from an animal (whether naive or immunised). As it was put in cross-examination and argument, phage bearing antibodies with other specificities than the one of interest "go down the sink". In my view this point has little bearing on the present issue. It does not alter the fact that, as explained above, a key aspect of the invention is the ability to select an antibody which is specific to the antigen of interest from amongst a potentially large number of antibodies which are specific to other antigens.

262. MedImmune's next point is that the specification refers in various places to the fact that the selection is based on affinity. In particular, at [0039] it speaks of aiding "selection of antibody specificities on the basis of affinity". In my view this does not assist MedImmune. It simply reflects the relationship between specificity and affinity as explained above.

263. MedImmune then says that "desired specificity" means that the binding molecule binds to the antigen of interest with a suitably high affinity. I accept this, but again I do not see that it assists MedImmune. It simply reflects the fact that, as the skilled team would be well aware, there is a threshold affinity before specificity to an antigen is recognised.

264. On this basis MedImmune argues as follows (to quote MedImmune's written closing submissions):

> "We submit that 'specificity' in a general sense means the binding or lack of binding (determined at a cut-off affinity

> chosen by the skilled addressee) to one or more antigens/epitopes in the universe of antigens/epitopes. The 'desired specificity' is the specificity towards the antigen of interest. A population has a range of binding specificities where there is any difference in specificity among members of the population."

In my view this submission, and in particular the last sentence, elides the distinction between specificity and affinity, and does not reflect the way in which the skilled team would understand the expression "a range of binding specificities" in context.

265. The strongest point made by counsel for MedImmune in support of MedImmune's construction was that the specification describes improving the affinity of antibodies by mutagenesis and selection of higher affinity antibodies, in particular in Examples 28, 29 and 35. In my judgment it does not follow that the skilled team would think that claim 5 of 511 covered mere selection of a high affinity binder from a range of affinities for the following reasons.

266. First, read in the context of specification as a whole, I consider that the skilled reader would understand these examples to be directed to improving the affinity of an antibody of desired specificity which has already been selected from a range of specificities. In the case of Example 28, this appears to be what is envisaged in [0396] (quoted in paragraph 239 above). Example 29 is concerned generally with increasing antibody diversity. While it talks about improving affinity as well as specificity, there is nothing to indicate that the Patentees contemplate selection merely on the basis of affinity as opposed to specificity. The best example from MedImmune's perspective is Example 35, since it involves changing the affinity of a particular binding molecule to a particular antigen, but again there is nothing to indicate that the Patentees contemplate selection merely on the basis of affinity as opposed to specificity.

267. Secondly, even if the skilled team reached the conclusion that these Examples, and in particular Example 35, did represent embodiments of the invention involving selection merely on the basis of affinity as opposed to specificity, the skilled team would appreciate that such embodiments might be the subject of divisional applications or patents. Counsel for MedImmune pointed out that at [0145] the specification draws attention to the fact that the claims are restricted to phagemids, but in my view this would not make the skilled team think this was the only respect in which the claims were narrower than the disclosure of the specification. For example, claim 5 is also limited to Fab antibody fragments (see integer [5]), but the use of other fragments is disclosed (notably scFv fragments), yet there is no statement equivalent to that in [0145].

268. Thirdly, the skilled team would conclude that the language of the claim read in context is not apt to cover selection merely on the basis of affinity as opposed to specificity for the reasons I have given above.

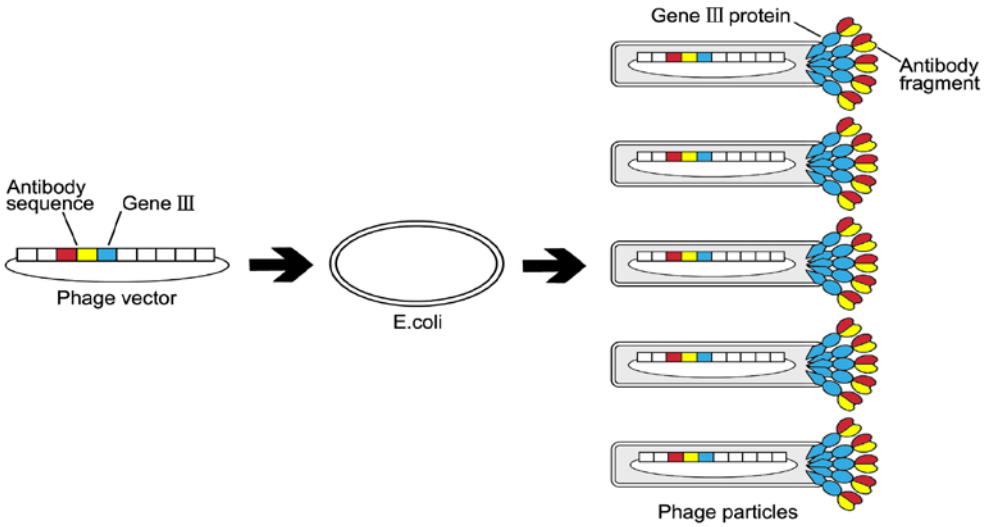
"A population of filamentous bacteriophage particles" and "each filamentous bacteriophage particle contains a phagemid genome"

269. As already discussed, integer [2] of claim 5 of 511 requires "a population of

filamentous bacteriophage particles displaying at their surface a population of binding molecules". Integer [4] requires that "each filamentous bacteriophage particle contains a phagemid genome comprising nucleic acid with a nucleotide sequence encoding the binding molecule expressed from the nucleic acid and displayed by the particle at its surface".

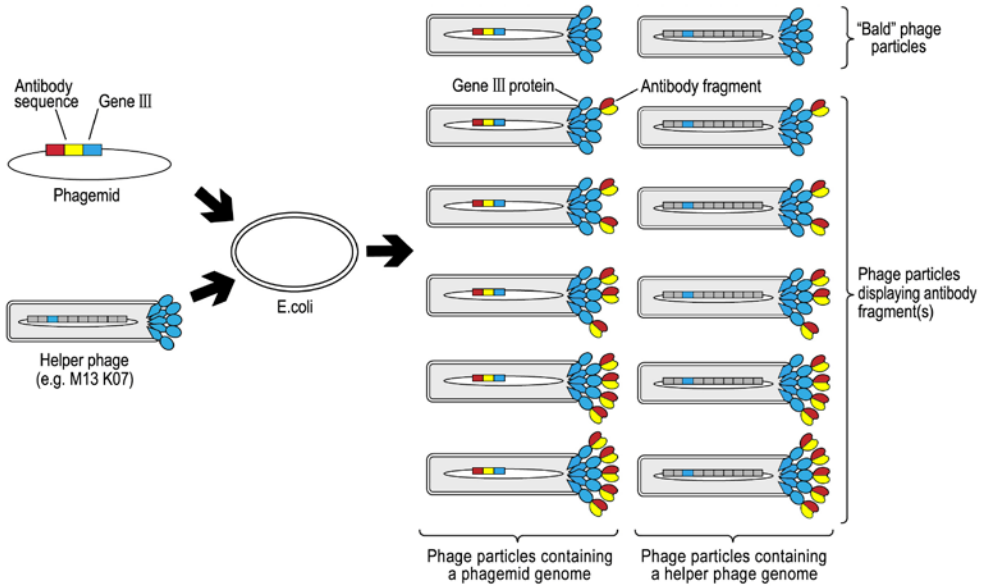
270. In order to explain the issues here, it is necessary first to explain a little more about the underlying technology. It is common ground that the Patents disclose the use both of phage systems and of two different types of phagemid system.

271. For present purposes the phage system can be illustrated by the following schematic diagram taken from Dr Teillaud's second report:



272. In this case, all the phage particles produced in the *E. coli* have a genome from the phage vector and display a fusion protein incorporating the yellow and red (heavy and light chain) antibody fragment sequences as well as pIII protein (blue). When the phage particles are screened by contact with an antigen, they all have the possibility to bind, because they all have antibody fragment displayed. Since this system does not involve a phagemid, it does not fall within claim 5 of 511 (but does fall within claim 1 of 777).

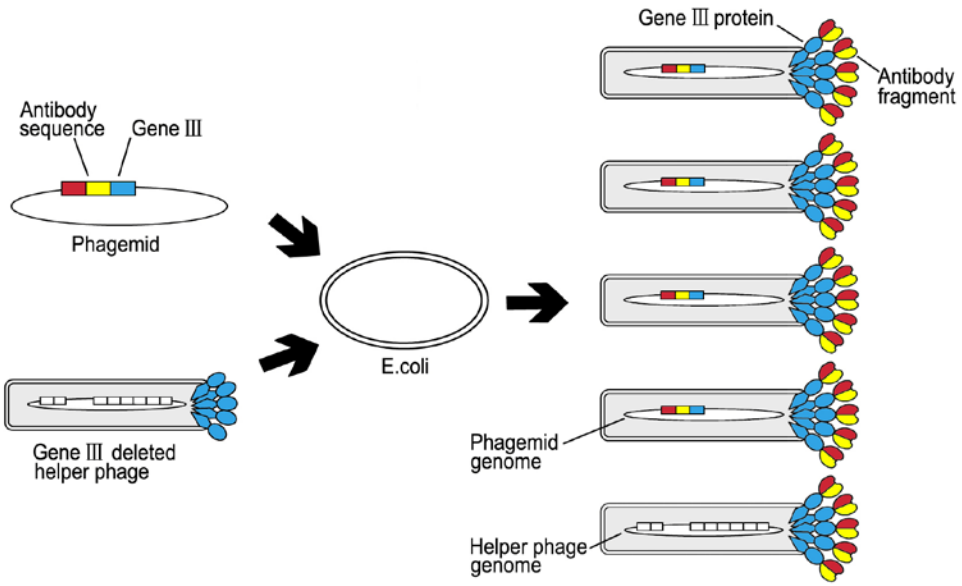
273. The first type of phagemid system uses a conventional helper phage such as M13K07. This can be illustrated by the following schematic diagram (again taken from Dr Teillaud's second report):



274. In this system, there are two sources of gene III proteins within the host bacteria, either of which might be incorporated into the coats of the progeny phage particles: some will be coded for by the phagemid (and hence will be fusion proteins which incorporate an antibody fragment), while others simply come from the helper phage (and hence will be normal gene III proteins). The actual number of fusion proteins incorporated and displayed on any given phage particle will be random. As shown in the diagram, varying numbers of antibody fragments will be displayed including one and zero (i.e. "bald" phage). As explained in paragraph 88 above, it is possible to manipulate the number of binding molecules that are displayed, but not to avoid the production of "bald" phage.

275. It is tempting to think that there is a direct connection between the phage which have the gene for the fusion protein and those which have the gene III fusion protein at their surface. But this is not correct: which genome the phage has and which gene III proteins are expressed on its surface are independent.

276. The second type of phagemid system uses gene III deletion helper phage i.e. helper phage where the coding sequence for gene III has been deleted. This can be illustrated by the following schematic diagram (again taken from Dr Teillaud's second report):



277. In this system there will only be one source of gene III proteins within the host bacteria: the helper phage DNA is incapable of giving rise to gene III proteins, and therefore all the gene III proteins will come from the phagemid (and hence will be fusion proteins which incorporate a binding molecule). Therefore, all progeny phage particles will display binding molecules via fusion to all their gene III proteins. There can be no "bald" phage. Furthermore, all of the phage particles display multiple binding molecules (multivalent display).

278. It should be noted, however, that the gene III deletion does not affect the fact that the genome of the phage particles will still sometimes come from the helper phage and contain no DNA sequence from the phagemid, and hence no DNA sequence for the antibody fragment.

279. The specification of 511 explains at [0038]-[0039] (quoted in paragraph 218 above) that there are pros and cons to each helper phage system. Where one is trying to discriminate between similar antibodies, because (to put it crudely) two copies of a relatively weak antibody may appear to have a higher affinity than one copy of a stronger antibody (referred to as the "avidity effect"), one would prefer to manipulate the system so that each phage displays one copy of the antibody to give a "true" comparison. For that purpose, one would use the normal helper phage set-up. To pick out a low affinity antibody, however, there is an advantage to using the gene III deleted helper phage because that gives the most copies of the antibody on the surface and hence, it may be hoped, the highest apparent affinity. The same point underlies the discussion at [0323]-[0324].

280. Against this background I can now turn to the issues on construction. The first issue is as to the meaning of the word "each" in integer [4]. For reasons that will appear, this leads on to a second issue, which is as to the meaning of the word "population" in integer [2].

281. Novartis contends that "each" means that each particle contains a phagemid genome encoding the binding molecule displayed by the particle on its surface. Novartis says

that in practice this means that substantially all of the particles must contain such a genome. The reason why Novartis accepts that the skilled team would understand the requirement only to be for substantially all of the particles to contain such a genome is that it is common ground that the skilled team would be aware from their common general knowledge that the phagemid genome only gets packaged into somewhere between 95% and 99% of the particles, the others having the helper phage genome. Thus the skilled team would not understand the word "each" to mean that 100% of the particles must contain phagemid genome, as this is not technically attainable (or least not with the phagemid systems available in 1990).

282. The consequence of Novartis' construction is that the claim is limited to the use of phagemid systems with gene III deletion helper phage. This is because phagemid systems with conventional helper phage produce large proportions of "bald" particles which do not contain a phagemid genome encoding a binding molecule displayed at the surface of the particle. A further difference, as explained above, is that phagemid systems with conventional helper phage can be manipulated to achieve monovalent display, while phagemid systems with gene III deletion helper phage result in multivalent display.

283. In support of this construction, Novartis relies not only on the wording of the claim, but also on three passages in the specification. The first is the passage in [0017] quoted in paragraph 217 above. This passage distinguishes the invention from the disclosure of Bass and the application by Protein Engineering Corporation ("Ladner"). In relation to Bass, it says that "a functional copy of gene III was always present in addition". In relation to Ladner, it says "some unaltered gene III protein will be present". It then says:

> "The embodiments of the present application do not do this. In embodiments where phagemid is rescued with M13K07 gene III deletion phage, there is no unaltered gene III present."

This is saying quite plainly that the invention is to be distinguished from the prior art on the basis that no unaltered gene III is present in the embodiments of the invention, only fusion gene III, and so the system will be multivalent with no "bald" phage. (For the avoidance of misunderstanding, it should be appreciated that the phraseology "In embodiments where" correctly recognises that this can be achieved otherwise than by use of a phagemid/gene III deletion helper phage system, namely by means of a pure filamentous bacteriophage. As is common ground, however, embodiments employing pure phage are excluded at [0145] and by the claim.)

284. Secondly, there is the passage at [0038]-[0039] quoted in paragraph 218 above. Although this recognises that the system based on conventional helper phage has advantages in some circumstances, it points out that in some cases it will be important to have multivalent display so as to take advantage of the avidity bonus, for example where selecting a binding molecule with low affinity. It ends by saying:

> "The applicants have therefore developed and used a phage which is deleted in gene III. This is completely novel."

This reinforces the message conveyed by the first passage that the novelty of the

invention lies in the use of gene III deleted helper phage (particularly once the skilled team appreciates that the use of pure phage is not part of the invention claimed in 511). Thus the skilled team would expect this to be reflected in the claims.

285. Thirdly, there is the passage at [0386]-[0387] quoted in paragraph 237 above. This emphasises the advantages of using the gene III deletion helper phage. Although not as significant as the first two passages, this would support the skilled team's understanding of the importance of this aspect of the invention.

286. Thus far, it seems to me that Novartis' construction is persuasive, and indeed MedImmune has little real answer to it. Although counsel for MedImmune submitted that Novartis's interpretation of integer [4] involved "mutilating the language" of it, it seems to me to be a perfectly natural reading. Nor was he able to offer a coherent alternative reading of the language. Furthermore, he had no convincing response to the points made by Novartis in relation to the three passages referred to above. He did argue that the skilled team would expect that, if the Patentees wanted to restrict the claims to gene III deletion helper phage, the claims would say so in terms rather than in a roundabout way. I am unimpressed with this argument, however. First, the fact that the limitation could have been more clearly expressed is not persuasive. Secondly, the restriction to phagemids is itself expressed in a somewhat oblique manner. Thirdly, the claim does not explicitly refer to the helper phage at all. Fourthly, on Novartis' construction the wording does have the result of confining the claim to the use of gene III deletion helper phage.

287. MedImmune's real answer to Novartis' construction does not lie in integer [4] at all, but in integer [2] and in particular the words "a population of filamentous bacteriophage particles". MedImmune contends that these words must be construed purposively having regard to the underlying science. MedImmune says that, so construed, the claim does read on to the use of conventional helper phage, as well as gene III deleted helper phage, for the following reasons.

288. In a phagemid system employing conventional helper phage, as shown in the diagram in paragraph 273 above, there are four possible types of particles: (i) bald particles containing helper phage genome; (ii) bald particles containing phagemid genome; (iii) fusion-protein-displaying particles containing helper phage genome; and (iv) fusion-protein-displaying particles containing phagemid genome. The bald particles, (i) and (ii), will fall through the column, be washed down the sink, and are of no interest to someone implementing the invention. Those containing helper phage genome (i) and (iii), are not useful and fall out of the picture upon further passage through bacteria or upon characterisation of their DNA. Again, therefore, they are of no interest to the scientist. Thus from a technical perspective, it will be apparent to the skilled person that the only particles of interest are class (iv).

289. MedImmune contends that, in those circumstances, it makes no sense to construe the claim as embracing classes (iii) and (iv), which is the effect of Novartis' construction. Furthermore, MedImmune says that there is an alternative reading of the claim which avoids this difficulty and does no violence to the language. This is that the population referred to in integer [2] consists of just the class (iv) particles. In those circumstances, it will be the case that "each" particle in that population contains a

phagemid genome encoding the binding molecule displayed by the particle on its surface as required by integer [4]. In addition, this reading of the claim is supported by the open language of "comprises" in integer [1], which admits of the possibility that other types of particles are also produced.

290. Ingenious though this argument is, I am unable to accept it for the following reasons. First, I consider that it is clear from the specification as a whole, and in particular passages such as [0126]-[0127], that the "population" referred to in integer [2] is the contents of the library, and not a sub-population. Secondly, there is no hint in the lengthy and detailed specification that the claim is to be read in the way suggested by MedImmune. Thirdly, if the claim is construed in this way, it means that there is no reference in the claim to the starting population, which would be strange. Fourthly, if the skilled team reads integer [2] as restricted to class (iv), it comes close to making integer [4] superfluous. Fifthly, I am unimpressed by the point about "comprises", which simply allows for the possibility of additional steps in the method. Sixthly and most importantly, this argument does not really provide an answer to Novartis' submission that the three passages in the specification discussed above clearly point to the claims being limited to the use of gene III deletion helper phage.

Construction of claim 1 of 777

291. Again there are two issues of construction of claim 1 of 777.

"By fusion with a gene III protein"

292. Integer [4] of claim 1 of 777 requires that the binding molecules are displayed at the surface of the phage particles "by fusion with a gene III protein". Novartis contends that the words "a gene III protein" mean a complete, or at least substantially complete, gene III protein. MedImmune contends that they embrace part of a gene III protein, and in particular a part consisting of a C-terminal domain with no N-terminal domain (i.e. less than half of the complete protein).

293. Novartis submits that its construction is supported by the following points. First, the wording of the claim is simple and clear. On its face, it appears to require fusion with at least one gene III protein.

294. Secondly, the skilled team would note that neither the claim nor the specification refer to fusion with a "fragment" of a gene III protein. This is in marked contrast to the repeated references to fragments of antibodies.

295. Thirdly, in cross-examination Professor Brammar was unable to identify any technical reason as to why the skilled reader would think that the claim embraced a gene III protein fragment. His reasoning for thinking that the claim embraced a fragment was based exclusively on the use of the indefinite article. He went on to explain that a truncated gene III protein was still a protein; but it does not follow that it is still a gene III protein. Novartis says that a better explanation for the use of the indefinite article is the fact that the particles contain multiple gene III proteins, and it is sufficient if the binding molecule is fused to one of them.

296. Fourthly, the skilled team would appreciate that, if phage is being used as the vector,

it must have a functioning gene III. If the gene III protein is truncated by removal of the N-terminal domain, then it will not be infective. Given that the focus of claim 1 of 777 is upon phage, with no reference to phagemids, the skilled team would not contemplate that the claim extended to fusion with a fragment of a gene III protein which did not include the N-terminal domain, since in those circumstances the invention will not work.

297. Fifthly, Novartis suggests that the skilled team would regard this understanding as being supported by [0017] which distances the invention from Bass and Ladner, since Bass' approach was one of partial gene III deletion, although I think that Novartis accepts that on its own this is a fairly weak point.

298. Sixthly, all the examples in the Patents use the procedure of inserting the DNA for the binding molecule at the end of the N-terminal domain of the full length gene III. Accordingly, there is no reason to believe that the skilled team would have thought that deleting and replacing the N-terminal domain of gene III was an option. On the contrary, the only example where the insertion was not performed at the N-terminus of a full length gene III, namely Example 11 in the Patents (Example 15 in PD3), failed to work. Even in this example, there is no suggestion that gene III could be significantly truncated.

299. MedImmune submits that its construction is supported by the following points. First, MedImmune says that the skilled team would understand that the purpose of the reference in claim 1 of 777 to "a gene III protein" was merely an indication as to which coat protein should be used. In other words, this requirement simply excludes the use of other proteins such as pVIII (which would be covered by claim 5 of 511).

300. Secondly, the domain structure and modularity of gene III was part of the skilled team's common general knowledge. Thus the skilled team would be aware that the N-terminus is needed for infectivity, and the C-terminus for morphogenesis. Furthermore, the skilled team would know that, when a phagemid system is used, the infectivity function of gene III will be provided by the wild-type gene III from the helper phage. They would appreciate that the only function that need be provided by the gene III fusion is the morphogenetic function of integrating the fusion into the phage coat. As Dr Logtenberg accepted, the skilled reader would therefore have understood that, if a truncated gene III protein which contained a C-terminal domain but not an N-terminal domain were used for the fusion, the wild-type copy would provide infectivity and the fusion to the truncated gene III protein would be displayed. In short, if the skilled team addressed its mind to this scenario, it would realise that it would make no difference to the way in which the invention worked if such a truncated gene III protein were used instead of a complete gene III protein.

301. In my view these arguments are quite finely balanced, but I have come to the conclusion that I prefer Novartis' construction. In my judgment the natural understanding of the skilled team of the expression "a gene III protein" in the context of the Patents would be that it meant a complete gene III protein for the first three reasons given by Novartis. In addition, the Patent states at [0112] that "the protein encoded by gene III has several domains…", thereby distinguishing the gene III protein from its constituent domains. I do not think that the skilled team would tend

to read the words "a gene III protein" as merely excluding the use of other coat proteins. The real question is the effect on the skilled team's understanding of MedImmune's second point. This is quite a powerful argument in favour of a broad interpretation. In the end, however, I am not quite persuaded by it for the fourth and sixth reasons given by Novartis. Given that the focus of 777 is phage, rather than phagemid, that use of just a C-terminal fragment would not work in phage and that there is nothing in the specification to suggest that use of such a fragment is contemplated, I do not consider that the skilled team would think that the Patentees intended to claim use of such a fragment.

"A population of filamentous bacteriophage particles" and "each filamentous bacteriophage particle contains nucleic acid"

302. The issue here is the same as in relation to claim 5 of 511 and it is common ground that the answer must be the same. The only difference is that claim 1 of 777 extends to the use of pure phage in addition to phagemids. (And hence there is no counterpart to [0145] of 511.) For the reasons indicated above, this does not affect the analysis.

Priority of the claimed inventions from PD3

The law

303. Both sides accepted as accurate the following summary of the relevant principles which I set out in *Intervet UK Ltd v Merial* [2010] EWHC 294 (Pat):

> "180. In order for a claimed invention to be entitled to priority from an earlier application, it must, in the words of section 5(2)(a) of the 1977 Act, be 'supported by matter disclosed' in that earlier application. Article 87(1) of the European Patent Convention expresses the requirement as being that priority can only be accorded in respect of 'the same invention' as one in the earlier application. Section 5 is one of the sections which is declared to be intended to have the same effect as the corresponding provision of the EPC: see section 130(7).
>
> 181. In case *G2/98* [2001] OJEPO 413, [2002] EPOR 167 the Enlarged Board of Appeal of the European Patent Office equated 'the same invention' in Article 87(1) with 'the same subject-matter' in Article 87(4). It expressed the requirement for claiming priority as follows:
>
> > 'The requirement for claiming priority of "the same invention", referred to in Article 87(1) EPC, means that priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.'
>
> 182. The Court of Appeal explained this requirement in *Unilin Beheer NV v Berry Floor NV* [2004] EWCA Civ 1021, [2005] FSR 6 at [48] as

follows:

> 'The approach is not formulaic: priority is a question about technical disclosure, explicit or implicit. Is there enough in the priority document to give the skilled man essentially the same information as forms the subject-matter of the claim and enables him to work the invention in accordance with that claim?'

183. As Kitchin J observed in *Abbott Laboratories Ltd v Evysio Medical Devices plc* [2008] EWHC 800 (Pat), [2008] RPC 23 at [228], after citing G2/98 and *Unilin v Berry*:

> 'So the important thing is not the consistory clause or the claims of the priority document but whether the disclosure as a whole is enabling and effectively gives the skilled person what is in the claim whose priority is in question. I would add that it must 'give' it directly and unambiguously. It is not sufficient that it may be an obvious development of what is disclosed.'"

304. I would add that the burden lies on the patentee to establish that the claims in issue are entitled to priority from the priority document in question, although it is usually convenient to proceed by considering the objections to the claim to priority advanced by the other party.

Claim 8 of 511

305. Novartis contends that claim 8 of 511 is not entitled to priority from PD3 for two reasons.

Phagemid and Fab

306. First, Novartis contends that PD3 does not expressly or implicitly disclose a filamentous bacteriophage particle containing a phagemid genome comprising nucleic acid with a nucleotide sequence encoding a Fab antibody molecule expressed from the nucleic acid and displayed by the particle at its surface as required by integers [3] and [4] of claim 5. There are two aspects to this contention. First, does PD3 disclose the use of a phagemid at all? Secondly, even if it does disclose the use of a phagemid, does it disclose the use of a phagemid to display a Fab fragment? In a nutshell, MedImmune contends that the use of a phagemid is disclosed in Example 1, specifically in the passage at page 25 lines 4-14 quoted in paragraph 195 above, and that the use of a phagemid to display a Fab fragment is disclosed in Example 7 when read in the light of Example 1. It is convenient to deal with these points in turn.

307. *Phagemid: Example 1*. As I have already said, the meaning of the paragraph at page 25 lines 4-14 is heavily disputed. There is no dispute that the passage is disclosing at least one alternative to the use of the two phage vectors described earlier in Example 1. A key point of dispute is whether the skilled team would read it as disclosing a single alternative or two separate alternatives or to be unclear in this respect. MedImmune says it discloses two separate alternatives (although on closer

examination the first of these itself contains two alternatives), whereas Novartis says that it discloses a single alternative or at least is unclear. (I note that in the Patents, the passage in question was amended and divided into two paragraphs ([0236]-[0237] in 511), making it clear that there are indeed two alternatives. This is strictly irrelevant to the issue under consideration, however.)

308. In support of its reading, MedImmune points out that the passage begins by saying that "alternative constructions" (i.e. plural) will be apparent to those skilled in the art. MedImmune then points out that the following sentence is divided into two parts by a semi-colon, and says that semi-colons are conventionally used to divide the items in a list. Accordingly, MedImmune says that the skilled team would read the sentence beginning "For example" as disclosing a first alternative before the semi-colon and a second and separate alternative after the semi-colon.

309. I do not find these arguments persuasive. The fact that the document says alternative constructions will be apparent does not necessarily mean that the document is going on to give multiple examples. It could equally well give a single example. As for the semi-colon, a semi-colon is normally used to divide the items in a list when the list is introduced a colon. There is neither a colon in the sentence starting "For example", nor any syntactical indication that it contains a list of items. Accordingly, I consider that the natural reading is that the semi-colon is being used as a punctuation mark which joins two linked statements. As a matter of punctuation and syntax, therefore, I prefer Novartis' reading. At the very least, the passage is poorly expressed if it is intended to convey two separate alternatives.

310. The matter does not end there, however. The skilled team must be treated as trying to make technical sense of the document. Furthermore, the passage in question begins by saying that alternative constructions "will be apparent to those skilled in the art" i.e. in the light of the skilled team's common general knowledge. Therefore the next question is whether it makes technical sense to read the sentence in question as disclosing a single alternative, even if that is what the punctuation and syntax appear to indicate. Here I think MedImmune is on stronger ground. MedImmune says that the skilled team would conclude that the sentence made technical sense if read as disclosing two separate alternatives, but not if read as disclosing a single alternative.

311. MedImmune says that the part of the sentence up to the semi-colon is about avoiding cell death, which was a known problem when working with gene III of filamentous phage. It is furthermore a problem discussed in PD3, but which is avoided by the use of fd-tet, as the readers of the document would understand. The sentence first suggests that M13 could be modified to avoid cell death. Professor Brammar's evidence was that one way of doing this would be to make the same alteration to M13 as was made to fd to make fd-tet. The sentence then goes on to suggest that the host bacteria could be modified to avoid cell death. Professor Brammar's evidence was that one way to do this would be to select for mutants of the *E. coli* host that are able to survive infection by a potentially lethal filamentous phage derivative.

312. Dr Logtenberg did not accept this reading when it was put to him in cross-examination, but his reasons were really linguistic rather than technical. In addition to reading the sentence as a single whole, he was troubled by the reference here to "its

gene III". As he pointed out, this appears to refer back to "host bacteria" as well "M13", but the host bacteria do not have gene III. MedImmune tries to answer this by saying it is obvious from the syntax that "its" relates back to the M13, since "its" is repeated and since "its" is singular but "bacteria" is plural. To my mind this is not obvious, and is another instance of the passage being badly written. Given that it does not make technical sense for "its gene III" to refer back to "host bacteria", however, I consider that the skilled team would conclude that, although badly written, the first part of the sentence is conveying the two alternatives described in paragraph 311 above. I should make it clear for the avoidance of doubt that I do not consider that it discloses the particular implementations of those ideas described by Professor Brammar.

313. MedImmune then says that the part of the sentence after the semi-colon suggests use of the well-known phagemid/helper phage system, as exemplified by pUC119/M13K07, as a separate alternative. Cell death is not an issue in this scenario, because the helper phage has a wild-type copy of all the phage genes. Furthermore, MedImmune says that even if the skilled team found this passage as a whole less then completely clear, they would at least find the reference to pUC119/M13K07 clear. As all the experts agreed, that was a commonly used system in 1990. This would fit with the earlier statement that "alternative constructions will be apparent".

314. Again, Dr Logtenberg's difficulty with this reading was really linguistic rather than technical. As he pointed out, this part of the sentence begins "the modified fd gene III", which appears to suggest an antecedent before the semi-colon, consistently with the use of the semi-colon. Again, as a matter of language I am sympathetic to this, but it does not make technical sense. From a technical perspective, the skilled team would appreciate that the authors must be referring back to what has been described previously in the specification and that they are referring to the antibody/gene III fusion. Next, as Professor Brammar accepted, the reference to "other modified protein" is somewhat confusing, since gene III is not a protein. But this is explicable on the basis that the authors mean a modified gene encoding another protein. Although it was suggested to Professor Brammar that the reference to "modified phage such as K07" was also confusing, he did not agree since M13K07 is indeed an example of a modified phage. Another point which I think Professor Brammar did accept is that the reference to "phage antibody genome" is somewhat inconsistent, since strictly it should say "phagemid antibody genome" if a use of phagemid is what is intended, particularly having regard to the definition of "phage antibody" given in PD3 page 6 lines 15-22 (quoted in paragraph 181 above) and the fact that a phagemid is not a virus. Given the clear reference to the pUC119 phagemid, however, I consider that the skilled team would conclude that this was merely loose use of language, consistently with the other infelicities in this passage I have noted.

315. Furthermore, if the sentence is read as describing a single alternative, it is very difficult to make technical sense of what that alternative is. In his first report Dr Logtenberg read it as disclosing a three-vector system ("a phage vector M13 with disrupted gene III, and presumably the antibody gene", "the pUC119 phagemid with a gene III" and "a modified M13K07 phage"), but he himself said that it was "unclear how these vectors were envisaged to operate together". A bravura attempt was made by counsel for Novartis in cross-examination of Professor Brammar to establish that it

could be read as disclosing a phagemid/helper phage system in which the helper phage's gene III is deleted. But this again is technically flawed for reasons it is unnecessary to go into. In any event, it was not an interpretation espoused by either Dr Huse or Dr Logtenberg. Nor was it an interpretation which counsel for Novartis pursued in his closing submissions. Rather, his submission, consistently with the evidence of Dr Huse and Dr Logtenberg, was that the sentence was confusing and unclear, and therefore did not clearly and unambiguously disclose the use of a phagemid/helper phage system.

316. My conclusion in the light of all the evidence is that, although this passage is poorly expressed as a matter of language, nevertheless it does make technical sense, and only makes technical sense, if interpreted in the manner contended for by MedImmune.

317. For completeness I should refer to two decisions of the European Patent Office touching on this point which were relied on by counsel for MedImmune. The first is a decision of the Opposition Division dated 15 April 2002 on oppositions by four opponents (including, as noted above, Dyax Corporation) to 877. The Opposition Division held at [20.4] that "those embodiments of claim 1 relating to the use of phagemids and corresponding helper phages for phage construction … are disclosed in an enabling way in the first priority document", specifically a passage at pages 20-21 corresponding to the disputed passage in PD3. This supports MedImmune's position, but it is difficult to place much weight on it for three reasons. First, it appears from the decision at [9.2(a)] that the opponents' argument was that the disclosure of phagemid and helper phage was not an enabling one rather than that they were not clearly disclosed at all. The Opposition Division held that the disclosure was enabling since the pUC119/M13K07 system was common general knowledge. Secondly, the Opposition Division only quoted and considered the part of the key sentence after the semi-colon. This in itself removes much of the potential ambiguity in the passage. Thirdly, it is not apparent that the Opposition Division had the benefit of the evidence and argument on this point which I received.

318. The second decision is a decision of Technical Board of Appeal 3.3.08 dated 18 September 2007 in case T 493/06, an appeal by the DKFZ against a decision of the Opposition Division to revoke a patent granted to the DKFZ (as to which, see below) pursuant to an opposition by CAT. In those proceedings CAT relied on the Application as a novelty-destroying citation pursuant to Article 54(3) EPC. For this purpose CAT needed to establish that the Application was entitled to priority from the fifth priority document filed on 15 May 1991 ("PD5"). In this context there was an issue as to whether the disclosure of the Application and of PD5 was limited to five specific phagemids mentioned in them. The Board held that the disclosure extended beyond the five specific phagemids. In this context the Board said at [14.1] that it was important that at the end of Example 1 "the reader of [the Application] is informed in general that plasmids with a single strand replication origin, such as pUC119, represent a logical alternative in the structure. These vectors … are known as phagemid vectors". The Board went on to note that the passages which supported this interpretation were also present in PD5. Although this decision again supports MedImmune's position, it is even more difficult to place weight on it for the following reasons. First, there was no issue as to priority from the earlier priority documents, and in particular PD3. Secondly, on any view PD5 contains much more

about phagemids than PD3. Indeed, it discloses five specific phagemids none of which are disclosed in PD3. Thirdly, in consequence there was no issue as to whether phagemids were disclosed, only as to the breadth of the disclosure. Fourthly, the Board did not base its conclusion solely on the disputed passage, but also upon a number of other passages, not all of which are present in PD3, including in particular Example 17.

319. *Phagemid and Fab: Example 7 read in the light of Example 1*. MedImmune does not suggest that there is an explicit disclosure of the use of phagemid to display Fab in Example 7. Rather, its contention is that there is an implicit disclosure of this when Example 7 is read in the light of Example 1.

320. In support of this contention, MedImmune makes two points. First, it says that Example 1 sets the scene for everything that follows. Secondly, it says that there are explicit links between Example 1 and Example 7. I shall consider these points in turn.

321. So far as the first point is concerned, it is correct that Example 1 discloses the construction of two vectors based on fd-tet that are used in subsequent examples. Thus Examples 2, 5 and 9 make use of the FDTPs/Xh vector and Example 3 makes use of the FDTPs/Bs vector. This lends support to the view that the skilled team would appreciate that the "alternative constructions" mentioned at the end of Example 1 could be used in a similar manner.

322. As for the second point, Example 7 begins with the following statement:

> "The aim of this example was to demonstrate that the scFv format used in example 2 was only one way of display antibody fragments in the pAb system."

MedImmune says that this presents Example 7 as an extension of Example 2, which as noted above makes use of one of the vectors created in Example 1. Furthermore, one of the vectors actually used in Example 7 is fdCAT2 from Example 5, which in turn is derived from FDTPs/Xh in Example 1. Again, this lends support to the view that the skilled team would appreciate that the "alternative constructions" mentioned at the end of Example 1 could be used in a similar manner. The reasoning of the Board of Appeal in T 493/07 with regard to Example 17 was to similar effect.

323. Novartis points out, however, that even if the skilled team did read PD3 as implicitly disclosing that the "alternative construction" of pUC119/M13K07 could be used in Example 7, that would still not disclose something falling within claim 5 of 511. As described above, in Example 7 the genes for the heavy chain of the Fab fragment are inserted into the phage nucleic acid, whereas the genes for the light chain are co-expressed in the bacterial cell from a separate plasmid vector. Thus even if pUC119/M13K07 were used instead of the phage vector, the nucleic acid encoding the binding molecule would not be packaged inside the bacteriophage particles, but only half of it.

324. MedImmune's answer to this is to rely on the passage at page 31 lines 21-27 (quoted in paragraph 208 above). As Dr Logtenberg accepted, this passage discloses the alternative possibility that both the heavy chain and the light chain can be encoded by

the phage. As Novartis points out, however, what is suggested is inserting the nucleic acid into the "phage genome", specifically "the related phage M13". There is no suggestion that both chains be encoded in a phagemid. Furthermore, as Professor Brammar accepted in cross-examination, there is no teaching that a Fab fragment will in fact be expressed on the surface of a phagemid particle if that were to be tried.

325. MedImmune's response to this is to rely on evidence given by Professor Brammar in his second report to the effect that the skilled team would appreciate that the expression cassette for the heavy and light chains of the Fab fragment could be inserted into the polycloning site of a pUC119 phagemid rather than the intergenic region of M13 phage as discussed in this passage. Professor Brammar did not suggest, however, that this possibility was actually disclosed by PD3. In the light of his evidence, it might have been an obvious possibility to the skilled team (subject to any argument as to their expectation of success); but that is not enough. Moreover, Dr Logtenberg did not think that the skilled team would read PD3 as disclosing that the phagemid/helper system could be used to encode both the heavy chain and the light chain of the Fab fragment, let alone in this way.

326. Accordingly, in my judgment PD3 does not clearly and unambiguously disclose combining the phagemid/helper phage alternative mentioned at the end of Example 1 with the expression of a Fab fragment described in Example 7 in such a way that both chains are encoded in the phagemid genome as required by integer [4] of claim 5. It follows that claims 5-8 of 511 are not entitled to priority from PD3.

Derivative

327. Novartis' second objection arises out the introduction of the definition of the term "derivative", which features in integers [4] and [5] of claim 8 of 511 and integers [11] and [13] of claim 1 of 777, in the Patents. Novartis contends that the introduction of the definition in and of itself broadened the scope of the invention. More particularly, Novartis contends that a specific instance of such broadening is that the Patents disclose and cover post-phage display mutation of the antibody fragment (i.e. by mutagenesis of the encoding DNA), when this is not disclosed by PD3. Although these points are closely related, it is convenient to consider them separately.

328. It is common ground that there is no definition of "derivative" in PD3. It is also common ground that the definition of "derivative" in the Patents (at [0083] in 511, quoted in paragraph 219 above) is a very broad one. Dr Teillaud's evidence was that, at its broadest, the term "derivative" covered any molecule which was derived from the parent polypeptide, even including a molecule in which every single amino acid in the original polypeptide had been changed. As I understood him, he interpreted the definition in the Patent as extending that far as well.

329. One might expect in these circumstances that it would be MedImmune's contention that "derivative" was a term of art, while Novartis contended that it was not a term of art. Surprisingly, the parties' positions are the converse of this. Novartis' position is that, in the general context of binding molecules such as antibodies, "derivative" was a term of art in 1990 which, absent anything in the specific context to indicate to the contrary, would be understood by the skilled team to indicate that the binding molecule had been altered in a manner which did not alter its binding properties. It

would thus include a product to which markers had been added or which was linked to other proteins such that function was added, rather than binding properties altered. Alternatively, it could be used to connote a change from e.g. an Fv or to an scFv. MedImmune disputes that "derivative" was a term of art in 1990.

330. Novartis' position was supported by the evidence of Dr Huse and Dr Logtenberg, but neither of them cited any textbooks or dictionaries containing definitions of "derivative". Two papers which used the term in a manner consistent with this understanding were put to Dr Teillaud in cross-examination, but it was not suggested that either of these were common general knowledge, still less the sort of publications the skilled team would turn to for a definition if in doubt. Furthermore, there was a minor difference between Dr Huse and Dr Logtenberg as to whether the term would include removal of a glycosylation site, which on Novartis' definition should really be excluded. Dr Huse thought that this was included, whereas Dr Logtenberg thought that this was borderline.

331. Two articles were put to Dr Logtenberg in cross-examination containing references to "mutated derivatives". Dr Logtenberg did not see this usage as inconsistent with what he considered to be the general understanding of the term, since the authors' meaning was clear from the specific context. I would add that, if "derivatives" was understood to include mutants, then the word "mutated" would be redundant.

332. Dr Teillaud did not agree that "derivative" was a term of art. On the contrary, his evidence was that it was not a well-defined scientific term with a clear meaning. Instead, it was a term that was used by many people with a broad meaning. How broadly it would be understood varied from person to person.

333. Considering the evidence as a whole, my conclusion is that "derivative" was not a term of art with a clear meaning in 1990. On the contrary, it was a term which, in the absence of a specific context making it clear what was meant, could be understood by different skilled persons in different ways.

334. Novartis submits that, if so, then it must follow that the introduction of the definition in the Patents broadened the disclosure, and hence the Patents are not entitled to priority. In my judgment this does not necessarily follow. It depends on how the word "derivative" would be understood by the skilled team in the context of PD3. If the skilled team would understand "derivative" in the context of PD3 to be intended to have a very broad meaning, then the introduction of the definition would make no change of substance to the disclosure. In order to demonstrate that there is a difference of substance, Novartis needs to show that the consequence of the introduction of the definition in the Patents, either by itself or in combination with other new matter, is to disclose something material to the invention which is not disclosed by PD3. I therefore turn to consider Novartis' second point.

335. Novartis says that the invention disclosed in PD3 is described at its broadest at page 10 lines 9-29 (quoted in paragraph 184 above). This comprises the following steps:

    i) producing a "package" (i.e. a phage which expresses a binding molecule, which may be an antibody or a fragment or derivative of an antibody) by inserting an encoding nucleotide sequence within the phage genome and

culturing the phage so that the binding molecule is expressed at its surface;

ii) panning with a particular epitope;

iii) separating the package from the epitope;

iv) recovering the package;

v) using the inserted nucleic acid in a recombinant system to produce the binding molecule separate from the phage.

336. By contrast, Novartis says, the Patents disclose the following invention:

i) producing a "package" (i.e. a phage which expresses a binding molecule, which may be an antibody or a fragment or derivative of an antibody) by inserting an encoding nucleotide sequence within the phage genome and culturing the phage so that the binding molecule is expressed at its surface;

ii) panning with a particular epitope;

iii) separating the package from the epitope;

iv) recovering the package;

v) recovering the DNA from the package and engaging in a program of mutagenesis so as to change any number of amino acids in the binding molecule as in an affinity maturation programme;

vi) using the mutated nucleic acid in a recombinant system to produce the mutated binding molecule separate from the phage.

337. I do not understand MedImmune to dispute that the Patents disclose, and claim 8 of 511 and claim 1 of 777 cover, the latter invention, subject to the fact that 511 is limited to the use of phagemids. (Indeed, as Novartis points out, this is the very aspect of the Patents that Novartis is alleged to have infringed.) MedImmune contends that this invention is also disclosed in PD3, as follows. First, MedImmune says that skilled readers would understand from PD3 that "derivatives" could be mutated derivatives. Secondly, MedImmune says that skilled readers would understand from PD3 that the derivatisation can take place after the phage display. I shall consider these points in turn.

338. In support of the first point, MedImmune relies upon (a) the mention at page 2 lines 22-23 (quoted in paragraph 175 above) of "monoclonal antibodies, their fragments and derivatives", (b) the statement at page 11 lines 26-27 (quoted in paragraph 184 above) that "the nucleotide sequence may be derived by the in vitro mutagenesis of an existing antibody coding sequence" and (c) the discussion of affinity maturation beginning at page 17 line 32 (partly quoted in paragraph 192 above), and in particular the statement at page 17 line 37 – page 18 line 3 that "The population/library of phage antibodies to be screened could be … created in vitro by mutagenising pre-existing phage antibodies".

339. So far as (a) is concerned, this is part of the description of the technical background to the invention. MedImmune relies on the fact that the use of mutation to alter binding sites in monoclonal antibodies was common general knowledge. But there is nothing in this passage to tell the skilled reader that the applicants are intending to refer to such mutants when they use the word "derivatives" here. As Novartis points out, this passage comes immediately after a reference to the construction of scFvs. Given that context, the skilled team is more likely to read "derivatives" here as meaning things like scFvs.

340. As to (b), this statement must be read in context. In context, this is the third possible method of obtaining the nucleotide sequence for insertion into the phage genome, the first two being from an immunised or non-immunised mammal. It is not talking about subsequent derivatisation of the binding molecule specific to the target epitope. Nor does it actually use the word "derivative", although it does use the word "derived".

341. As for (c), this passage is again talking about a method of creating the library of antibodies to be screened. It is not talking about subsequent derivatisation of the binding molecule specific to the target epitope. This passage does not even use the word "derived". Furthermore, the subsequent reference to "mutant phage antibody" points away from MedImmune's construction, since these species are described as "mutants", not "derivatives".

342. In support of the second point, MedImmune relies primarily upon the opening paragraph at page 1 lines 3-15 (quoted in paragraph 173 above). MedImmune contends that this is a clear and unambiguous statement that the derivatising step can take place as part of the final production step in a recombinant system after phage display. No specific evidence was cited in support of this contention in MedImmune's closing submissions, however, and I cannot see how the skilled team is supposed to get this out of the passage in question. To the extent that MedImmune is relying upon Dr Teillaud's evidence in support of this submission, I consider that Dr Teillaud failed to distinguish between the message which would be conveyed by PD3 to a skilled team who had not seen the Patents from the message conveyed by the Patents. MedImmune also relies on a similar statement at page 16 lines 8-12, and my answer is the same.

343. I therefore conclude that PD3 does not disclose post-phage display mutation of antibodies (step (v) in paragraph 336 above). It follows that claim 8 of 511 is not entitled to priority from PD3.

Claim 1 of 777

344. Novartis contends that claim 1 is not entitled to priority from PD3 for the same reason as the second of the two reasons I have considered in relation to claim 8 of 511. It is common ground that the answer is the same in both cases.

The prior art

345. Although at earlier stages of the proceedings Novartis relied on a more extensive list of prior art, in his closing submissions counsel for Novartis confined the case to just two items.

Parmley & Smith

346. I have introduced this paper in paragraph 170 above. The first part of the paper after the summary quoted there is an introduction at pages 205-206. This begins with the observation that protein-encoding genes are routinely isolated from recombinant DNA libraries of 10^5 - 10^6 clones in vectors such as lambda phage, using antibodies to screen plaques for the target antigen. It identifies two limitations with this: rare sequences are easily missed, and screening libraries larger than 10^6 clones is "an arduous undertaking". The paper says it describes a class of filamentous phage vectors with the promise of isolating target clones from libraries of 10^9 clones. This is achieved by the use of "fusion phage", first described in Smith, in which foreign DNA fragments are expressed as part of a fusion protein on the surface of the virions. Fusion phage bearing a specific target antigen can be selected by affinity to an antibody directed to that antigen much more easily and effectively than conventional screening of large numbers of clones.

347. The introduction goes on to explain that the cloning site for the fusion phage lies in gene III. It then says that the paper reports improvements in the design of fusion-phage vectors and in the method of affinity purification. The vector design was improved in two ways. First, the cloning site was moved from between the N-terminal and C-terminal domains, to 2-3 amino acids in from the N-terminal end, leaving the majority of the gene III sequence uninterrupted. Second, the parent vector used was fd-tet phage. A number of advantages stemming from these improvements are identified, in particular a reduction of the effect of inserts on pIII function. The procedure for affinity purification was improved by reacting the phage library with biotinylated antibody directed against the target gene product and then "panning" it on a streptavidin-coated plate. The authors call this "biopanning", and say that it allows isolation of phage carrying a target insert from a mock library containing a 10^8 fold excess of phage without the insert.

348. Following a detailed description of the materials and methods at pages 306-310, the results are set out at pages 310-314. The fd-tet phage was mutagenised to create two different restriction sites, leading to vectors called fUSE1 and fUSE2. A number of different nucleotide sequences were inserted into these, so as to generate five fusion phage as follows:

    i) fUSE1-T7 contained a 20 base pair sequence inserted into the fUSE1 vector (i.e. encoding a peptide fragment about 6 amino acids in length).

    ii) fNANP contained a 54 base pair sequence inserted into the fUSE2 vector (encoding about 18 amino acids).

    iii) fBACK contained the same insert as fNANP, spliced in a backwards direction.

    iv) fUSE1-Lac71 contained a 71 base pair fragment of the lacZ gene (an *E. coli* gene which encodes β-galactosidase) (encoding about 23 amino acids).

    v) fUSE1-Lac335 contained a 335 base pair fragment of the lacZ gene (encoding about 111 amino acids).

349. Having produced these constructs, the authors conducted a number of experiments in order to assess the particle yield of the clones, the infectivity of the clones and the ability of the peptides encoded by the inserts to be bound by known antibodies (thus confirming display of these peptides). The results of these experiments are summarised in Table 1. None of their pIII fusion proteins had a significant effect on the yield of phage particles produced following propagation in *E. coli*. However, a number of the inserts did affect the infectivity of the phage particles. In particular, the inserts in fUSE1-Lac71 and fNANP approximately halved infectivity, while the Lac335 insert led to a more than 20 fold reduction in infectivity.

350. The reduction in infectivity of the fusion phage with the largest insert is discussed at page 311. The authors say this "may be primarily due to increased breakdown of recombinant pIII". They go on to discuss a Western blot of the fUSE1-Lac335 protein shown in Fig 2, which they suggest shows the presence of (i) intact recombinant pIII, (ii) pIII from which the foreign amino acids have been proteolytically removed and (iii) an additional breakdown product for which they postulate two possible causes. The authors comment:

> "It is entirely possible that the reduced infectivity of fUSE1-Lac335 virions is largely due to this breakdown. Despite its reduced infectivity, fUSE1-Lac335 can be effectively affinity purified as will be demonstrated in the next section."

351. The authors go on to describe biopanning using anti- β-galactosidase antibody. The results shown in Table II demonstrate that a portion of the lacZ protein was displayed on the surface of the phage. In addition, in the case of fUSE1-Lac335, an overall enrichment factor of 10^6 was achieved after two rounds of biopanning.

352. The discussion section at pages 314-316 is divided into six sub-sections. The first of these is central to the dispute in the present case, and so I shall quote it in full:

> **"(a) fUSE vectors display foreign antigenic determinants with little loss of phage function**
>
> The new fusion phage vectors, fUSE1 and fUSE2, accept inserts in gene III with little or no loss of phage function; inserts are stable. The foreign [amino acids] encoded in the inserts are expressed on the surface of the phage; two clones carrying fragments of a target gene were shown to express determinants recognized by antibody to the gene product. These results demonstrate the ability of fUSE vectors to accept inserts up to 335 bp (perhaps more) and express the foreign [amino acids] encoded in the inserts on the surface of the virion.
>
> Some inserts by their very nature will affect pIII function. Inserts that contain anchor domains or other hydrophobic segments may stop transfer of pH1 into the host membrane (Davis and Model, 1995) and presumably would not be tolerated. Inserts that exceed 335 bp may lead to excessive

> breakdown of the fusion protein or otherwise impair pIII function, so for the time being we recommended [sic] using fragments of 100-300 bp."

353. In sub-section (b), headed "fUSE vectors as antibody-selectable expression vectors", the authors contrast their new vectors with conventional expression vectors such as λgt11 which lead to expression of the amino acids encoded by the foreign DNA insert in the cytoplasm:

> "In fUSE vectors, in contrast, the amino acids encoded by the foreign inserts are displayed on the virion itself. This allows recombinant phage to be purified in infectious form by affinity to antibody; thus antibody is used directly to *select* for the desired clones."

354. In sub-section (d), headed "cDNA libraries: comparison of λgt11 and fusion phage", the authors compare their new vectors with convention lambda vectors in terms of their cloning ability and the difficulty of isolating a clone of interest. They conclude:

> "Screening a λgt11 library of 10^5-10^6 clones is an arduous undertaking requiring relatively large amounts of antibody. Biopanning, on the other hand, has the potential of isolating rare fusion phage clones from libraries with as many as 10^9 productive clones with only two biopannings and an intermediate amplification. It also requires minute amounts of antibody… "

355. The next sub-section again merits quotation in full:

> **"(e) Prospects for an 'epitope library'**
>
> An 'epitope library' would contain, say, 10^8 clones expressing a short, synthetic random coding sequence. Such a library might be expected to contain clones reactive with almost any anti-protein antibody, since protein epitopes are typically about 6 [amino acids] long and virtually all 64 million 6 [amino acid] epitopes would be represented multiple times in different contexts. Biopanning the epitope library with an antibody of interest and sequencing the inserts in a number of positive clones might provide information about the epitope(s) recognized by the antibody, information that could be used, for example, to design vaccines, identify genes, or map epitopes without the need to clone the relevant natural gene fragments."

The Banbury Conference

356. The Banbury Conference was jointly organised by Professor Lerner of Scripps and Dr Winter of the MRC Laboratory of Molecular Biology, although in the event Dr Winter was unable to attend. The letter dated 28 November 1989 which was sent to invite participants to attend is of some interest and relevance. It summarises the

background to the conference as follows:

> "Recently the separate groups of Winter and Lerner have cloned and expressed the antibody repertoire in *E. coli* using plasmid or lambda phage technology (Sastry et al. Proc. *Natl. Acad. Sci. USA* 1989; Ward et al *Nature* 1989; Orlandi et al *Natl. Acad. Sci.* 1989; Huse et al, In Press, *Science*). Extensions of their results open the possibility of circumventing the hybridoma methodology to prepare antibodies and ultimately may lead to a generic antibody library which would obviate the need to immunize animals. As one begins to approach these goals, questions concerning the size and screening of the antibody repertoire emerge. This meeting will address these issues and hopefully speed up progress toward creating antibodies *in vitro*."

357. Professor Smith and Dr Huse were among about 30 participants at the conference. Professor Smith gave his talk on 26 April 1990. There is no dispute that Professor Smith's talk was "made available to the public".

358. Professor Smith set out his recollection of what he said on that occasion, as well as other relevant matters, in a witness statement dated 9 December 2010. In his statement, he said that, in order to maintain impartiality, he had not agreed to keep his discussions with Novartis' solicitors confidential, but had agreed he would notify them if contacted by any party, and that he would communicate with other parties on the same basis. He was interviewed by MedImmune's solicitors by video link on 15 April 2011, and a transcript of that interview (annotated by Professor Smith with his corrections and comments) was voluntarily disclosed by MedImmune at trial.

359. Professor Smith gave evidence by video link. I found him to be an entirely straightforward and reliable witness. He had a fairly good recollection of the talk, and his recollection had been assisted by finding some notes and slides he had prepared for the talk. In addition, it emerged that he had been deposed for the purposes of proceedings between Morphosys AG and CAT in Washington DC in May 2002, during the course of which he had discussed his talk and the surrounding circumstances. Much of the cross-examination of Professor Smith was directed to the work he did before and after giving the talk and to his thinking during that period, rather than to the actual content of his talk. That evidence is mainly relevant to the question of obviousness, but I have taken it into account in so far as it bears on the question of what he said. That may be summarised as follows.

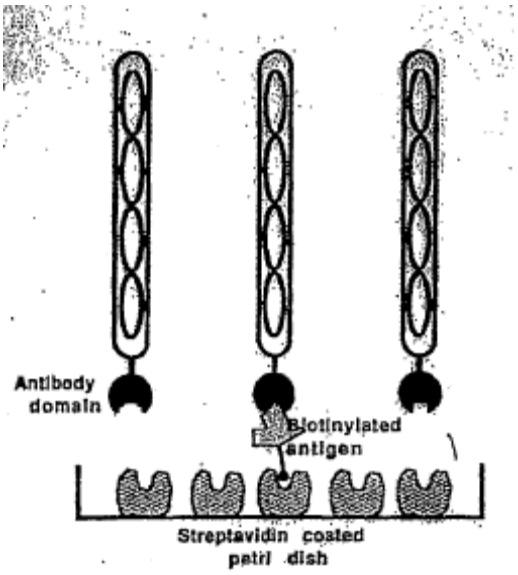
360. In the first part of his presentation, Professor Smith described in general terms the work that was the subject of Scott and Smith, which at that time had been submitted for publication but not yet published. In particular, he explained that a fusion phage could be created with a foreign DNA insert in gene III and that foreign peptides were consequently displayed on pIII in a manner which allowed pIII to retain its function. He introduced at an early stage in his talk the idea of putting a "single-chain antibody" or SCA (i.e. an scFv), on a fusion phage as a means of creating a "paratope" (antibody) library.

361. Next Professor Smith discussed the epitope library referred to in Scott & Smith. He described the use of degenerate oligonucleotides to produce a library of all the possible hexapeptides.

362. Professor Smith then talked about his technique of "biopanning", that is to say, affinity purification on a plate as described in Parmley & Smith. He explained that his group had shown that the presence of a peptide on pIII did not destroy the infectivity of the phage. He also explained that this enabled fusion phage, which were eluted from the plate, to be propagated and sequenced to identify the nucleotide sequence which corresponded to the peptide expressed on the fusion phage.

363. Professor Smith went on to say that Terry Fieser at Scripps had made the monoclonal antibodies MbA and MbM which bind to residues 79-84 of myohemerythrin (referred to as "DFLEKI"). He presented a table showing the results up to three rounds of affinity purification when the monoclonal antibodies were confronted (i.e. panned) with "all" (tens of millions of) the hexapeptides.

364. Professor Smith then said that the same approach "might be useful in screening an antibody library with antibody displayed on pIII and antigen on the plate", reversing the roles of the antibody and antigen. He illustrated this proposal with the following slide:



365. Professor Smith explained that his group were going to test this approach by attempting to express an anti-fluorescein SCA on pIII. He also suggested that, if such an experiment showed that fusion phage expressing this SCA could bind to fluorescein antigen in a panning experiment, this approach might work to identify SCAs from a library of SCAs.

366. At this point Professor Smith raised the question "Will it fold right?", recognising the possibility that in such an environment the conformation of the SCA might be compromised. He explained that some of the pIII protein was embedded in the inner membrane, with the bulk in the periplasm, which was then transferred into the growing virion. He went on, however, to say that, if folding were a concern, use could

be made of a known approach for producing recombinant proteins in bacterial cells, where a process of denaturation using 6M urea at pH 2.2 and renaturation is employed in order to achieve the required folding. Such an approach was potentially feasible in the context of fusion phage because phage could survive the conditions involved.

367. Professor Smith then said that, although degradation might be an impediment to the successful display of large peptides, as had been suggested in Parmley & Smith, the contrary view was that it might be of benefit. The "lon" and "deg" systems of bacteria exist to remove malfolded proteins. He therefore suggested that such degradation might result in the removal of malfolded SCAs, which might work in the experimenter's favour and make the detection of correctly-folded SCAs (if they were not degraded) cleaner.

368. Professor Smith also suggested that, if the SCA on the surface of the fusion phage interfered with the phage's ability subsequently to infect bacteria, it could simply be removed with trypsin.

369. Professor Smith then introduced the idea that an SCA which had been isolated from a fusion phage could repeatedly be mutated and selected for better and better binding.

370. Finally, Professor Smith described two approaches to making a library. One was to construct antibody libraries from the natural repertoire. The other was to make a synthetic library using the degenerate oligonucleotide approach similar to that which he had used to create his hexapeptide library: this would produce random CDRs with various specificities. He made the case for the latter as a preferred strategy.

371. During the interview on 15 April 2011, Professor Smith was asked if he could summarise what he thought he was communicating in April 1990. He replied:

> "Of course, the primary idea was that it is really worth pursuing antibodies displayed on filamentous phage, which we now call phage antibodies, as a new way of expanding cloning the immune response, as Greg Winter's group put it, because it would allow for selection of very rare antibodies for antigen-binding out of huge libraries.
>
> So that idea of phage antibody libraries was very vigorously put forth and I was trying to promote this idea as being something to try."

372. In cross-examination he was asked about various concerns he had at the time about what he was proposing and the extent to which he conveyed those concerns to his audience. I will deal with the concerns themselves below, but in relation to the extent to which he articulated those concerns his evidence was as follows:

> "Q. And did you to your recollection express those concerns to the people at Banbury?
> A. I do not think I used complicated language that is like the language that you are using. You have to realise that I was trying to sell this as an idea to try. That was my goal in

this talk. I was hoping to try it myself, but I also was interested in recruiting other people to try it. So I do not think I was parsing out in any sort of detail the exact nature of the hurdles that had to be crossed. I mentioned them would be more like it. I think it is fair to say that I was trying to be upbeat about the possibility of this technology.

Q. And no doubt your audience realised that?

A. I think at lot of them did realise that, yes.

…

Q. Very well, professor. In any case, you recognised it was a challenge.

A. Certainly.

Q. And you conveyed to the audience that it was a challenge.

A. Yes.

…

MR. JUSTICE ARNOLD: … Can you go back to what you were asked about the Banbury Conference. Mr. Meade was asking you some questions about the extent to which you had articulated to the participants in the conference your concerns about what you were proposing. In answering those questions, you said that this was an idea that you were interested in doing yourself, but you were also trying to recruit others. I am not sure I have got your language exactly accurate, but that is roughly what you said. Could you just explain to me a little more what you mean by that.

A. I thought that if people who worked in the area of expressing the cloned antibodies, who get interested in using phage display for creating phage antibody libraries, that would be a really big advance in the field and it would also be a big advance for a phage display. Although I was very interested in doing the experiments myself, in fact I would have been very glad to have published the first experiment on phage antibodies, I was also really interested in getting other people to work on it as well.

Q. So you were encouraging ----

A. That was why I was not disappointed really when I saw the McCafferty et al paper.

Q. So do I understand from that that you were encouraging the participants to try it themselves as well?

A. Yes. I am not sure I would say that in so many words I said, 'Hey, come on, why don't you guys do this?' but since I was giving out the idea freely, I think the implication was that I was interested in getting people to try this themselves."

373. Dr Huse no longer recalled what Professor Smith had said in his talk. It emerged, however, that in his 1999 declaration Dr Huse had said this:

"In fact, in February 1990, at the Banberry [sic] meeting for

> combinatorial chemistry, Cold Spring Harbor N.Y., George Smith and I discussed that the display of antibody fragments was feasible in filamentous bacteriophage."

374. Both the date and the description of the meeting are slightly inaccurate. Furthermore, the way this is expressed suggests Dr Huse was referring to a private discussion between Professor Smith and himself rather than to Professor Smith's talk. Nevertheless, this evidence does provide a small degree of corroboration for Professor Smith's evidence that his talk was optimistic in its tenor.

Obviousness

375. A patent will be invalid for lack of inventive step if the invention claimed in it was obvious to a person skilled in the art having regard to the state of the art at the priority date. The familiar structured approach to the assessment of allegations of obviousness first articulated by the Court of Appeal in *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd* [1985] RPC 59 was re-stated by Jacob LJ in *Pozzoli v BDMO SA* [2007] EWCA Civ 588, [2007] FSR 37 at [23] as follows:

> "(1)(a) Identify the notional 'person skilled in the art';
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the 'state of the art' and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?"

376. In both *H. Lundbeck A/S v Generics (UK) Ltd* [2008] EWCA Civ 311, [2008] RPC 19 at [24] and *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] RPC 28 at [42] Lord Hoffmann approved without qualification the following statement of principle by Kitchin J at first instance in the former case:

> "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success."

377. When considering the fourth *Pozzoli* step, it is often relevant to consider whether what is claimed arises from taking a step which was obvious to try with a fair expectation of success. As Lord Hoffmann said in *Conor* at [42]:

> "In the Court of Appeal, Jacob LJ dealt comprehensively with the question of when an invention could be considered obvious on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, by saying that the notion of something being obvious to try was useful only in a case where there was a fair expectation of success. How much of an expectation would be needed depended on the particular facts of the case."

378. The jurisprudence of the Technical Boards of Appeal of the EPO is to similar effect: in the context of biotechnology patents, see generally *Case Law of the Boards of Appeal of the European Patent Office* (6th ed) at pages 177-180. Counsel for MedImmune particularly relied upon the following statement of principle by the Board in T296/93 *Biogen/Hepatitis B* [1995] OJ EPO 627 at [7.4.4], which has frequently been cited subsequently:

> "... The fact that other persons (or teams) were also working on the same project might suggest that is was 'obvious to try' or that it was 'an interesting area to explore', but it does not necessarily imply that there was 'a reasonable expectation of success'. 'A reasonable expectation of success', which should not be confused with the understandable 'hope to succeed', implies the ability of the skilled person to reasonably predict, on the basis of the existing knowledge before the starting of a research project, a successful conclusion to the said project within acceptable time limits. The more unexplored a technical field of research is, the more difficult is the making of predictions about its successful conclusion and, consequently, the lower the expectation of success."

As counsel for MedImmune pointed out, this statement of the law requires not merely a reasonable expectation of success, but also an expectation of success within a reasonable time.

379. The primary evidence on the question of obviousness is that of properly qualified expert witnesses. Secondary evidence must be kept firmly in its place: *Mölnycke AB v Procter & Gamble Ltd* [1994] RPC 49 at 112. This does not mean that secondary evidence cannot sometimes be of considerable value: *Schlumberger v Electromagnetic* (cited above) at [76]-[85]. As Laddie J explained in *Pfizer Ltd's Patent* [2001] FSR 16 at [63]-[64], evidence of what actual researchers in the field were doing at the time may be persuasive, but must be examined with care to see if it sheds light on what the notional skilled person with common general knowledge and the prior art would do.

The skilled team, the common general knowledge and the inventive concept

380. I have identified the skilled team and their common general knowledge above. I also have construed the claims. For the purpose of considering obviousness, however, I think this is a case where it is useful to concentrate on the core inventive concept, which is the way in which both sides argued it. In this connection, it should be noted that MedImmune does not contend that claims 6, 7 or 8 of 511 are independently valid over claim 5, and accordingly it is only necessary to consider claim 5. Nor does MedImmune contend that claim 1 of 777 is inventive if claim 5 of 511 is not. Nor did MedImmune suggest that the limitations in claim 5 of 511 to phagemids and Fab fragments mattered for the purposes of obviousness. Nor did MedImmune suggest that it made any difference if I construed the claims as being limited to gene III deleted helper phage, as I have. Accordingly, the core inventive concept can be summarised as a method consisting of two steps: (i) producing a population of phage particles displaying at their surface binding molecules having a range of binding specificities wherein each particle contains nucleic acid encoding the binding molecule; and (ii) selecting particles displaying a binding molecule with a desired specificity by contacting the population of particles with a target epitope or antigen to which the binding molecule of interest binds.

General points

381. Before turning to consider obviousness over the two items of prior art, it is convenient to consider three general points.

382. The first concerns the status of phage display generally in November 1990. By that time Professor Smith had published Smith, Parmley & Smith and Scott & Smith. Counsel for MedImmune submitted that phage display was an unproven technique in November 1990, and no one had done anything of practical utility with it. I do not accept this. As counsel for Novartis pointed out, in addition to Professor Smith's work, at least three other groups had published work on phage display by November 1990: de la Cruz *et al* (at the USA's National Institute of Allergy and Infectious Diseases), "Immunogenicity and epitope mapping of foreign sequences via genetically engineered filamentous phage", *J. Biol. Chem.*, 263, 4318-4322 (March 1988); Devlin *et al* (of Cetus Corporation); "Random peptide libraries: a source of specific protein binding molecules, *Science*, 249, 404-406 (July 1990); and Cwirla *et al* (of Affymax, Inc.), "Peptides on phage: a vast library of peptides for identifying ligands", *Proc. Natl. Acad. Sci. USA*, 87, 6378-6382 (August 1990). Furthermore, it is clear from the evidence discussed below that other groups were using the technique, including in relation to antibodies, but had not yet published their work. Accordingly, as I have previously said, it is likely that skilled teams in the field of antibody engineering were aware of the basic concept of phage display. In any event, I consider that the evidence shows that phage display was an established technique, although it is fair to say that it was not in routine use as at November 1990.

383. The second concerns the extent to which there was a need for an improved screening system for antibodies in 1990, and hence a motive to find one. Dr Huse gave evidence that it was possible to screen large libraries using plaque lift, whereas Professor Brammar's evidence was that this was burdensome. While Dr Huse's evidence is

supported by the views expressed in Huse, looking at the evidence as a whole it seems to me that Parmley & Smith is more representative of the skilled team's attitude when it describes screening a library of 10^5-10^6 clones as "an arduous undertaking". Furthermore, plaque lift did not give one direct access to the encoding DNA for the protein of interest. Thus I consider that PD3 and the Patents are accurate in saying that there was a need for a better screening system, and hence a motive to find one. Against this, counsel for MedImmune relied on evidence given by Dr Huse to the effect that the skilled team would hesitate before using a new screening system in preference to the tried and tested one. No doubt this is so, but it is beside the point if the skilled team is considering whether a proposal for a new technique is reasonably likely to work.

384. The third point concerns the number and extent of the possible avenues of research into this problem. There is very little evidence on this topic. Although it is not the case that antibody phage display was the only available solution in November 1990, it appears that there were relatively few other potential solutions to the problem.

Obviousness over Parmley & Smith

385. In closing submissions counsel for Novartis did not press Novartis' contention that the claimed inventions are obvious in the light of Parmley & Smith, although he did not abandon it, preferring to concentrate his fire on obviousness in the light of Professor Smith's talk at the Banbury Conference. I nevertheless consider that it is important to consider it before turning to consider the Banbury Conference. This is for three reasons. First, Professor Smith's talk built on Parmley & Smith. Secondly, it is common ground that, if the skilled team were to consider implementing the proposal made by Professor Smith at the Banbury Conference, they would read Parmley & Smith before going further if they were not already acquainted with it. Thirdly, Parmley & Smith is central both to one of MedImmune's attacks on Dr Huse's objectivity and more generally to Dr Huse's reasoning on the question of obviousness.

386. The following points should be noted about the disclosure of Parmley & Smith. First, the authors' underlying objective was to clone genes. The idea was that by the antigen-antibody binding one could pick out the DNA for the gene encoding the protein to which one had the antibody. Since the authors only used part of the coding sequence for the protein of interest, however, it would still be necessary to use that to probe a DNA library to obtain the complete sequence. On the other hand, the main focus of the paper is the improved fusion phage vectors and the improved affinity purification method. As the paper makes clear, the potential applications of these improved techniques go beyond cloning genes. In particular, the paper suggests that they could be used to create and screen an epitope library.

387. Secondly, the affinity purification method disclosed in Parmley & Smith has two advantages as a screening system compared to plaque lift, namely it removes the need to keep the antigen in the solid phase and the phage particles are themselves in infectious form and so can be taken forward for characterisation or other steps.

388. Thirdly, Parmley & Smith is concerned with expressing antigen fragments, not antibody fragments.

389. Fourthly, the inserts used in Parmley & Smith were linear epitopes. Although the lac335 insert would have had some secondary structure when displayed on the surface of the phage, there was no requirement for tertiary folding. No doubt for this reason, Parmley & Smith says nothing at all about folding.

390. Fifthly, the infectivity decreased as the size of the insert increased.

391. Sixthly, there was significant breakdown of recombinant pIII in the phage with the lac335 insert.

392. *The difference*. Bearing in mind the points discussed in paragraph 380 above, the key difference between Parmley & Smith and the core inventive concept is that Parmley & Smith only discloses antigen phage display, whereas the invention involves antibody phage display.

393. *Was it obvious?* Dr Huse's opinion in summary was that Parmley & Smith made it obvious to try displaying antibody fragments on the surface of the phage and panning with an antigen instead of displaying antigen fragments and panning with an antibody, since conceptually one was a mirror image of the other, and that Parmley & Smith would give the skilled team a reasonable expectation of success.

394. Professor Brammar's opinion in summary was that, although the skilled team might consider reversing the roles of antigen and antibody, Parmley & Smith would not give them a reasonable expectation that this would be successful. The key reasons for this opinion were as follows:

    i) The linear epitopes used in Parmley & Smith are relatively small polypeptides. Furthermore, they do not need to have a particular tertiary structure in order to function. Thus it was not necessary for Parmley & Smith's purposes to ensure that the polypeptide expressed on the surface of the phage folded correctly.

    ii) By contrast, antibodies are typically larger molecules. This is true even of antibody fragments such as Fabs and scFvs. More importantly, it is critical to antibody function that the antibody or fragment is correctly folded so as to have the right tertiary structure to "lock onto" the epitope.

    iii) If antibody phage display is to be successful, the antibody fragment must fold correctly even though the antibody chains would be attached to a phage protein that was part of a phage particle.

    iv) Parmley & Smith would positively discourage the skilled team from thinking that antibody fragments could be successfully displayed. In this regard the skilled team would note in particular the reduced infectivity of the largest insert, the suggestion that this may be due to increased breakdown of recombinant pIII and, above all, the recommendation to use fragments of 100-300 base pairs. An scFv would be encoded by at least twice as many base pairs, and a Fab by even more.

395. Dr Teillaud's evidence was to the same effect.

396. Before considering these views further, it is important to note that it was common ground between the experts that the teaching in Parmley & Smith is sufficient to enable the skilled team to carry out phage display of an antibody fragment, by using the fd-tet vector at the N terminal end of the gene III protein. Professor Brammar was asked about this by reference to McCafferty:

> "MR. THORLEY: …. Is there anything in this paper which you believe is necessary to achieve success which would not be something carried out by the skilled person implementing Parmley and Smith? Is there some magic trick in McCafferty to making it work or does it just work?
> A. I know of no magic trick and ----
> MR. JUSTICE ARNOLD: Well, let us get away from the expression 'magic trick'. Is there anything described in McCafferty that strikes you as clever above and beyond implementing Parmley and Smith?
> A. No, my Lord, except the sense that they have gone against the advice of Parmley and Smith and decided to do it anyway and made it work.
> Q. I appreciate your point about going against the advice. Concentrating on the 'and they made it work', there is no technical procedure that they adopted to make it work that was out of the ordinary at that time. Is that correct?
> A. Yes, I think that is a correct statement."

397. Returning to Dr Huse's opinion, counsel for MedImmune emphasised that Dr Huse was not merely inventive, but also had thought of the invention before reading Parmley & Smith. Dr Huse's evidence was that he got the idea in about the second half of 1988 from the combination of Smith (which discloses phage display) and Better (which discloses bacterial expression of Fab in the periplasm). As counsel for MedImmune pointed out, this is quite a leap. Furthermore, as I have commented above, it inevitably made it difficult for Dr Huse to read Parmley & Smith through the eyes of an uninventive skilled person who had not had the idea before reading it. On the other hand, it does not necessarily invalidate Dr Huse's analysis of the scientific content of Parmley & Smith. This is particularly so given that the key question is whether it would give the skilled team a reasonable expectation of success.

398. As noted above, another submission made by counsel for MedImmune in this connection was that Dr Huse had changed his reasons for saying that the invention was obvious to him. Counsel suggested that Dr Huse had moved from saying that it was obvious over a combination of Smith with Orlandi/Sastry/Ward/Huse to saying that it was obvious over a combination of Smith with Better. I do not accept this. It is true that in his report Dr Huse said that he had "been discussing early ideas for antibody libraries at around that time" and that it was apparent to him that phage display would be useful in that context, but (a) he did not refer to any of the library papers, (b) Dr Huse started work on combinatorial libraries at Scripps in 1989 and (c) I do not read the sentence in question as saying that this made antibody phage display obvious, rather that it was an obvious application of it. It is also true that Dr Huse's reasons for saying that the invention was obvious to him were more fully explained

and clarified in cross-examination, but I do not regard this as amounting to a significant change in his reasoning.

399. As for Professor Brammar and Dr Teillaud, counsel for Novartis submitted that their evidence should be given less weight than that of Dr Huse because they were less representative of the skilled team. For the reasons given above, I agree that they are less representative in term of their expertise. But it is not possible for me simply to prefer the views of Dr Huse both because he is not representative of the skilled team for different reasons and because what matters, as Jacob LJ often pointed out, are the experts' reasons.

400. What is decisive in the present case is the evidence concerning the questions of size, infectivity, breakdown and folding identified above. Dr Huse, Professor Brammar and Dr Teillaud were all agreed that size *per se* was not an issue. So far as infectivity is concerned, as Dr Huse pointed out, Parmley & Smith expressly states that the lac335 fusion phage could be effectively affinity-purified despite its reduced infectivity. Nevertheless, I think it is clear that the skilled team would be concerned at the reduced infectivity, and the suggestion that it was due to breakdown. Thus the main points are breakdown and folding. Dr Huse's evidence was the skilled team would have a reasonable expectation of success despite what was said about the former and the absence of any discussion of the latter, whereas Professor Brammar and Dr Teillaud disagreed.

401. Both Professor Brammar and Dr Teillaud highlighted the statement in Parmley & Smith that:

> "Inserts that exceed 335 bp may lead to excessive breakdown of the fusion protein or otherwise impair pIII function, so for the time being we recommended using fragments of 100-300 bp."

As noted above, Dr Huse considered this statement to be ambiguous. It is not necessary to go into his reasons, which relate to the fact he did not consider it surprising that there was proteolysis of the particular insert Parmley & Smith had chosen to use since it was a fragment of much larger protein domain, and hence would have exposed parts of the protein that would not ordinarily be exposed to the relevant enzymes. The question is how the uninventive skilled team would react to it.

402. In my judgment this passage would be understood by the skilled team as a clear recommendation to use inserts of less than 300 bp because of the potential for excessive breakdown or other problems with pIII function if larger inserts were used. This reading is supported not merely by the evidence of Professor Brammar and Dr Teillaud, but also by four other pieces of evidence.

403. The first is Bass. Having briefly summarised Smith, Parmley & Smith and Scott & Smith, as well as Cwirla *et al* and Devlin *et al*, this states:

> "There are, however, several important limitations in using such fusion phage to identity altered peptides or proteins with new or enhanced binding properties. First, it has been shown

> [citing Parmley & Smith] that fusion phage are useful only for displaying proteins of less than 100 and preferably less than 50 resides, because large inserts presumably disrupt the function of gene III and therefore phage assembly infectivity…."

Dr Huse's evidence was that, when he first read this, he thought it was a self-serving statement and that he continued to be of that opinion. It is fair to say that it goes slightly further than the relevant passage in Parmley & Smith itself does. Even so, it seems to me that this supports the view that the skilled team would be discouraged by that passage.

404. To similar effect is the following statement in United States Patent No. 5,849,500, a patent whose claimed priority date is 8 July 1991 and one of whose inventors was Professor Dübel (as to whom, see below), at column 2 lines 9-12:

> "However, fusion phage have been shown to be mainly useful for displaying small inserts, probably, because the large inserts have an adverse effect on the infectivity of pIII (Parmlee [sic] and Smith…"

Furthermore, Professor Dübel's evidence was that, looking back, he thought that this was a reasonable conclusion.

405. Thirdly, in a submission to the USPTO in support of US Patent Application No. 08/471,662, one of the family of applications deriving from the Ixsys application derived above, attorneys acting for AME on 21 September 1998 submitted *inter alia* that:

> "The description in [Parmley & Smith] of the applicability of bacteriophage expression for the display of short epitope sequences provides no motivation to use a bacteriophage system for the expression of a first and second polypeptide that form heteromeric receptors."

On its own, this is simply advocacy; but Dr Huse accepted that it was a true statement.

406. The final piece of evidence is a declaration made by Professor Smith himself in 1995, which I shall discuss below.

407. In addition, the skilled team would note that Parmley & Smith says nothing at all about folding. It would therefore give the skilled reader no reason for expecting that a larger protein fragment would fold successfully. Although the skilled team might form their own view on this, in the absence of any consideration of the matter in Parmley & Smith, this would involve a degree of speculation.

408. For these reasons I do not consider that Parmley & Smith would lead the skilled team to believe that phage display of antibody fragments had a reasonable prospect of success. I therefore conclude that, notwithstanding the points made above about the motive to find a better screening system and the shortage of alternative solutions, the

claimed inventions are not obvious over Parmley & Smith. This conclusion is consistent with the decision of the Opposition Division concerning 877 at [22.3]-[22.4].

Obviousness over the Banbury Conference disclosure

409. Professor Smith's talk at the Banbury Conference went further than Parmley & Smith in four key respects. First, Professor Smith explicitly proposed phage display of antibodies. Secondly, he stated that he was going to try this approach by attempting to express an scFv on pIII. Thirdly, he discussed the possible problems that might be encountered, and potential solutions to those problems if they were. In particular, he discussed the possibility that the protein might not fold correctly, and a potential solution if it turned out that it did not. Fourthly, he suggested that (contrary to the view taken in Parmley & Smith) breakdown might actually assist the experimenter rather than represent a problem.

410. *The difference*. Although Professor Smith's talk at the Banbury Conference is not an anticipation of any of the claims in issue, the only real difference between his disclosure and the core inventive concept is that Professor Smith had not actually got as far as doing an actual experiment involving antibody phage display.

411. *Was it obvious?* For the reasons I have just given, I consider that there can be no serious dispute that Professor Smith's talk made it obvious to try phage display of antibodies provided that there was a sufficient expectation of success having regard to the other factors considered above. The only question is whether it would have given the skilled team a reasonable expectation of success within a reasonable time.

412. The starting part here is the overall impression the skilled team would have received from the talk as to whether Professor Smith himself was expecting success. I have quoted the key passages in his evidence on this point in paragraph 372 above. Counsel for MedImmune emphasised the answer in which Professor Smith accepted that he conveyed that it was a challenge, while counsel for Novartis emphasised the other answers. My assessment of the evidence as a whole is that the message Professor Smith conveyed was a positive one: he was reasonably confident of success, while recognising that success was not guaranteed because there were potential problems. Furthermore, as the skilled team would have appreciated, his confidence was not the result of blind optimism, but of the work and scientific analysis he had undertaken.

413. Dr Huse's opinion was that the skilled team would have had a reasonable expectation of success in the light of Professor Smith's talk. He was asked in cross-examination about a series of concerns that Professor Smith either expressed or had in mind, and replied as follows:

> "Q. But in terms of the factors that are identified here, proteolytic systems, folding, background and pulling out the specific antibody from the library, and what he called the overwhelming background of non-specific binding, those would all be reasonable anxieties that the ordinary skilled person considering antibody phage display in 1990, listening to Professor Smith at Banbury, would have, are they not?

A. Anxieties as to the extent that it would work.
Q. Yes. You agree?
A. Right. It is certainly going to work over some extent; and the bigger the extent, the better.
Q. The question is, 'Can you actually pull the clone out?' At the end of the day, that is the question, is it not?
A. The question is, 'What percentage of clones are you going to be able to pull out? How often is it going to be successful?' These are the factors that you are going to optimise to make it more generally successful rather than less generally successful."

414. A little later, he said that "this is a question about the limits of the technology rather than the functionality of the technology". I asked him about this:

"MR. JUSTICE ARNOLD: …
On the one hand, Professor Smith says he was, to use his expression, 'very vigorously putting forth this idea and trying to promote this as being something to try' and, on the other hand, he is recognising what Mr. Meade has described as anxieties. Your response to that is, 'That is all about the limits of the technology.'
Trying to put yourself into the shoes of the ordinary skilled person, hearing what Professor Smith had said at the Banbury Conference, in your opinion, would they be sufficiently encouraged by the overall message to go away and try it or not?
A. Yes.
Q. Can you just briefly explain why?
A. Because any new technology has limitations about the range over which it is going to work. I think Professor Smith is giving us here the idea that there is going to be some range it is going to work, but you have got to be cautious about assuming exactly how big that range is."

415. Professor Brammar's evidence on this topic was not entirely consistent. At an early stage in cross-examination he said that Professor Smith's proposal of making a single chain antibody via phage display was "a very good idea that he wanted to pursue". Later, however, he described it "a hell of a long shot". He then explained that a factor in this assessment was that Professor Smith was a leader in the field, whereas he was not. He also said that he had been somewhat scarred by his own early experiences with protein folding. Nevertheless, he went on to accept that the skilled team would conclude, even taking into account what was said in Parmley & Smith, that Professor Smith was confident that it was worth trying:

"Q. When you came back on the hypothesis that you were at Banbury and you came back and read Parmley and Smith, would you not say to yourself that the mere fact that Professor Smith was intending to go ahead with -- I think he was scFv's,

was he not -- must indicate that he has some confidence that he can go beyond 300 base pairs?

A. Yes. I would put it slightly differently, but you will not be unhappy with what I say.

Q. How very civil of you.

A. He would be confident that it is worth trying. I would never get the impression that he was confident that it would work, but he was confident enough to say, 'I am going to try it, it is worth doing, but I am aware of the possible reasons for failure and I will try to deal with them'."

In my view it follows that the skilled team would have a reasonable expectation of success if they were to try it themselves.

416. As to how long the experiment would take, Professor Brammar pointed out that in practice obtaining a suitable clone or sequence for an scFv was not very easy. Once that was to hand, however, it would not take long:

> "… If you got the clone, someone sent you that, and you knew its sequence, then to just put it into a phage vector or a phagemid vector and try the experiment and see what happened we are talking of months, a few months, six months maybe. It depends on the skills and how well things go, but that order of magnitude. Once you have got the clone, it is not a long period to where you are first testing whether it has worked or not."

417. Dr Teillaud also accepted that the skilled team would conclude, even taking into account what was said in Parmley & Smith, that Professor Smith considered that it was worth trying:

> "Q. …. The person listening at the Banbury Conference, I would suggest to you, if they knew about Parmley and Smith or saw the reservation in Parmley and Smith about the size of the insert would have said to themselves, whatever Dr. Smith has done in the past 18 months, something must have encouraged him to think that it was worthwhile to try an antibody fragment of 750 base pairs.
>
> A. Yes, indeed, it is likely so. It is why I said it was surprising to me that he did not make any experiment in this interval of time about antibodies. …"

418. Counsel for MedImmune submitted that a similar question to Professor Brammar was put on a wrong basis, since Professor Smith accepted that he had done no work on antibody phage display since November 1988 and would have communicated this to the audience. I do not accept this submission. As the audience would have appreciated, Professor Smith had done work on phage display since Parmley & Smith was published in September 1988, albeit not antibody phage display. In particular, he had done the work on an epitope library described in Scott & Smith, which he summarised in his talk. Indeed, it is probable that he would have mentioned that that paper was in press since he had submitted the manuscript only a month before (on 27 March 1990). Furthermore, a comparison of what Professor Smith said in his talk and

Parmley & Smith would have revealed to the skilled team that (as one would expect) his *thinking* had moved on between September 1988 (or more, accurately June 1988, when Parmley & Smith was submitted) and April 1990, as indeed it had (see below). Again, I consider that it follows that the skilled team would have a reasonable expectation of success if they were to try the experiment themselves.

419. Dr Teillaud also agreed that the experiment was not a lot of work:

> "Q. Let me suggest this. The first thing you would want to try would be to see whether you could successfully insert either a VH or an scFv fragment.
> A. You mean in terms of molecular DNA, yes. To insert, I mean, to insert into the sequence of the phage, also phagemid.
> Q. Exactly, in the way that Parmley and Smith did, except now you are inserting an antibody fragment rather than an epitope.
> A. Yes.
> Q. How much work is involved in doing that?
> A. It is a cloning. Once you know the site, you have to think about the cloning site. I guess it is not a lot of work to do that."

420. Subject to consideration of the secondary evidence relied on by each side, the conclusion which I draw from the evidence is that Professor Smith's talk at the Banbury Conference would have given the skilled team a reasonable expectation of success within a reasonable time. Not merely did he explicitly propose antibody phage display, but in addition he said that he was going to do the experiment. Furthermore, he addressed the concerns which arose out of Parmley & Smith and gave reasons as to why he nevertheless considered the experiment worth carrying out, as well as explaining potential solutions if problems were encountered. Finally, his tone was one of encouragement.

421. Counsel for MedImmune pointed out that there was no evidence that any of the other attendees at the Banbury Conference went away and tried antibody phage display and submitted that this was "a significant hole in Novartis' case". I am not persuaded by this. Banbury was attended by a small number of people, approximately 30. Moreover, as counsel for MedImmune himself pointed out in another context, although the focus of the conference was "cloning the immune response", some of those attending had wider interests. Furthermore, at least one of the attendees, namely Dr Huse, had already had the idea of antibody phage display. Yet further, another attendee, Dr Angray Kang, had either already started work on it or started shortly afterwards, as I shall discuss below. In any event, the fact that Professor Smith told the audience that he was going to do the experiment would be a sufficient explanation for none of them duplicating his effort.

422. *Secondary evidence: Professor Smith's own work.* Counsel for MedImmune relied strongly upon Professor Smith's own work as evidence of non-obviousness, and in particular of the absence of a reasonable prospect of success within a reasonable time. There are four main aspects to this. First, the circumstances in which Professor Smith had the idea, and in particular what he said in a grant application that he made at that

time. Secondly, his own thought processes at the time of the Banbury Conference. Thirdly, what happened when he actually did the experiment. Fourthly, what he said in a declaration submitted to the USPTO. I will consider these in turn.

423. So far as the first point is concerned, Professor Smith explained that he had read Bird within days of publication on 21 October 1988. At that time, he was well aware of the work of Dr Winter's group at the MRC/CAT, Professor Lerner's group at Scripps and others to express recombinant antibody genes in bacterial hosts. One of the goals of that work was to be able to screen libraries of recombinant antibodies for the ability to bind any given antigen. The recombinant antibody constructs in that work were large (at least about 500 amino acids) and involved two polypeptide chains. Single-chain antibodies, in contrast, were much shorter (only about 250 amino acids) and comprised only one polypeptide chain. It was immediately apparent to Professor Smith that such simplified antibodies might be successfully displayed on phage display vectors such as fUSE5. Libraries of such constructs might be screened with immobilised antigen selectors, using the same affinity-selection approach that had worked in the case of phage peptide libraries. Affinity selection would substantially expand the scale on which recombinant antibodies could be screened compared to the screening approaches then in use. This provided a strong motivation to use larger inserts than Professor Smith had used in Parmley & Smith, and he did not consider the recommendation he had made there against using larger inserts to be a deterrent.

424. As a result, Professor Smith added new sections to a revised grant application that he had just submitted to the US National Institutes of Health in time for the 1 November 1988 deadline. Professor Smith had previously submitted a grant application for his epitope library research which had been refused in June 1988, and his revised proposal attempted to address various concerns raised by the reviewers of the earlier application. In the revised application he stated in the summary:

> "I also hope to construct a library of fusion phage displaying cloned antibodies with a vast array of different antigen-binding specificities, so that clones encoding antibodies of defined specificity can be affinity-purified with antigen. This way of obtaining monoclonal antibodies would be much easier than present methods …"

425. In the introduction to his research plan at pages 11-12 of the application, Professor Smith addressed the concerns which had been raised by the reviewers of his previous application, and concluded:

> "Finally, let me plea for 5 years in return for a much curtailed budget. It's obvious that I'll need that long, especially considering that my laboratory will have been unfunded for over a year and that I'll have to train a new technician. Perhaps the project seems 'speculative,' but what can I reasonably be expected to be able to report that will make it decisively less so after 2 years' funding (when I'll be forced to renew if I get only 3 years) - even granted that my vision is thoroughly sound in all essentials and that I undertake the task with commendable

competence and energy, as indeed I will?"

426. Later in the application, at pages 27-30, he discussed his proposal to create "a library of 'infectious antibodies'". Having outlined what he proposed to do, he set out "responses to various problems I may encounter". In this section he discussed (i) cleavage with trypsin, (ii) renaturation, (iii) proteolysis of pIII fusion proteins (suggesting that "natural proteolysis might have the salutary effect of removing improperly folded scab [i.e. scFv] moieties") and (iv) enhancing performance with phage and host mutations. He went on to outline a "critical test" involving cloning a number of scFvs of known specificity to make a mock library and biopanning for one. He concluded by describing the construction of a diverse library and biopanning that with a wide range of antigens, saying this was "probably 5 years in the future".

427. Counsel for MedImmune submitted that these statements showed that Professor Smith was planning a substantial, lengthy and speculative research project, and thus that he himself did not have a reasonable expectation of success within a reasonable time frame. I do not accept this. These statements were made on 1 November 1988, some 18 months before Professor Smith's talk at the Banbury Conference. By the time of the Conference, he had not only done further work on phage display (namely the Scott & Smith work), his grant application having been successful, but also he had had more time to think his idea through. Moreover, the statements must be read in context. As can be seen from the quotation in paragraph 425 above, and is clearer still from the passages which precede it, Professor Smith was frustrated by refusal of his previous application, which had resulted in his laboratory being unfunded for over a year. It is clear that he did not think that the concerns raised by the reviewers had been scientifically well-founded. Although Professor Smith accepted in cross-examination that the project described in the application was speculative, at least so far as the antibody phage display was concerned, it appears from the document that it was the reviewers who had described his epitope library proposal as speculative, and that at the time Professor Smith did not agree with this. Finally, the time scale envisaged is clearly driven both by Professor Smith's need for funding, particularly given the consequences of the refusal of the previous application, such as the need to train a new technician, and by the "much curtailed budget", which only allowed for one research assistant. It also reflects the fact that he intended first to work on the epitope library, as indeed he did, and that at the end of the five years he hoped to be screening large libraries with multiple antigens.

428. Turning to Professor Smith's thought processes at the time of Banbury Conference, Professor Smith accepted that he had harboured a number of concerns about what he was proposing to do. The two main ones concerned folding and non-specific stickiness. With regard to folding, he said during the interview that this "loomed large in his thinking". It remains the case, however, that he specifically addressed this concern in his talk, that it did not discourage him from carrying out the experiment and that he conveyed to the audience that it did not discourage him. Non-specific stickiness was another matter which he had in mind as being a potential challenge. But he was not sufficiently concerned about this to mention it either in Parmley & Smith or in his talk.

429. As for the experiment itself, Professor Smith had hoped to have started it by the time

of the Banbury Conference, but it had taken longer than expected to get the scFv clone from Genex because of delays in getting a strain transfer agreement finalised by the parties' lawyers. The project was started by a graduate student in the summer of 1990, and then carried on by Professor Smith himself with the assistance of a technician. Counsel for MedImmune understandably relied on Professor Smith's explanation that he did not assign it to a PhD student because it was "pretty speculative" whereas "you want to give PhD projects that are a little surer than this was". In some ways this is the best piece of evidence in MedImmune's favour, but again it must be taken in context. I understood Professor Smith to mean that he would want to assign a project to a PhD student which was more clearly certain of success. (It appears that he did not have a post-doctoral student available to do the work at the time.) Professor Smith accepted that he could not confidently say in advance, "Oh yes, that is going to work"; but equally he was clear that he thought that there was reasonable likelihood of success.

430. Counsel for MedImmune also relied on the results of a phage antibody experiment which Professor Smith carried out in early 1991. (It should be noted that four laboratory notebooks containing details of Professor Smith's work during this period were lost by the US postal service later in the 1990s. This is one of the few experiments for which some records survive.) This experiment involved the anti-fluorescein scFv clone which Professor Smith had obtained from Genex and a mutant which did not bind fluorescein. Professor Smith panned these with fluorescein and rhodamine. The experiment was a success in that it showed that the fusion phage with the anti-fluorescein scFv was able to bind specifically to fluorescein rather than rhodamine, while the mutant did not bind to fluorescein.

431. Professor Smith's evidence was that he was disappointed with the results, in that the discrimination between specific and non-specific binding was only about 100-fold. Professor Smith was disappointed because he had obtained higher levels of discrimination with his phage epitopes: he had obtained 1000-fold enrichment in Smith, and up to a million-fold subsequently. The fact remains, however, that the experiment worked. Furthermore, the claims of the Patents do not require any particular level of discrimination. Indeed, the result is very comparable to Examples 4 and 6 in the Patents, in both of which there is quite a lot of background noise. Although the experiment is not strictly comparable to Example 10, the level of enrichment achieved in the latter after one round of purification was only one order of magnitude better. Moreover, the first round experiment did not work when the initial ratio was $1:2.5 \times 10^6$, but only when it was lower. In saying this, I am not overlooking the fact that Professor Smith's experiment did not quite arrive at implementing the core inventive concept, since it does not appear to have involved selection by binding from a population with a range of specificities (or at least it is not clear that it did). It nevertheless demonstrated the principle of antibody phage display.

432. Furthermore, Professor Smith did not pursue the work further because by then McCafferty had been published. In this regard he commented in his witness statement:

> "I was satisfied that antibody phage display … was being pursued by the CAT group and by others, including the group

> at Scripps. I also did not regard myself as having any claim to scientific priority in the field of phage antibodies, because I considered phage display of antibodies to be a fairly obvious extension of the newly-invented single-chain antibodies and our published work on phage display in general (especially … Parmley and Smith …) to the ongoing work by Greg Winter's group, Lerner's group at Scripps, and others, whose efforts to 'clone the immune response' were very prominent in the community of molecular biologists by the end of 1988.
>
> I have been asked whether I would have continued work on phage display of antibodies were it not for the fact that CAT and Scripps were also working on it. I am sure that I would have done so, as I believed that the strategy was sound and the approach had enormous potential."

433. This takes me to the final point. Counsel for MedImmune relied on a declaration made by Professor Smith on 30 June 1995 in support of US Patent Application 08/322,352 entitled "Binding Molecules Which are Displayed on the Surface of Filamentous Phage" filed on 13 October 1994, in respect of which Professor Smith was a co-inventor and co-applicant. It appears that this application was a continuation in part of an application filed by Charles Ladner and others of Genex in February 1987. Subsequently, for reasons that are unclear, Professor Smith was asked by Genex, and agreed, to become a co-applicant. In about 1991, Genex's patent portfolio was acquired by Enzon, Inc. The declaration was submitted by Enzon's attorneys in connection with a response to a rejection of the application by the examiner. Some time after 1995 the application was abandoned. For that reason, as I understand it, the application remains unpublished.

434. In the declaration, Professor Smith expressed the opinion at paragraph 2 that Smith and Parmley & Smith in combination with US Patent No. 5,132,405 "would neither have taught nor suggested the claimed invention to one of skill in the art for the reasons stated below". He went on to discuss the disclosure of Huston, Smith and Parmley & Smith. When discussing Parmley & Smith, he emphasised the recommendation to use fragments of 100-300 bp. In paragraph 13 he concluded:

> "The conformational constraint posed upon an SCA [i.e. scFv] not in solution but on the surface of a filamentous phage, the expected instability of an insert of the length of a SCA and observed degradation of the products of such inserts, as well as the possibility of periplasmic degradation, rendered the success to express a functional SCA on the surface of a filamentous phage quite unpredictable at the time of filing. No reasonable expectation of success was available from my work on antigen fusions in 'Smith and 'Parmley & Smith'."

435. The date as at which Professor Smith was expressing this opinion is unclear. The end of the first sentence refers to "the time of filing", which would appear to mean February 1987, yet Parmley & Smith was not published until September 1988.

Professor Smith accepted, however, that the declaration accurately represented his thinking prior to reading Bird in late October 1988. As I understand his evidence, the reason why he expressed a different opinion in the passage from his witness statement in the present case which I have quoted in paragraph 432 above is that that passage was considering the position after the publication of Bird, and indeed as at late 1990.

436. As I have already said, I consider that this declaration, and in particular paragraph 13, supports the conclusion which I have reached in relation to obviousness over Parmley & Smith. In my judgment, however, it does not assist MedImmune in relation to obviousness over Professor Smith's talk at the Banbury Conference. Nothing is said about that talk in the declaration; as discussed above, the talk went further than Parmley & Smith in a number of respects; and it addressed the concerns expressed in Parmley & Smith.

437. *Secondary evidence: reaction to the invention*. MedImmune also relied upon evidence as to the reaction to the invention as supporting the view that it was not obvious. The principal evidence relied on by counsel for MedImmune in this regard, however, was Dr Teillaud's first report. I cannot place much weight on Dr Teillaud's own view that the invention was "a major development and breakthrough", however, given that he was not in the field at the time and the manner in which he came into it. Dr Teillaud said that he believed that this was a view shared by many immunologists, but he gave no details of this. Still less did he exhibit any contemporaneous reactions. My impression from the evidence as a whole is that McCafferty was seen as a significant paper and that antibody phage display has proved to be a useful technique. I am not persuaded, however, that either point demonstrates that the claimed inventiveness were not obvious in the light of Professor Smith's talk at the Banbury Conference.

438. *Secondary evidence: other people who had the idea.* Novartis relied on the fact that a number of individuals or groups had the idea of antibody phage display at around the same time. MedImmune did not dispute this, but contended that they were all inventive people who had applied for patents in respect of the invention.

439. It appears from the evidence that one of the first people to have the idea was Dr Huse. As I have said, however, Novartis accept that he was an inventive individual. Furthermore, he arrived at the invention without the benefit of Parmley & Smith, let alone Professor Smith's talk at the Banbury Conference. It follows that the fact that he had the idea does not show that the invention was obvious over the latter. On the other hand, I do not regard the fact that he applied for a patent as significant given his explanations as to the reason for the application and as to what he regarded as inventive within it.

440. The second person who had the idea was Professor Smith. On the evidence, I consider that he too was an inventive person. As I have discussed, he had the idea in the light of his own work on phage display down to Parmley & Smith combined with Bird. Again, it follows that the fact that he had the idea does not show that the invention was obvious over his talk at the Banbury Conference. On the other hand, I again do not regard the fact that he joined in a patent application as significant given that the original application was filed by Genex in February 1987. I have already considered Professor Smith's declaration in support of the application.

441. The third group of people who had the idea was, of course, the inventors, and in particular the sub-set who published McCafferty. There is no evidence before me as to the circumstances in which they arrived at the idea. I note that McCafferty was submitted on 29 August 1990. As one would expect, Professor Smith's three papers are among the references cited. So too are Ward and Huse. One cannot draw any conclusions from this, however.

442. The fourth group of people who had the idea were Professor Dübel and his collaborator Frank Breitling. Professor Dübel gave evidence about this. At the material time, he and Frank Breitling were both PhD students. Professor Dübel was studying cell differentiation pathways and developmental biology of hydra at the University of Heidelberg, while Dr Breitling was working on tubulin, and later kinases and cell cycle proteins, at the DKFZ. Dr Breitling introduced Professor Dübel to Smith and Parmley & Smith, and they came up with the idea that, instead of epitopes, antibodies could be screened in this way. Professor Dübel described this in his witness statement as follows:

> "In 1989, Frank Breitling and I decided that phage display might be a good method for screening large libraries of antibody genes for a particular specificity. After George Smith's work displaying epitopes on phage for screening of epitope libraries with specific antibodies, the idea that antibodies, instead of epitopes, could be screened in this way seemed to us to be a straight-forward step to take at the time. All the essential elements of the techniques we proposed to use had already been published. For example, Plückthun and Skerra had already shown expression of soluble antibody fragments in E.coli (assembly of Fv fragments in the periplasm, and later, Fab assembly in the periplasm)."

443. Professor Dübel and Dr Breitling began laboratory work in August 1989. They made various preparations, such as designing and building a PCR machine, designing and creating oligonucleotide primers, isolating RNA from human blood and creating a cDNA library. They also requested antibody clones from both Dr Plückthun and Dr Winter, although they had no idea that anyone else was working on antibody phage display. Dr Winter sent them an anti-lysozyme scFv clone, although it was a lower affinity variant than the one they had requested. They used this as a model antibody in their experiments.

444. By February 1990 Professor Dübel and Dr Breitling had produced a Fab fragment library, but they failed to isolate antibodies from these libraries that bound antigen using plaque lift. After further experiments in spring 1990, they turned their attention to scFv fragments and phage display.

445. Using anti-lysozyme antibody genes, they created an scFv by inserting a linker of their own design between the heavy and light chain variable regions. By the middle of August 1990, they had created a phagemid vector and demonstrated the production of the scFv-pIII fusion protein. The phagemid vector was based on pUC119 with additional sequences coding for the scFv and gene III protein from M13 phage

incorporated. Following the teaching of Parmley & Smith, they inserted the antibody genes at 5' end of the gene III sequence, so that the scFv was expressed at the N terminus of the gene III protein. By January 1991 they had successfully enriched the correct phage out of a large excess of other phage on a matrix presenting the antigen.

446. Shortly after completing these experiments, Professor Dübel and Dr Breitling together with three co-authors submitted a paper describing them to the journal *EMBO*. *EMBO* rejected the paper on the basis that the same experiments had just been published in McCafferty. As Professor Dübel commented:

> "We felt that this was not correct and perhaps a little unfair, since our paper reported use of a phagemid vector instead of a phage vector which we considered important for library screening since the presentation of the antibody fragment was regulated independently from phage production, and we expected this to be an advantage in regard of library propagation. In our view the use of phagemid techniques made library creation more efficient and easier, and was a different implementation of the phage display technology which had not been published for antibodies before."

Accordingly, they re-submitted the paper to *Gene* in February 1991, and it was published in August 1991.

447. Counsel for MedImmune submitted that Professor Dübel and Dr Breitling were not representative of the skilled team in terms of their background and experience. I do not accept this. It is true that they were new to the field of antibody engineering and relatively inexperienced, but Professor Dübel's evidence was that he had read all the papers which I have found to be common general knowledge. In addition, they had read Professor Smith's two papers.

448. Counsel for MedImmune also submitted that Professor Dübel was of an inventive disposition. I accept this submission, which is supported by the fact that he is a co-inventor of 21 different patent families.

449. In his witness statement Professor Dübel expressed the view that phage display of antibody fragments had been an obvious idea prior to publication of McCafferty. He maintained this view in cross examination. Against this, counsel for MedImmune relied on several strands of evidence as showing that the idea had not been obvious to him at the time.

450. The most important of these was that Professor Dübel and his collaborators had applied for a patent for antibody phage display. The priority application was filed in Germany on 8 July 1991, and International Application No. PCT/EP92/01524 was filed on 7 June 1992 (subsequently published as WO 93/01288). The resulting family of patents includes European Patent No. 0 547 201, which as noted above was revoked pursuant to an opposition by CAT, and US Patent No. 5,849,500 entitled "Phagemid for antibody screening", which has been licensed. When this point was put to him, however, Professor Dübel's response was as follows:

> "Q. Do you see any inconsistency between saying you thought the idea was obvious and now being an inventor on a patent to antibody phage display which indeed has been licensed out?
>
> A. Yes, but we know there are at least three other groups working on the same thing and also other patents were on the same thing made at the same time. You can see from that that the idea obviously was around and we were not the only ones to work on that. Actually we were very late with our patent as far as I remember from what I know about the other patents. I do not see the connection between the patent, because the patent is a kind of commercial protection law and it not necessarily has to do with the academic process of getting the idea, the proof of principle."

I accept that Professor Dübel regarded the idea as an obvious one, but it does not necessarily follow that the idea would have been obvious to the skilled team.

451. My conclusion in relation to Professor Dübel's evidence is that it would support Novartis' case that the claimed inventions are obvious over Parmley & Smith were it not for that fact that Professor Dübel is inventive. Given that Professor Dübel was not present at the Banbury Conference, his evidence does not directly support Novartis' case that the claimed inventions are obvious over Professor Smith's talk. In my view, however, it does provide some support for the proposition that the skilled team would have a reasonable expectation of success within a reasonable period of time in the light of that talk. In this regard, it is less significant that he is inventive.

452. The final group of people who had the idea were Dr Kang and his collaborators at Scripps. Dr Kang was appointed as an Assistant Professor of Molecular Biology at Scripps in July 1990, having spent some time there as a post-doctoral student previously. He is now a Reader in the Molecular and Applied Biosciences Department in the School of Life Sciences at the University of Westminster. Novartis submitted a witness statement from Dr Kang which dealt very briefly with this topic, and MedImmune did not require him to attend for cross-examination. All Dr Kang says that is that, in 1990 and early 1991, he worked in a team in the area of phage display and antibody engineering. Specifically, the team worked on assembling combinatorial Fab libraries on phage surfaces using phagemid vectors with helper phage rescue to select combinatorial Fab fused to gene VIII protein. This work was completed by late February 1991 and is described in a paper submitted on 6 March 1991: Kang et al, "Linkage of recognition and replication functions by assembling combinatorial antibody Fab libraries along phage surfaces", *Proc. Natl. Acad. Sci. USA*, 888, 4363-4366 (1991). As one would expect, among the cited references are Parmley & Smith and Scott & Smith. So too are Skerra & Plückthun, Better, Orlandi, Sastry, Ward and Huse.

453. Dr Kang was one of the attendees at the Banbury Conference, but there is no evidence as to whether he attended Professor Smith's talk or, if so, what impact, if any, it had on the subsequent work of Dr Kang and his colleagues.

454. As counsel for MedImmune pointed out, Dr Kang and two of his colleagues also

applied for a patent. A priority application was filed in the USA on 10 April 1991, and International Application No. WO 92/18619 was filed on 10 April 1992 (subsequently published as WO 92/18619).

455. It is difficult to draw any firm conclusion from the work of Dr Kang and his colleagues in the absence of further evidence. The most I think one can say is that it lends some slight support to the notion that the art was moving in the direction of antibody phage display.

456. *Overall conclusion*. Taking all of the different factors and evidence discussed above into account, my conclusion is that the claimed inventions were obvious in the light of Professor Smith's talk at the Banbury Conference. Professor Smith explicitly proposed antibody phage display, and the skilled team would have had a reasonable expectation that this would succeed in a reasonable period of time.

457. I note that the Opposition Division rejected the allegation that 877 was obvious over Professor Smith's talk at the Banbury Conference. This was on the ground, however, that "the contents of the oral disclosure by Dr Smith in April 1990 have not been sufficiently substantiated": see [17.2]. It appears that the only evidence before the Opposition Division on this point was a declaration of Dr Plückthun (which is not in evidence before me) and Professor Smith's grant application. By contrast, in the present case I have had the benefit of detailed evidence from Professor Smith. Furthermore, in the light of that evidence, MedImmune did not dispute the content of the disclosure.

Insufficiency

The law

458. A patent is invalid "if the specification does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art" (section 72(1)(c) of the 1977 Act). Unlike section 32(1)(f) of the Patents Act 1949, the 1977 Act does not provide that it is a ground of invalidity that "any claim of the complete specification is not fairly based on the matter disclosed in the specification". This is because no such ground is provided for by the EPC. Nor has the position changed in this respect following the coming into force of EPC 2000.

459. The House of Lords has three times had to consider the extent to which a patent may be invalid on the ground of insufficiency as a result of excessive breadth of the claims, rather than a result of an inability on the part of the skilled person to carry out the invention in at least one way given the description of it in the patent and common general knowledge (sometimes called "classical insufficiency").

460. The first case was *Biogen Inc v Medeva plc* [1997] RPC 49. In that case the patent in suit related to a DNA sequence coding for hepatitis B virus ("HBV") antigen. It claimed priority from a priority document referred to as "Biogen I". The patentee accepted that the patent was invalid if the claim to priority failed. Claim 1 was as follows:

> "A recombinant DNA molecule characterised by a DNA

> sequence coding for a polypeptide or a fragment thereof displaying HBV antigen specificity, said DNA sequence being operatively linked to an expression control sequence in the recombinant DNA molecule and being expressed to produce a polypeptide displaying HBV antigen specificity when a suitable host cell transformed with said recombinant molecule is cultured, the transformed host cell not producing any human serum proteins and any primate serum proteins other than the polypeptide displaying HBV antigen specificity."

461. The claim was to a product ("a DNA molecule") identified partly by the way it had been made ("recombinant") and partly by what it did (the words following "characterised by"). It generalised in two ways what had been specifically disclosed in Biogen 1, first the results achieved and secondly the method that had been used. The patent did not disclose any method for making the antigens which had not been disclosed in Biogen 1.

462. At the date of Biogen 1, the only available source of DNA from HBV was the infective particle itself (the "Dane particle"). Biogen 1 disclosed that, because of lack of information about the coding sequences, fragments of Dane particle DNA were made with restriction enzymes chosen simply on the basis that they were likely to cleave the particle into the largest fragments. Using a standard plasmid, a recombinant DNA molecule had been made from these large fragments which was then expressed by conventional means in a conventional bacterial host. The patent, however, claimed any recombinant DNA molecule which expressed the genes of any HBV antigen in any host cell, and any method of making a DNA molecule which would achieve the necessary expression.

463. Once the DNA sequence of the Dane particle had become known, no one would have chosen restriction enzymes on the basis of cleaving the DNA into the largest fragments. Enzymes would be chosen to digest the sites closest to the relevant gene or the part of the gene which expressed an antigenic fragment of the polypeptide. That was what the defendant had done.

464. Aldous J held that the patent was valid and infringed. The Court of Appeal held that the patent was invalid because (i) it was not entitled to priority from Biogen I, (ii) the invention was obvious at the date of Biogen I anyway and (iii) the patent was insufficient. The House of Lords reversed the Court of Appeal's conclusion with regard to obviousness, but upheld its conclusions with regard to priority and insufficiency.

465. The principal speech was given by Lord Hoffmann, with whom Lords Goff of Chieveley, Browne-Wilkinson, Mustill and Slynn of Hadley agreed. For present purposes, I can concentrate on three key passages. Each of these deals with the question of priority, but Lord Hoffmann explained that the essential issue and his reasoning were the same in relation to insufficiency.

466. The first passage is at page 48 line 40 – page 49 line 22:

> "In fact the [Technical] Board [of Appeal of the EPO] in [case

> T292/85] *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.'"

467. The second passage is at page 50 line 36 – page 51 line 8:

> "But the fact that the skilled man following the teaching of Biogen 1 would have been able to make HBcAg and HBsAg in bacterial cells, or indeed in any cells, does not conclude the matter. I think that in concentrating upon the question of whether Professor Murray's invention could, so to speak, deliver the goods across the full width of the patent or priority

> document, the courts and the E.P.O. allowed their attention to be diverted from what seems to me in this particular case the critical issue. It is not whether the claimed invention could deliver the goods, but whether the claims cover other ways in which they might be delivered: ways which owe nothing to the teaching of the patent or any principle which it disclosed.
>
> 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."

468. The third passage is at page 51 line 42 – page 52 line 22:

> "I return therefore to consider the technical contribution to the art which Professor Murray made in 1978 and disclosed in Biogen 1. As it seems to me, it consisted in showing that despite the uncertainties which then existed over the DNA of the Dane particle - in particular, whether it included the antigen genes and whether it had introns - known recombinant techniques could nevertheless be used to make the antigens in a prokaryotic host cell. As I have said, I accept the judge's findings that the method was shown to be capable of making both antigens and I am willing to accept that it would work in any otherwise suitable host cell. Does this contribution justify a claim to a monopoly of *any* recombinant method of making the antigens? In my view it does not. The claimed invention is too broad. Its excessive breadth is due, not to the inability of the teaching to produce all the promised results, but to the fact that the same results could be produced by different means. Professor Murray had won a brilliant Napoleonic victory in cutting through the uncertainties which existed in his day to achieve the desired result. But his success did not in my view establish any new principle which his successors had to follow if they were to achieve the same results. The inventive step, as I have said, was the idea of trying to express unsequenced eukaryotic DNA in a prokaryotic host. Biogen 1 discloses that the way to do it is to choose the restriction enzymes likely to cleave the Dane particle DNA into the largest fragments. This,

> if anything, was the original element in what Professor Murray did. But once the DNA had been sequenced, no one would choose restriction enzymes on this basis. They would choose those which digested the sites closest to the relevant gene or the part of the gene which expressed an antigenic fragment of the polypeptide. The metaphor used by one of the witnesses was that before the genome had been sequenced everyone was working in the dark. Professor Murray invented a way of working with the genome in the dark. But he did not switch on the light and once the light was on his method was no longer needed. Nor, once they could use vectors for mammalian cells, would they be concerned with the same problem of introns which had so exercised those skilled in the art in 1978. Of course there might be other problems, but Biogen 1 did not teach how to solve them. The respondents Medeva, who use restriction enzymes based on knowledge of the HBV genome and mammalian host cells, owe nothing to Professor Murray's invention."

469. The key points which emerge from these passages are as follows:

i) A claim will be invalid for insufficiency if the breadth of the claim exceeds the technical contribution to the art made by the invention. As Lord Hoffmann confirmed elsewhere in his opinion, it follows that it is not necessarily enough to disclose one way of performing the invention in the specification.

ii) The breadth of the claim will exceed the technical contribution if the claim covers ways of achieving the desired result which owe nothing to the patent or any principle it discloses. Two classes of this are where the patent claims results which it does not enable, such as making a wider class of products when it enables only one and discloses no principle to enable the others to be made, and where the patent claims 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.

iii) The patent in *Biogen v Medeva* was invalid because it was an example of the second class of objectionable claim.

470. The second case was *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2004] UKHL 46, [2005] RPC 9. In that case, Kirin-Amgen was the proprietor of a patent relating to the production of erythropoietin ("EPO") by recombinant means. Claim 19 was as follows:

> "A recombinant polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in Table VI or Table V or any allelic variant or derivative thereof … characterised by being the product of eucaryotic expression of an exogenous DNA sequence and which has higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources."

471. Kirin-Amgen alleged that Hoechst had infringed this claim by importation of recombinant EPO made by TKT by a process which was different to that described by the specification. Hoechst alleged that claim 19 was invalid for insufficiency on four grounds, the first of which was that, if the claim covered EPO made by a form of recombinant DNA technology, it was insufficient because the specification did not enable TKT's process. Neuberger J (as he then was) held that claim 19 was invalid for insufficiency, although not on this ground. His conclusion was reversed by the Court of Appeal, but reinstated by the House of Lords. The leading speech was again given by Lord Hoffmann, with whom Lords Hope of Craighead, Rodger of Earlsferry, Walker of Gestingthorpe and Brown of Eaton-under-Heywood agreed.

472. Lord Hoffmann held that claim 19 on its true construction did not cover EPO made by TKT's process. Accordingly, the first ground of insufficiency did not arise. Lord Hoffmann nevertheless discussed it. Although his remarks on this point are obiter, they have considerable persuasive authority. His view was that, if the claim on its true construction had covered TKT's process, "the breadth of claim objection may well have been a good one". His reasons were as follows:

> "112. [The passage in Lord Hoffmann's speech in *Biogen v Medeva* referring to a 'principle of general application'] 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.
>
> 114. In my opinion the facts did not support the application of this principle. Assuming the claims can be read, as the judge thought, to include any way of making EPO by recombinant

> DNA technology, the specification does not disclose a way of making it in sufficiently general terms to include the TKT process. It discloses only how to make EPO by introducing exogenous DNA coding for EPO into a host cell. The TKT method is not a version of this process which, although untried, could reasonably be expected to work just as well. It is different."

473. The third case was *Generics (UK) Ltd v H. Lundbeck A/S* [2009] UKHL 12, [2009] RPC 13. In that case, Lundbeck was the proprietor of a patent for escitalopram, which was the (+) enantiomer of citalopram, a known selective serotonin reuptake inhibitor. Escitalopram had superior properties. Claim 1 was a product claim and was directed to the (+) enantiomer and salts thereof. Claim 3 was to a pharmaceutical composition in unit dosage form containing the compound of claim 1. Generics and other attacked the validity of the patent on the grounds of lack of novelty, obviousness and insufficiency. Kitchin J rejected the allegations of lack of novelty and obviousness, but held claims 1 and 3 of the patent were invalid for insufficiency because they claimed the enantiomer made by any method, but the specification disclosed only two ways of making it. The Court of Appeal upheld his conclusions on lack of novelty and obviousness, but held that claims 1 and 3 were not invalid on the ground of insufficiency. This conclusion was upheld by the House of Lords.

474. The principal speeches were given by Lords Walker of Gestingthorpe, Mance and Neuberger of Abbotsbury. Lord Phillips of Worth Maravers said that they reached the same conclusion for the same reasons, and agreed with all of them. Lord Scott of Foscote agreed with Lord Neuberger. Lord Walker said he understood his reasons to be essentially the same as those of Lords Mance and Neuberger, and Lord Neuberger said that he understood that his reasons to be effectively the same as those of Lords Walker and Mance. In these circumstances, it is not easy to quote particular passages from just one opinion as representing the reasoning of at least a majority of the panel.

475. For present purposes, I think the House's reasoning can be summarised as follows:

i) The House agreed with Lord Hoffmann in *Biogen v Medeva* that it was important for United Kingdom patent law to be aligned, so far as possible, with the jurisprudence of the EPO. Furthermore, the House also agreed with Lord Hoffmann that the statement of principle which he quoted from *Exxon/Fuel oils* correctly stated the law (see Lord Walker at [14], [19], [35]-[39], Lord Mance at [46]-[47], [55], Lord Neuberger at [83], [87]-[89], [96]-[98]).

ii) The House considered that the instant case was to be distinguished from *Biogen v Medeva* because it was concerned with claim to a single chemical compound whereas *Biogen v Medeva* concerned a product-by-process claim of broad scope (see Lord Walker at [10]-[13], [25]-[28], Lord Mance at [49]-[53], [55], Lord Neuberger at [69], [93]-[95], [98]-[99]).

iii) It was a mistake to equate the technical contribution of the claim with its inventive concept. In the instant case, the technical contribution made by claims 1 and 3 was the product, and not the process by which it was made,

> even though the inventive step lay in finding a way to make the product. It followed that the breadth of the claim did not exceed the technical contribution which the invention made to the art (see Lord Walker at [29]-[34], Lord Mance at [44], [52]-[55], Lord Neuberger at [75]-[78], [98], [101]).

476. In addition to these three decisions of the House of Lords, I was also referred to three decisions of the Technical Board of Appeal and a recent first instance decision in this country. I will consider these in chronological order.

477. The first TBA decision is case T 292/85 *Genentech I/Polypeptide expression* [1989] OJ EPO 275. This decision was cited by Lord Hoffmann in both *Biogen v Medeva* and *Kirin-Amgen v Hoechst* and it was mentioned by both Lord Walker and Lord Neuberger in *Generics v Lundbeck*. It remains a leading case in the jurisprudence of the Boards of Appeal. As can be seen, Lord Hoffmann regarded this as a case where the patent disclosed a principle of general application, and therefore a broad claim was justified. Counsel for MedImmune placed particular reliance upon [3.1.2], in which the Board rejected the suggestion that the skilled person should be able to make embodiments falling within the claims without invention:

> "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. This Board concurs with the decision of another Board (T 68/85 - 3.3.1., *Synergistic herbicides*, OJ EPO 1987, 228) in which the possibility of using functional terminology in claims was approved if 'such features cannot otherwise be defined more precisely without restricting the scope of the invention' and their reduction to practice was not an undue burden. The Board sees no valid reason why this should not be equally true for the field of biotechnology as in other fields of technology. 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."

478. The second decision is case T 923/92 *Genentech/Human t-PA* [1996] OJ EPO 564. Counsel for Novartis relied on the part of the Board's decision dealing with claim 2 according to two auxiliary requests. In both requests, claim 2 was concerned with the preparation of derivatives of an amino acid sequence the subject of claim 1, such derivatives having "human tissue plasminogen activator function". The Board observed that human t-PA was a molecule with multiple functions. The specification contained at least four different definitions of a "human tissue plasminogen activator function". In these circumstances the Board held that the requirement in the claim could be interpreted as covering any of the functions of human t-PA. On this basis the

Board concluded at [27] that these claims were both insufficient and lacking in clarity on the following grounds:

> "This definition shows that the subject matter of claim 2 relates to a vast catalogue of derivatives of human t-PA of unspecified structure having any unspecified function of human t-PA. There is no dispute that the present description provides a disclosure of the production of human t-PA in a recombinant system. However, in the Board's judgement, the examples and the information given are not sufficient to allow a person skilled in the art, using common general knowledge, to perform the invention without undue burden in the whole area claimed, especially in consideration of the broad functional meaning attributed to the quoted parameter. Claim 2 leaves the skilled addressee guessing as to whether any derivative of human t-PA which fulfils only one of the functions typical of this molecule is a derivative meant by the claim. In this respect, the Board, in line with the quoted case law, considers the patent in suit to be insufficient and thus to contravene the requirements of Article 83 EPC. Furthermore, the area covered by the claim is not clearly defined, which is contrary to the provisions of Article 84 EPC."

479. As counsel for MedImmune pointed out, however, the TBA went on to consider a further auxiliary request in which the requirement for "human tissue plasminogen activator function" was defined more specifically as "in particular, it is capable of catalyzing the conversion of plasminogen to plasmin, it binds to fibrin, and is classified as a t-PA based on immunological properties". The Board considered that this limitation dealt with its concerns as to the clarity and sufficiency of the broader claims. With regard to the sufficiency of this claim, the Board held as follows:

> "43. The Appellants object that the disclosure of the present invention is not sufficiently clear and complete for it to be carried out by the skilled person. In particular, they submit that:
> …
>
> (v) Not a single example of a functional derivative is provided in the description of the patent in suit. Though, a wealth of possible derivatives are claimed. This is nothing more than an invitation to carry out a research programme in order to find suitable derivatives of human t-PA (cf. decision T 435/91 supra).
>
> 44. In respect of the above objections, the Board's view is as follows:
>
> ...
>
> (v) When given a basic molecular structure (here: the nucleotide sequence and deduced amino acid sequence of human t-PA)

> and an activity to be tested (here: capability of catalyzing the conversion of plasminogen to plasmin, binding to fibrin, and t-PA's immunological properties), the average skilled person can be expected to be able to prepare without application of inventive skill or undue experimentation generic functional derivatives of the molecule by way of amino acid deletion, substitution, insertion, addition or replacement within the framework of routine trials.
>
> 45. In summary, in the Board's judgement, none of the objections put forward by the Appellants can lead to the conclusion that the disclosure of the claimed subject-matter is not sufficiently clear and complete for it to be carried out by a person skilled in the art. Consequently, the requirements of Article 83 EPC are met by the patent in suit."

480. The third decision is case T 1063/06 *Bayer Schering Pharma AG/Reach-through claim* [2009] OJ EPO 516. This was an appeal by Bayer from a refusal of the application by the Examining Division. The application was founded on an appreciation that soluble guanylate cyclase could be stimulated in a mechanism independent of acting on the enzyme's heme group. A screening method was disclosed which enabled the skilled person to find other molecules that worked in this way. Bayer contended that broad patent protection was appropriate. Claim 1 was a second medical use claim to "Use of compounds, which are also capable of stimulating the soluble guanylate cyclase independently of the heme group in the enzyme, to manufacture medicaments for the treatment of cardiovascular disorders such as angina pectoris, ischaemia and cardiac insufficiency". Various additional limitations were proposed by way of auxiliary requests. The Board upheld the Examining Division's conclusion that the claimed inventions were insufficiently disclosed.

481. The Board's reasoning was based on the fact that the compounds used in the claim were not defined in terms of their chemical structure, their composition or other verifiable parameters, but solely in terms of their capacity to stimulate guanylate cyclase, which the skilled person could only ascertain by means of the screening method disclosed. The essence of the Board's reasoning can be seen from the following passage in [5.2]:

> "… In selecting chemical compounds possessing the necessary capability, all [the skilled person] has to rely on is the information provided in the application in suit. In the absence of any selection rule in the application in suit, not even in the form of a structure-activity relationship on the basis of which he could identity from the outset suitable compound classes, the skilled person must resort to trial-and-error experimentation on arbitrarily selected compounds using the screening method cited in the application in suit to identify within the host of possible alternative compounds those which stimulate the soluble guanylate cyclase independently of the heme group in

> the enzyme. Nor does he have any information at his disposal in the application in suit leading necessarily and directly towards success through the evaluation of initial failures. Nor would the simple structural identification of one suitable compound class of general formula (I) in the application in suit be of any help to the skilled person. To find all the suitable alternatives, he would therefore have to test every conceivable chemical compound for the claimed capability; this represents for the skilled person an invitation to perform a research programme and thus an undue burden …"

482. Counsel for Novartis particularly relied on the following statement at [5.3]:

> "Moreover, the fact that claim 1 is formulated as a 'reach-through claim' [defined earlier by the Board as 'a claim to future inventions based on the one now being disclosed'] would cast doubt on the sufficiency of the invention's disclosure throughout the entire area claimed, since this open-ended formulation as stated above in point 2 is also directed at future inventions based on the present one, i.e. inventions not yet made by the priority date of the application in suit."

This statement must be read in context, however. As can be seen from the word "Moreover", the Board was only proffering this as a supplementary reason for doubting the sufficiency of the claim in circumstances where it had already concluded that the applicant was requiring the skilled person to engage in a research project and claiming any successes he might come up with. It cannot have been intending to say that a claim which covers embodiments the making of which requires invention is necessarily bad for insufficiency, since that would run counter to the well-established jurisprudence of the Boards of Appeal discussed above.

483. In the recent case of *H. Lundbeck A/S v Norpharma SpA* [2011] EWHC 907 (Pat) the patent in suit related to a method of making 5-carboxyphthalide ("5-cbx"). 5-cbx was an intermediate used in the manufacture of citalopram. Claim 22 was for:

> "A process for the synthesis of citalopram, in which a process for the synthesis of [5-cbx] according to claim 1 is contained."

484. Lundbeck applied to revoke the patent on various grounds, one of which was that claim 22 was invalid on the ground of insufficiency. Floyd J rejected this allegation for the following reasons:

> "141. Lundbeck's pleaded case is:
>
> > '(a) the Patent discloses a process for producing [5-cbx] and not a process extending to the production of citalopram;
> >
> > (b) in the alternative, insofar as the Patent discloses how to make citalopram from 5-cbx, it does so only by reference to a method described in International Patent

> Application WO 000243431 and in Italian Patent Application IT1999MI0001724 and not by any other methods. For this reason claim 22 is objectionable insofar as it extends to other ways of making citalopram from 5-cbx.'

142. Lundbeck elaborated the first point in the following way. Claim 22 is what Lundbeck call a 'reach-through' claim. This is intended to convey the notion that the inventive concept of the claim lies in how to make 5-cbx, not in how to make citalopram from 5-cbx. Lundbeck point out that, although the addition of the step of making citalopram narrows the claim in some respects, it enables Infosint to complain of the importation of citalopram made from 5-cbx abroad, when this would not have been possible if the patent only had claims to a process for making 5-cbx. Lundbeck submits that the monopoly in these circumstances extends beyond the contribution to the art.

143. I cannot accept this submission. The technical contribution of claim 22 is making citalopram via 5-cbx made by the process of claim 1. So a monopoly which prevents dealings in citalopram made in that way does not extend beyond the contribution. Points made about the consequent scope of protection have nothing to do with insufficiency.

144. The objection pleaded in sub-paragraph (b) relies on passages in the judgment Lord Hoffmann in *Biogen* as subsequently explained by the House of Lords in *Lundbeck v Generics.* Lundbeck rely on the fact that a process claim needs to be sufficient across its entire breadth. The 614 patent discloses only some ways of making citalopram from 5-cbx, not all the ways.

145. Claim 22 is a claim to the general principle of using 5-cbx made by the claim 1 process to make citalopram. Insofar as it relates to making citalopram from 5-cbx it is claimed in entirely general terms. One could reasonably expect the invention to work with any process which produced citalopram from 5-cbx. As such it would have been enabled provided it taught one method by which to make citalopram from 5-cbx. There is no suggestion that the skilled person would have encountered any difficulty in doing so."

The present case

485. Turning to the present case, it is common ground that the claims with which I am concerned are method claims of fairly broad scope, and not claims to a single product. To that extent, the present case is much closer to *Biogen v Medeva* and *Kirin-Amgen v Hoechst* than it is to *Generics v Lundbeck* or even *Lundbeck v Norpharma*.

486. Novartis contends that the breadth of claim 8 of 511 and claim 1 of 777 exceed the technical contribution to the art made by the invention. Novartis characterises the claims as "reach-through claims by stealth", on the basis that they claim the results of research by others extending well beyond the teaching of the specification. Thus in the present case, ranibizumab is alleged to infringe these claims even though (a) the specification does not mention antibodies for the treatment of age-related macular degeneration, (b) the specification does not identify the monoclonal antibody with which Genentech started, (c) the specification does not teach the skilled person how to humanise such a murine antibody, (d) the specification does not teach the team what changes are required to improve the affinity of the humanised antibody and (e) the specification teaches the skilled team nothing about the other techniques which Genentech employed, in particular alanine scanning, crystallography and Biacore (see below for explanations of these matters).

487. Novartis says that its complaint is particularly strong if the claims are construed as MedImmune contends, but runs even if they are construed as Novartis contends. It is convenient to consider the objection on the assumption (contrary to my conclusion) that the claims are to be construed as MedImmune contends. On this basis, as discussed above, the claims extend to post-phage display mutation of (i) identifying a target, (ii) making an antibody library, (iii) screening that library by phage display, (iv) mutating the antibody fragment that is identified by phage display to improve its binding properties and (v) making that mutant in a recombinant system. Novartis says that the technical contribution of the Patents lies solely in step (iii), and that the Patents teach the skilled team nothing about steps (i), (ii), (iv) or (v). Furthermore, Novartis says that, even so far as step (iii) is concerned, the technical contribution made by the Patents is merely that screening by phage display is faster and easier than screening by plaque lift. According to Novartis, there is no evidence to show that the patented method is superior to prior art methods such as plaque lift in terms of finding binding molecules, although MedImmune disputes this.

488. Counsel for Novartis sought to reinforce this case by making two supplementary points. The first is that one of the advantages of phage display is that it makes it easier to screen large libraries. This is only a benefit when screening large naïve (or possibly immunised) libraries for the purpose of identifying new specificities. There is no need to screen a large library if all one is seeking to do is to improve the affinity of an antibody which has already been identified. As discussed below, the largest library screened by Genentech in the development of ranibizumab was 3.2×10^6. This could readily be screened by plaque lift. The second point is that, as all the experts agreed, improving the affinity of an antibody to a given antigen remains a difficult challenge even now.

489. MedImmune contends that the breadth of the claims is justified by the technical contribution made by the invention. MedImmune submits that the invention disclosed the Patents is a principle of general application as explained by Lord Hoffmann in *Biogen v Medeva* and *Kirin-Amgen v Hoechst* and by the TBA in *Genentech I/Polypeptide expression*. Accordingly, it says that the claims are sufficient.

490. A striking aspect of Novartis' case is that Novartis accepts that there is no objection to claim 5 of 511, or even claims 6 and 7, on the ground of insufficiency, yet it contends

that the additional features in claim 8 make it objectionable even though it is common ground that they were common general knowledge. Novartis seeks to make a virtue of this point by arguing that it cannot be right that the effective reach of the claim can be extended by the addition of features which are not inventive. While I have some sympathy with this point (as I shall explain when I come to discuss the issue of infringement), I agree with Floyd J in *Lundbeck v Norpharma* at [142]-[143] that it has little bearing on the issue of sufficiency.

491. In my judgment MedImmune is correct to characterise the invention disclosed in the Patents as a principle of general application. At its core, it is a technique for selecting a binding molecule of interest from amongst a potentially large population of other binding molecules. The technique does not depend on the precise identity of the binding molecule. On the contrary, part of the usefulness of technique is that it can be applied to a diverse range of binding molecules, fragments and derivatives. Nor does the technique depend on the precise application which the user has in mind. Nor does implementation of the technique for the purpose of a new application involve undue burden on the part of the skilled team. I accept that affinity maturation is difficult and potentially burdensome, but the claims do not require the skilled team to carry out affinity maturation at all, nor if they do to improve the affinity of the binding molecule to any particular extent. It follows that the present case is not on all fours with T1063/06, as counsel for Novartis submitted, but clearly distinguishable from it.

492. For these reasons I conclude that neither claim 8 of 511 nor claim 1 of 777 is invalid on the ground of insufficiency.

Added matter

The law

493. A patent is invalid if "the matter disclosed in the specification of the patent extends beyond that disclosed in the application for the patent, as filed" (section 72(1)(d) of the 1977 Act). The test for added matter was stated by Aldous J in *Bonzel v Intervention Ltd (No 3)* [1991] RPC 553 at 574 as follows:

> "The decision as to whether there was an extension of disclosure must be made on a comparison of the two documents read through the eyes of a skilled addressee. The task of the Court is threefold:
>
> (1) To ascertain through the eyes of the skilled addressee what is disclosed, both explicitly and implicitly in the application.
>
> (2) To do the same in respect of the patent [as proposed to be amended].
>
> (3) To compare the two disclosures and decide whether any subject matter relevant to the invention has been added whether by deletion or addition. The comparison is strict in the sense that subject matter will be added unless such matter is clearly and unambiguously disclosed in the application either explicitly or implicitly."

494. More recently, Jacob LJ stated the law in *Vector Corp v Glatt Air Techniques Ltd* [2007] EWCA Civ 805, [2008] RPC 10 as follows:

> "4. In *Richardson-Vicks' Patent* [1995] RPC 568 at 576 I summarised the rule in a single sentence:
>
> > 'I think the test of added matter is whether a skilled man would, upon looking at the amended specification, learn anything about the invention which he could not learn from the unamended specification.'
>
> I went on to quote Aldous J in *Bonzel.* His formulation is helpful and has stood the test of time.
>
> 5. The reason for the rule was explained by the Enlarged Board of Appeal of the EPO in G1/93 *ADVANCED SEMICONDUCTOR PRODUCTS/Limiting feature* [1995] EPOR 97 at [Reasons 9]:
>
> > 'With regard to Article 123(2) EPC, the underlying idea is clearly that an applicant shall not be allowed to improve his position by adding subject-matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying upon the content of the original application.'
>
> 6. Mr Richard Arnold QC provided a clear articulation as to how the legal security of third parties would be affected if this were not the rule:
>
> > 'The applicant or patentee could gain an unwarranted advantage in two ways if subject-matter could be added: first, he could circumvent the "first-to-file" rule, namely that the first person to apply to patent an invention is entitled to the resulting patent; and secondly, he could gain a different monopoly to that which the originally filed subject-matter justified.'
>
> 7. Kitchin J has recently helpfully elaborated upon the *Bonzel* formulation in *European Central Bank v Document Security Systems* [2007] EWHC 600 (Pat), 26th March 2007:
>
> > '[97] A number of points emerge from this formulation which have a particular bearing on the present case and merit a little elaboration. First, it requires the court to construe both the original application and specification to determine what they disclose. For this purpose the claims form part of the disclosure (s.130(3) of the Act), though clearly not everything which falls within the scope of the claims is necessarily disclosed.

> [98] Second, it is the court which must carry out the exercise and it must do so through the eyes of the skilled addressee. Such a person will approach the documents with the benefit of the common general knowledge.
>
> [99] Third, the two disclosures must be compared to see whether any subject matter relevant to the invention has been added. This comparison is a strict one. Subject matter will be added unless it is clearly and unambiguously disclosed in the application as filed.
>
> [100] Fourth, it is appropriate to consider what has been disclosed both expressly and implicitly. Thus the addition of a reference to that which the skilled person would take for granted does not matter: *DSM NV's Patent* [2001] RPC 25 at [195]-[202]. On the other hand, it is to be emphasised that this is not an obviousness test. A patentee is not permitted to add matter by amendment which would have been obvious to the skilled person from the application.
>
> [101] Fifth, the issue is whether subject matter relevant to the invention has been added. In case G1/93, *Advanced Semiconductor Products*, the Enlarged Board of Appeal of the EPO stated (at paragraph [9] of its reasons) that the idea underlying Art. 123(2) is that that an applicant should not be allowed to improve his position by adding subject matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying on the content of the original application. At paragraph [16] it explained that whether an added feature which limits the scope of protection is contrary to Art. 123(2) must be determined from all the circumstances. If it provides a technical contribution to the subject matter of the claimed invention then it would give an unwarranted advantage to the patentee. If, on the other hand, the feature merely excludes protection for part of the subject matter of the claimed invention as covered by the application as filed, the adding of such a feature cannot reasonably be considered to give any unwarranted advantage to the applicant. Nor does it adversely affect the interests of third parties.
>
> [102] Sixth, it is important to avoid hindsight. Care must be taken to consider the disclosure of the application through the eyes of a skilled person who has not seen the amended specification and consequently does not know what he is looking for. This is particularly important where the subject matter is said to be implicitly disclosed in the original specification.'

8. When amendment of a granted patent is being considered, the

> comparison to be made is between the *application* for the patent, as opposed to the granted patent, and the proposed amendment (see the definition of 'additional matter' in s.76(1)(b)). It follows that by and large the form of the granted patent itself does not come into the comparison. This case was to some extent overcomplicated by looking at the granted patent, particularly the granted claim 1.

9. A particular, and sometimes subtle, form of extended subject matter (what our Act calls 'additional matter') is what goes by the jargon term 'intermediate generalisation'. Pumfrey J described this in *Palmaz's European Patents* [1999] RPC 47, 71 as follows:

> 'If the specification discloses distinct sub-classes of the overall inventive concept, then it should be possible to amend down to one or other of those sub-classes, whether or not they are presented as inventively distinct in the specification before amendment. The difficulty comes when it is sought to take features which are only disclosed in a particular context and which are not disclosed as having any inventive significance and introduce them into the claim deprived of that context. This is a process sometimes called "intermediate generalisation".'"

The present case

495. Novartis advances a single, short allegation of added matter. Claim 31 of the Application is as follows:

> "A method according to any one of claims 26 to 30, wherein nucleic acid derived from a selected or screened rgdp is used to express said sbp member or a fragment or derivative thereof in a recombinant host organism."

496. Claim 31 is dependent on *inter alia* claim 26 which is as follows:

> "A method according to anyone of the preceding claims wherein the rgdps formed by said expression are selected or screened to provide an individual sbp member or a mixed population of said sbp members associated in their respective rgdps with nucleic acid encoding said sbp member or a polypeptide chain thereof."

497. Claim 26 is dependent on *inter alia* claim 1 which is as follows:

> "A method of producing a multimeric member of a specific binding pair (sbp), which method comprises: expressing in a recombinant host organism a first polypeptide chain of said sbp member or a genetically diverse population of that type of sbp member fused to a component of a secreted replicable genetic

> display package (rgdp) which thereby displays said polypeptide at the surface of the package, and expressing in a recombinant host organism a second polypeptide chain of said multimer and causing or, allowing the polypeptide chains to come together to form said multimer as part of said rgdp, at least one of said polypeptide chains being expressed from nucleic acid that is capable of being packaged using said component therefor, whereby the genetic material of each said rgdp encodes a said polypeptide chain."

498. As can be seen from claim 1, "rgdb" is an abbreviation for "recombinant genetic display package" and "sbp" is an abbreviation for "specific binding pair". These are both expressions defined in the application (at page 14 lines 10-22 and page 13 lines 37-48 respectively), the latter being the same as that contained in the Patents (quoted in paragraph 219 above). The application also contains a definition of "derivative" (at page 17 lines 22-33), which again is essentially the same as that contained in the Patents (quoted in paragraph 219 above).

499. Novartis says that claim 31 of the Application embraces a class of processes which express fragments or derivatives of a member of a specific binding pair including fragments or derivatives which have no binding specificity for the target epitope or antigen. Novartis contrasts this with claim 5 of 511 and claim 1 of 777, in both of which the fragments or derivatives must have binding specificity for the target epitope or antigen. Novartis contends that this amounts to an impermissible intermediate generalisation.

500. I do not accept this contention. The Application states at page 23 lines 29-35 (emphasis added):

> "The present invention also provides rgdps as defined above and *members of specific binding pairs e.g. binding molecules* such as antibodies, enzymes, receptors, *fragments and derivatives thereof*, obtainable by use of any of the above defined methods. The derivatives may comprise members of the specific binding pairs fused to another molecule such as an enzyme of a Fc tail"

501. Furthermore, the definition of "specific binding pair" in the application states that "the pair have the property of binding specifically to each other".

502. Thus there is a clear disclosure in the application of fragments and derivatives of binding molecules that have binding specificity. The claims of the Patents in issue do not disclose any new matter. The fact that claim 31 of the Application was framed more broadly in this respect is immaterial.

Development of ranibizumab

503. Age-related macular degeneration is caused by abnormal blood vessels proliferating and damaging the retina. Human vascular endothelial growth factor (VEGF) promotes endothelial cell proliferation and neovascularisation, as well as vascular permeability.

Ranibizumab is an anti-VEGF antibody which reverses or at least halts these processes.

504. Genentech's development of ranibizumab has been described in a number of published papers (Baca *et al*, "Antibody Humanization Using Monovalent Phage Display", *J. Biol. Chem.*, 272, 10678-10684 (1997); Presta et al, "Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumours and Other Disorders", *Cancer Res.*, 57, 4593-4599 (1997); Muller *et al*, "VEGF and the Fab fragment of a humanized neutralizing antibody: crystal structure of the complex at 2.4Å resolution and mutational analysis of the interface", *Structure*, 6, 1153-1167 (1998); Chen *et al*, "Selection and Analysis of an Optimized Anti-VEGF Antibody: Crystal Structure of an Affinity-Matured Fab in Complex with Antigen", *J. Mol. Biol.*, 293, 865-881 (1999)). Ranibizumab is also the subject of a Genentech patent. Nevertheless aspects of the development remain confidential. Fortunately, it is not necessary to describe any of the confidential aspects for the purposes of this judgment. Nor is it necessary to describe the development in great detail. For present purposes the development may be summarised as follows.

505. Genentech's starting point was a mouse monoclonal antibody specific to VEGF called MAb A4.6.1, which was generated in hybridoma cells using monoclonal techniques (see Kim *et al*, "The vascular endothelial growth-factor proteins: identification of biologically relevant regions by neutralizing monoclonal antibodies", *Growth Factors*, 7, 53-64 (1992)). This was transformed into ranibizumab in eleven steps. Without going into detail, these steps were as follows.

Step 1

506. It was first necessary to humanise the MAb A4.61 mouse antibody in order to reduce the adverse HAMA response which the injection of a mouse antibody would cause in humans. Humanisation was achieved by sequencing MAb A4.6.1 and then carrying out site-directed mutagenesis to the DNA sequence for a pre-existing human Fab fragment to match its heavy and light chain CDR regions with those found in MAb A4.6.1.

Step 2

507. This humanised Fab sequence was then inserted into a phagemid vector containing a fragment of gene III protein (amino acids 249-406, the C-terminal domain of gene III protein) at position 249. The heavy chain was fused to the expressed gene III protein fragment, while the light chain was expressed directly in soluble form in the periplasm. This phagemid construct was called pMB4-19.

508. The humanised Fab expressed by the pMB4-19 construct exhibited a reduction in binding to VEGF compared to the mouse anti-VEGF antibody from which it was derived (see Presta et al). As a result, Genentech attempted mutagenesis to improve the binding affinity of the humanised Fab for VEGF. After each mutagenesis stage, the best clones were identified using phage display. Between the creation of pMB4-19 and the final clone which codes for ranibizumab, known as Y0317, Genentech carried out three separate sets of phage display experiments.

Step 3

509. The light and heavy chains of pMB4-19 were mutagenised to create four libraries.

Step 4

510. The libraries were subjected to seven rounds of phage display using M13K07 helper phage to select ten clones for sequencing. One of these was chosen for further work, called phagemid phMB4-19-1.6.

Step 5

511. Phagemid phMB4-19-1.6 was then subjected to further site-directed mutagenesis steps in the heavy and light chains resulting in variant Y0101.

Step 6

512. Y0101 was mutagenised by targeted randomisation of certain residues in the CDRs of the heavy and light chains. Following this, a second set of phage display experiments were carried out to select the best clones – nine rounds in all. Again, a phagemid vector and M13K07 helper phage was used. Although the mutations did not result in the identification of a clone with any higher affinity for VEGF, one clone – pY0192 – was selected with higher levels of expression and sequenced. This greater expression assisted in the later phage display step to obtain more functional Fab-displaying phage. However these mutations were later removed from the final clone - Y0317 - encoding ranibizumab.

Step 7

513. Clone pY0192 was subjected to alanine scanning. Alanine scanning involves the sequential substitution of amino acids in a binding molecule by alanine. Since alanine is small and inert, its contribution to binding is limited. Binding tests can therefore be performed in order to assess the impact of each substitution on binding, and in that way gain information as to the importance of the original amino acid to binding.

Step 8

514. Clone pY0192 was subjected to randomised mutagenesis of certain target residues, based on the alanine scanning results from step 7 and also data obtained from crystallography studies of another anti-VEGF antibody in the Genentech portfolio, called Fab-12. Seventeen new libraries were generated (15 focussing on mutations in the V_H region and two in the V_L region, in the CDRs which create the antigen binding site).

Step 9

515. Each library was subjected to seven rounds of phage display, again using a phagemid vector and M13K07 helper phage. A pool of 195 clones enriched for higher affinity binders was picked from the 17 libraries. The affinity of 19 of these 195 clones was tested using Biacore, a proprietary system of surface plasmon resonance, which is

more powerful than ELISA. Clones Y0238-3 (with beneficial amino acid mutations in the CDR-H3 region) and Y0243-1 (with beneficial amino acid mutations in the CDR-H1 region) were identified as having the highest binding affinities.

Step 10

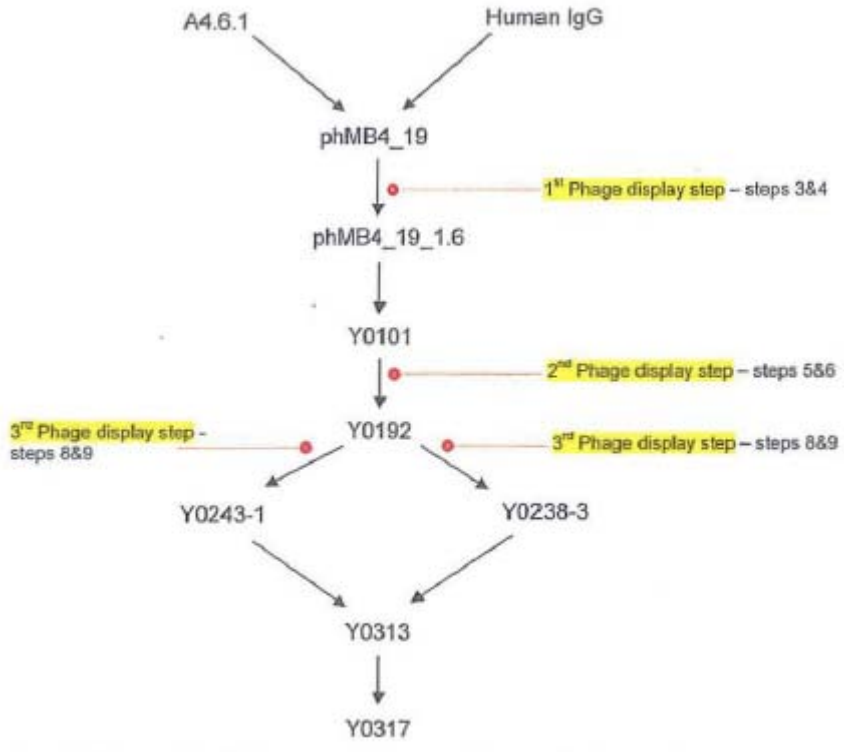
516. The most promising clones identified in step 9, Y0238-3 and Y0243-1, were then combined by adjusting the CDR-H3 amino acid sequence in Y0243-1 to match that amino acid sequence in Y0238-3 to produce Y0313-1. This was achieved by site-directed mutagenesis to the underlying DNA encoding for Y0243-1.

Step 11

517. The CDR-L1 region of Y0313-1 was then adjusted to match that of clone Y0101 (identified at the end of the first round of phage display) to remove the mutations in Y0192 which contributed to higher levels of expression. This was again achieved by site-directed mutagenesis to the underlying DNA encoding for Y0313-1. The resulting clone, Y0317, is the clone for ranibizumab.

In summary

518. The genesis of Y0317 is conveniently summarised in an annotated version of figure 1 of Novartis' Product and Process Description contained in Dr Teillaud's first report which I reproduce below:



519. Subsequently a production vector was created using the sequence of Y0137. This is used by Genentech to produce commercial quantities of ranibizumab which are supplied to Novartis for sale in Europe.

Infringement: did the process fall within the claims?

520. MedImmune contends that the method of the claims was carried out, at least, in Genentech's third round of phage display, when clones Y0243-1 and Y0238-3 were identified, together with the subsequent creation of Y0317 and its use for recombinant production of ranibizumab. Novartis disputes that what Genentech did satisfied the requirements of the claims in the following respects.

521. In the case of claim 5 of 511, the first point taken by Novartis is that Genentech did not produce a population of particles having "a range of binding specificities" since it started with an antibody specific to the antigen of interest and the subsequent steps undertaken by Genentech to improve the affinity of the humanised antibody did not satisfy this requirement. The second point is that Genentech did not produce particles "each" of which contained phagemid genome encoding the binding molecule displayed at its surface, because it used conventional M13K07 helper phage and not gene III deletion helper phage.

522. In the case of claim 1 of 777, the first point taken by Novartis is that Genentech did not use "a gene III protein" because it used a C-terminal domain fragment. The second point is again that Genentech did not produce particles "each" of which contained phagemid genome encoding the binding molecule displayed at its surface, because it used M13K07 helper phage and not gene III deletion helper phage.

523. It is common ground that, with one exception, the resolution of these issues depends on the issues of construction which I have determined above. The exception is that MedImmune contends that the requirement for production of a population of particles having "a range of binding specificities" is satisfied even on Novartis' construction. In support of this contention MedImmune submits that the expert evidence shows that, even though it was not Genentech's objective, specificities to other antigens will have been created in the libraries used in the third round of phage display.

524. Dr Teillaud's evidence was that, "with so many different amino acid substitutions, you can expect that they have recreated [sic] a library with unknown specificities". He went on to say, however:

> "Q. And is it possible to tell for any particular mutant whether it just lost specificity or whether it was specific for something else?
>
> A. I think you have to test it. You can speculate, but I think basically you have to test it."

525. Dr Logtenberg's evidence was he would "speculate that some antibody fragments with unknown specificities were inadvertently made by Genentech". As he explained, however, the library in question theoretically contained 3.2 million members, but in practice there would be something like 30,000 variants of the binding molecule which were successfully displayed. He went on :

> "If one makes 30,000 variants of that, something that is really well adjusted to where it binds to, the chance of getting another binder to

> something else is very slim. Having said that, and I think that is what I mean and probably most people would say to you, if you search the universe of possible antigens, including everything that is on the moon, we would probably find another specificity. That is all we are saying."

526. In my judgment this evidence does not establish, even on the balance of probabilities, that Genentech produced "a range of specificities". Dr Teillaud was clear that the only way in which one could tell whether additional specificities were produced was by testing. Genentech did not test for other specificities since it was not attempting to produce any others as it already had an antibody which was specific to the antigen of interest. Nor would it have gained any benefit whatsoever from producing other specificities inadvertently. Dr Logtenberg's acknowledgement that it was probable that one would find another specificity if one searched the entire universe of antigens, including everything on the moon, is not enough to show that in the real world, or California to be more precise, Genentech did in fact produce another specificity. The skilled team would not regard the claim as extending to specificities to antigens found only on the moon.

527. Accordingly, I conclude that the process whereby Genentech produced ranibizumab did not fall within either claim 5 of 511 or claim 1 of 777. It follows that Novartis has not infringed those claims.

Infringement: is the product obtained directly by means of the process?

528. Even if ranibizumab was produced by a process falling within claim 8 of 511 or claim 1 of 777, Novartis disputes that ranibizumab is a product obtained directly by means of the process of those claims. It advances two arguments in this connection. First, it contends that ranibizumab does not infringe under the law as it existed prior to the European Parliament and Council Directive 98/44/EC on the legal protection of biotechnological inventions of 6 July 1998 ("the Biotech Directive" or just "the Directive"). Secondly, and in the alternative, it contends that ranibizumab does not infringe by virtue of the Biotech Directive.

Infringement under the law prior to the Biotech Directive

529. Section 60(1)(c) of the Patents Act 1977 provides:

> "Subject to the provisions of this section, a person infringes a patent for an invention if, but only if, while the patent is in force, he does any of the following things in the United Kingdom in relation to the invention without the consent of the proprietor of the patent, that is to say—
>
> …
>
> (c) where the invention is a process, he disposes of, offers to dispose of, uses or imports any product obtained directly by means of that process or keeps any such product whether for disposal or otherwise."

530. Section 60 is declared by section 130(7) to be intended to have the same effect as the corresponding provisions of the European Patent Convention and the Community Patent Convention. These are Article 64(2) EPC and Article 25(c) CPC respectively. Article 64(2) EPC provides:

> "If the subject-matter of the European patent is a process, the protection conferred by the patent shall extend to the products obtained directly by such process."

Article 25(c) CPC provides:

> "A Community patent shall confer on its proprietor the right to prevent all third parties not having his consent:
>
> …
>
> (c) from offering, putting on the market, using or importing or stocking for these purposes the product obtained directly by a process which is the subject-matter of the patent."

531. This wording was present in the drafts of both conventions from a very early stage and does not appear to have been the subject of any deliberation in the discussions leading up to the conventions. Thus the *travaux préparatoires* do not assist. On the other hand, it is well established that the language had its origin in the German Patents Act of 1891. That Act used the word *unmittelbar*, which is the same word as appears in the German texts of the EPC and CPC where the English texts use the word "directly".

532. For completeness, it may also be noted that Article 28(1)(b) of the Agreement on Trade-related Aspects of Intellectual Property Rights (commonly known as "TRIPS"), which forms Annex 1C to the Agreement establishing the World Trade Organisation, provides:

> "A patent shall confer on its owner the following exclusive rights:
>
> …
>
> (b) where the subject-matter of the patent is a process, to prevent third parties not having the owner's consent from the act of using the process, and from the acts of: using, offering for sale, selling or importing for these purposes at least the product obtained directly by that process."

533. The leading English authority on section 60(1)(c) is the decision of the Court of Appeal in *Pioneer Electronics Capital Inc v Warner Music Manufacturing Europe GmbH* [1997] RPC 757. In that case the patents in suit related to processes used in the manufacture of compact discs. In one action the patent alleged to have been infringed claimed a method for forming a metallic layer for use as a stamper in moulding disc

replicas. A metallic film was first evaporated onto the recording layer of a master recording, the inventive step lying in the low pressure at which this was done, and another metallic film was then superimposed by electroplating to form an integral metallic layer which was then separated from the rest of the material. In the other action the three patents alleged to have been infringed related to the production of the master recording. The plaintiffs alleged that the defendants had infringed the patents pursuant to section 60(1)(c).

534. The defendants applied to strike out the writs and statements of claim as disclosing no reasonable cause of action. They admitted the manufacture in Germany and the importation into and sale in the United Kingdom of the allegedly infringing compact discs. It was agreed for the purpose of the applications that the defendants' manufacturing process included steps as claimed in the patents. The metallic layer (referred to as the "father") was then used to produce a number of positive impressions ("mothers") each of which was used to produce a number of negative impressions ("sons"). These were then used in the pressing process by which the compact discs were mass-produced. The defendants contended that there had been no infringement because the discs were not obtained directly by means of the processes claimed in the patents as required by section 60(1)(c). Aldous J held that the actions were unsustainable and must be struck out. In reaching this conclusion, he relied in particular upon an article by the late Dr Karl Bruchhausen expounding German law on the point published in 1979, two lengthy extracts from which Aldous J quoted in his judgment at 495-497. The second extract includes the following passage:

> "The Dusseldorf Higher Regional Court [in a decision in 1977] and also *Hahn* and *Flesche* allow themselves to be guided by the desire to provide the proprietors of process patents with effective protection against the possibility that, after the patented teaching was made use of in a patent-free foreign country to make intermediates, the imported end products obtained abroad from the intermediates are put into circulation in the territory of the patent. This desire to ensure that the patent proprietor gets his due reward for the disclosure of his invention when his invention is taken advantage of in the territory of his patent through the sale of the end products is perfectly legitimate and commendable. However, if the inventor fails to ensure adequate protection for his invention through an appropriate form of words in his patent, an interpretation which has his interests at heart must not lead to a broad interpretation of the concept of 'direct products of a process' which is no longer covered by the wording and legislative intentions.
>
> The West German Supreme Court has left it to the inventor, whether in the case of an invention which concerns the manufacture of a new substance from which new substances with surprising useful properties can be manufactured, he will be satisfied with the protection for the production process up to stage of the intermediate or whether he wants to extend his

> protection to the overall process, including the making of the end product, which latter option may be disadvantageous for him if the further processing of the intermediate to the end-product take place in the patent-free foreign country or in the non-industrial sector, since in those cases he will not have a weapon against the use of the process (B.G.H.Z. 51, 378, 387 - Disiloxan). In addition the inventor in the case of such inventions has the option of achieving, through an appropriate wording of the claims, that not only the process up to and including the manufacture of the intermediate but also the overall process via the manufacture of the intermediate and up to and including further processing to the end product is put under protection."

535. The plaintiffs' appeal to the Court of Appeal was dismissed. In his judgment Nourse LJ, with whom Leggatt and Schiemann LJJ agreed, reviewed the law in Germany in some detail. He referred to an article by Dr Bruchhausen published in 1961 as well as to the one in 1979, and to nine out of 13 German decisions cited which ranged from 1897 to 1977. The last of these decisions was the 1977 decision of the Düsseldorf Oberlandesgericht (Higher Regional Court i.e. Court of Appeal) which Dr Bruckhausen had discussed in his 1979 article. Nourse LJ cited certain extracts from a translation of the judgment, including the following:

> "Therefore the issue ultimately is whether the product made by the invention is altered by further processing in essential properties …
>
> The question as to which properties are essential in the sense mentioned must consequently be asked again from patent-legal aspects and having regard to the concrete invention. Since it is crucial for the indispensable evaluative judgment to what extent the inventive step is embodied in, and marks, the end-product at issue, it is especially important to what extent further changes affect specifically those properties of the product of the patent which are essential from the aspect of the concrete inventive concept and were the reason for the patent being granted in the first place …
>
> … the sole criterion is to what extent the changes affect the essence of the product. Even the subsequent change to the chemical structure therefore does not necessarily lead to the loss of 'directness'; on the contrary, the question to be examined is which significance any change to the chemical structure has from the aspect of the concrete inventive concept."

536. From his review of the German authorities Nourse LJ concluded at 771:

> "This review of the relevant German authorities between 1897 and 1977 demonstrates their interconnection with a consistent

> thread: the product obtained directly by means of a patented process is the product with which the process ends; it does not cease to be the product so obtained if it is subjected to further processing which does not cause it to lose its identity, there being no such loss where it retains its essential characteristics. That was the test applied by the Düsseldorf Oberlandesgericht in 1977 no less than by the Reichsgericht in 1909 (the Ossal case) and 1916 (binding agents for pigment dyes). Indeed the essence of Dr. Bruchhausen's criticisms of the Düsseldorf decision, as I understand them, was not so much that an incorrect test had been adopted as that it had been incorrectly applied to the facts of the case."

537. Nourse LJ went on to review more briefly the law in the Netherlands, Switzerland and Denmark. He expressed his conclusion as follows at 774:

> "Since the authorities in the Netherlands, Switzerland, Denmark and Austria disclose no difference of approach from that adopted in Germany, the loss of identity test may be taken to represent the test adopted by European law. The question whether the product with which the patented process ends retains its essential characteristics or not being one of fact and degree, there will often be difficulty in applying the test to the facts of particular cases. In the present case … there is no such difficulty. In my judgment the actions are bound to fail and Aldous J. was right to strike them out."

538. More recently, infringement under section 60(1)(c) has been considered in two cases at first instance. In the first, *Halliburton Energy Services Inc v Smith International (North Sea) Ltd* [2005] EWHC 1623 (Pat), [2006] RPC 2, Halliburton was the proprietor of a European patent (referred to as the Force Balancing patent) for a method of designing a roller-cone drill bit for use in drilling oil and gas wells involving an iterative process of calculation. Although not required by the claims, in practice this involved the use of a computer model. Pumfrey J held that, if it had been valid, it would have been infringed pursuant to section 60(1)(c) for the following reasons:

> "93. … Smith do not design or manufacture bits within the jurisdiction, so infringement of claim 3 is alleged by virtue of subs.60(1)(c) of the Patents Act 1977. The invention is a process, and so the product sold in the United Kingdom must be obtained directly by means of the claimed process. 'Obtained directly' has been considered in two cases cited to me, particularly *Pioneer Electronics Capital Inc v Warner Music Manufacturing Europe GmbH* [1997] R.P.C. 757 , and a decision *Halbleiter-bauelemente* in the Landgericht Düsseldorf May 6, 1997. The Court of Appeal have held that 'obtained directly' means 'without intermediary' or immediately. This seems to exclude the possibility of further processing: but the

> *Halbleiterbauelemente* case suggests that further use or processing may take place provided that its effect is not to obscure the qualities of the product directly obtained.
>
> 94. The result of the performance of the claimed method is, if I am right on the question of construction, a CAD file containing a design of bit balanced under design conditions. The CAD file is input to a numerically controlled milling machine to produce (separately) the cones, either milled in one piece with the teeth or with recesses to receive the inserts, which are themselves milled to the design recorded in the CAD file. The cones are then assembled with the associated bearings, seals and other ironmongery into a bit body. Is the result 'directly obtained' by means of the process?
>
> 95. Smith's approach to this question is understandably to point to the design as the endpoint of the claimed process, and to decompose the subsequent manufacturing process into as many steps as reasonably possible. Whatever is using the CAD files resulting from a session with the simulation software is not obtained directly by use of the process but (I paraphrase) by employing the design in further manufacture. They identify the following [six] steps as producing 'an independent article which is not the thing that came out of the claimed process': …
>
> 96. I do not think that it is sensible to view manufacture and design as in some way resulting in separate products. Design is no doubt interesting in the abstract, but when it is used it cannot be divorced from the article made to it. The Registered Designs Act 1949 and its predecessors encouraged lawyers to consider a design as something complete in itself and distinct from any article, but from the point of view of a bit designer the design exists only as a depiction of a bit that is to be made and used. There is no doubt that the criterion with which the claimed method is concerned depend upon the bit shape as a whole (I shall discuss this further when I consider insufficiency) and it follows, it seems to me, that there is no intermediate between this method and the resulting bit, which is as much the direct product of the design process as it is the product of the manufacturing process of which the design is part."

This passage is unaffected by the Court of Appeal's subsequent dismissal of Halliburton's appeal against Pumfrey J's finding that the Force Balancing patent was invalid for insufficiency ([2006] EWCA Civ 1715).

539. With respect to the late Pumfrey J, I do not agree that the Court of Appeal in *Pioneer v Warner* excluded the possibility of further processing. On the contrary, it decided that a product could be obtained directly from a claimed process despite further processing provided that there was no loss of identity, there being no such loss where

it retained its essential characteristics. Pumfrey J's reference to the *Halbleiterbauelemente* case (which was not cited to me) suggests that German courts were continuing to apply the loss of identity test in 1997. As for his actual decision, it seems to me that it is perfectly consistent with *Pioneer v Warner*.

540. In *Monsanto Technology LLC v Cargill International SA* [2006] EWHC 2864 (Pat) and [2007] EWHC 2257 (Pat), [2008] FSR 7 Monsanto was the proprietor of a European patent relating to glyphosate tolerant 5-enolpyruvylshikimate-3-phosphate synthases. Glyphosate (which is sold by Monsanto under the trade mark Roundup) is a non-selective herbicide which works by inhibiting the enzyme 5-enol-pyruvylshikimate-3-phosphate synthase ("EPSPS"), which plays an important role in the growth of plants. The patent described a new class of EPSPS enzymes, referred to as "Class II enzymes", which were not sensitive to glyphosate. Plants containing such enzymes survived the use of glyphosate, whilst weeds were destroyed. The genes encoding these Class II enzymes had been isolated from three different bacteria, one of which was *Agrobacterium tumefaciens* sp strain CP4. Monsanto had inserted the CP4 gene (or to be precise, a gene with a single mutation in it referred to as the "RuR EPSPS gene") into the DNA of a soybean plant it had called Roundup Ready or RuR soybean plant. As a result, the RuR soybean plant produced a Class II EPSPS enzyme called CP4R (also known as CP4-EPSPS), which was glyphosate-resistant. The RuR soybean was cultivated on a large scale in Argentina, where there was no patent protection for the invention. Cargill bought soy beans grown from RuR seeds, from which they or others manufactured soy meal which they imported into the United Kingdom. The action concerned 5,000 tonnes of meal shipped on the MV *Podhale*.

541. Prior to trial Cargill applied to strike out, alternatively for summary judgment dismissing, the claim for infringement of the method claims in the patent (and in two other patents then in issue) on the ground that it was unarguable that the soy meal was a product obtained directly by means of the process of those claims. Monsanto then applied for Cargill's application itself to be summarily dismissed or adjourned to trial on the ground that it was manifest that this was an issue requiring a trial for its proper resolution. Warren J acceded to Monsanto's application. During the course of his judgment he said this:

> "31. Mr. Watson [counsel for Cargill], as I understand it, says that the starting point is the product and then an objective assessment is to be taken of whether the process results in a loss of the essential characteristics of that product. In the present case the product is the original plant created by the process but even if one ignores the fact that the soymeal is not produced from that product but from its progeny and assumes that it is the original plant which has produced the soymeal, the process of producing meal from plant is such, it is argued for Cargill, as inevitably to destroy the essential characteristics of the plant.
>
> 32. Mr. Tappin [counsel for Monsanto] says that this is the wrong approach and that one can only assess the essential characteristics of the product by reference to the inventive

> concept which has led to the patent in the first place. It is therefore arguable that the central characteristics of the plant have, on his submissions, indeed been retained in the meal but this is an issue of fact and degree which can only be judged after receipt of evidence with which it is not appropriate or proportionate to deal on a summary application.
>
> 33. Mr. Watson says, correctly, that I am bound by the Court of Appeal which lays down the test which I have set out and submits that no reference is made in that test to any inventive concept. However Nourse LJ in adopting that test specifically referred to it as the test applied by the Düsseldorf Oberlandesgericht in 1977 and in its decision that court certainly did refer to inventive concept in the context of the legal patent aspects. It is at least strongly arguable, and if it were necessary for me to decide I would do so in that sense, that Nourse LJ was indicating his acceptance of the test and approach adopted by that court, including its reference to the patent legal aspects and having regard to the concrete invention or inventive concept. Certainly, in deciding whether or not to grant summary judgment I consider that Mr. Tappin's approach is probably right and that Mr. Watson's approach is probably wrong. I do not need to make a final determination on that issue, it will be a matter for the judge at trial or at a full hearing of the summary judgment application."

542. Warren J went on to refer at [35] to "a just subsequent decision of the Düsseldorf Oberlandesgericht in a case concerning semiconductor assembly elements". That decision has not been cited to me either. I infer that it was a decision on appeal from the decision of the Landgericht in the *Halbleiterbauelemente* case mentioned by Pumfrey J. Whether that is so or not, it does not appear from Warren J's description of it to take matters much further.

543. At trial Pumfrey J found as a fact that the Podhale meal contained some genomic DNA which included the RuR EPSPS gene. He nevertheless held that the method claims in the patent had not been infringed under section 60(1)(c) for the following reasons:

> "34. In *Pioneer Electronics Capital Inc v Warner Music Manufacturing Europe GmbH* [1997] R.P.C. 757 the Court of Appeal accepted the following submission at 764:
>
> > 'Mr Prescott QC and Mr Howe QC, for the defendants, submitted that the first step, as always, is to construe the claims in each patent. Here their construction is not in doubt. In 649 the process ends with the production of the father; in each of the others with the production of the master. They and they alone are the products obtained directly by means of the processes. Mr

> Prescott and Mr Howe accepted that a product can be further processed without losing its identity, in which event it remains the product obtained directly by means of the patented process. The question whether it has lost its identity depends on whether it no longer retains its essential characteristics. It is only for that purpose that a consideration of essential characteristics is appropriate. There is no free-standing "essential characteristics" test. Mr Prescott and Mr Howe further submitted that here there is no identity between the masters and the finished discs. Father, mother and son are each separate products with identities different from that of the master. However you look at it, the finished discs cannot properly be described as products obtained directly by means of the patented processes.'

35. The Court of Appeal accepted that the obverse situation was one in which the intermediate product had lost its identity and had become something else. The products of many, if not most, intermediate processes in chemical cases will suffer that fate. I take it that prima facie the phrase 'directly obtained by means of the process' means 'the immediate product of the process', or, where the patented process is an intermediate stage in the manufacture of some ultimate product, that product, but only if the product of the intermediate process still retains its identity. In most cases, the assessment will be a matter of fact and degree but not always - *Pioneer v Warner* was a strike-out case.

36. What here is the process? So far as the allegation of infringement is concerned, it is defined by the method claim 14 (new claim 5). This opens with the words 'a method of producing genetically transformed plants …' and the steps of the method commence with the insertion into the genome of a plant cell a double-stranded recombinant DNA molecule having the prescribed characteristics. This is hardly an everyday operation: it will have been carried out only on the parent of every strain of Round Up Ready soybeans. In fact, it appears to have been done once so far as this action is concerned: the plant identified in Example 3 and Table X of the patent as 13640/40–3 is the parent of all Round Up Ready soybean plants….

37. The transformation of this plant was many generations ago. Since then, soybeans have been grown by seedsmen or retained by farmers for planting; the plants have been grown and the new beans harvested; and after some generations the harvested beans have been processed into the meal in the *Podhale* cargo. I accept that all the Round Up Ready soybean plants in

> Argentina are lineal descendants of this original plant, and I can see how it can be said that this huge mountain of soybean meal (5,000 tonnes on the *Podhale* alone) can be described as the ultimate product of the original transformation of the parent plant. But I cannot see that it can be properly described as the direct product of that transformation, a phrase I would reserve for the original transformed plant. This aspect of the claim must fail.
>
> 38. Monsanto says that the product has retained its essential characteristics. The meal comes from beans produced by a plant which contained the Round Up Ready sequence. It was the sequence that made the invention patentable, and the sequence has survived. Even though the meal comes from beans which are not the beans from the plant which underwent the original transformation, that is enough. I think this has nothing to do with the product of the process at all. It might be extravagant to say that the generation of plants producing the beans from which the *Podhale* meal was manufactured did not have an atom in common with the original transformed plant, but it must be close to the truth. I think that Monsanto's argument confuses the informational content of what passed between the generations (the Round Up Ready genomic sequence) with the product, which is just soybean meal with no special intrinsic characteristics from one of the generations of plants. Put another way, it is difficult to see how anything has survived into the meal if the sequence has not. It cannot be told apart from non-Round Up Ready meal unless it contains traces of the gene, in which case other claims are relevant. What has not survived is the original transformed plant. I should add that I think it is dangerous to talk of reproductive material having in some way passed between the generations. While no doubt some reproductive material does pass between the first and second generations the same material does not pass further. Copies pass thereafter."

544. In my view this decision is a helpful illustration of the application of the loss of identity test in a biotechnological context, but it does not really add anything so far as the law is concerned. (As will appear, however, the decision is also relevant background to Novartis' argument under the Biotech Directive.)

545. Counsel for Novartis accepted that, if the loss of identity test adopted in *Pioneer v Warner* was applied in the present case, then ranibizumab was a product obtained directly by the processes of claim 8 of 511 and claim 1 of 777. He submitted, however, that the present case should be distinguished from *Pioneer v Warner*. In summary, he argued as follows:

i) Novartis is not alleged by MedImmune to have infringed claims 5, 6 and 7 of 511. It follows that ranibizumab is not a product obtained directly by the

process of those claims.

ii) Claim 8 is a subsidiary claim which is dependent on each of claims 5, 6 and 7. It is a narrower claim than claims 5, 6 and 7 in the sense that it requires the presence of more features before a process falls within in it. Ordinarily, where a broad independent claim is not infringed, it necessarily follows that a narrower subsidiary claim is not infringed either. Yet in the present case it is said that ranibizumab infringes claim 8, even though it does not infringe claims 5, 6 and 7. That indicates that something is wrong.

iii) That is even more so given that the invention, if any, lies within claim 5, that the additional features added by claims 6, 7 and 8 were common general knowledge and that none of those claims is alleged by MedImmune to be have independent validity over claim 5.

iv) In essence, claim 5 is to a method of identifying a desired molecule, while claim 8 is to method of manufacturing the molecule so identified. Ranibizumab is not a product obtained directly by the identification process. It is only as a result of adding a conventional manufacturing process that MedImmune is able to allege infringement.

v) Although the position is superficially different in the case of claim 1 of 777 in that a single claim is involved, it remains the case that ranibizumab is not a product obtained directly by the process of the inventive steps in claim 1, namely the identification steps. It is only as a result of the inclusion of further, non-inventive, manufacturing steps in the claim that MedImmune is able to allege that ranibizumab infringes.

vi) For these reasons it cannot be right to apply the loss of identity test without qualification in a case such as the present. Furthermore, the test cannot depend on the precise manner in which the claims of the patent in suit are drafted. Instead, the test which should be applied is to focus upon the inventive claim, or inventive part of the claim, and ask whether the allegedly infringing product is obtained directly from that process.

546. In my view this is an attractive argument, and one I have some sympathy with. Nevertheless I am unable to accept it for the following reasons. First, *Pioneer v Warner* is binding upon me. The loss of identity test adopted by the Court of Appeal in that case is a general test stated without qualifications. While it is true that, as Warren J noted in *Monsanto v Cargill*, the Court of Appeal considered that the Düsseldorf Oberlandesgericht in 1977 had articulated the correct test, even if it had not correctly applied that test to the facts of the case and that the Düsseldorf Oberlandesgericht referred in this context to the inventive concept, there is no reason to think that the Düsseldorf Oberlandesgericht was referring to anything other than the inventive concept of the relevant claim. Furthermore, as Pumfrey J noted in *Monsanto v Cargill*, the Court of Appeal accepted a submission the starting point of which was the correct construction of the claim in issue.

547. Secondly, both Aldous J and the Court of Appeal treated Dr Bruchhausen's analysis as authoritative. As can be seen from the passage quoted in paragraph 534 above, he

was of the opinion that the issue depended on the manner in which the claims were drafted and that it was legitimate for the patentee to obtain protection going beyond an inventive intermediate by framing claims to the whole process.

548. Thirdly, the argument is fundamentally one about territoriality. Novartis does not dispute that, if MedImmune is right on construction, then the invention of claim 5 of 511 and the corresponding part of claim 1 of 777 was used by Genentech to produce ranibizumab. What Novartis is really saying is that MedImmune should have to sue Genentech for patent infringement in the USA, rather than Novartis in this country. While I agree that the patent system is territorial, it is not rigidly so: see, for example, *Menashe Business Mercantile Ltd v William Hill Ltd* [2002] EWCA Civ 1702, [2003] 1 WLR 1462 and *Virgin Atlantic Airways Ltd v Delta Air Lines Inc* [2011] EWCA Civ 162. There is nothing inherently objectionable about affording MedImmune a remedy in this country given that ranibizumab is sold here. Nor do Article 64(2) EPC and Article 25(c) CPC compel the conclusion that this should be excluded.

549. For these reasons I conclude that, if ranibizumab was produced by a process falling within claim 8 of 511 and claim 1 of 777, it would be a product obtained directly by means of that process. On that hypothesis, Novartis would have infringed those claims subject to its argument based on the Biotech Directive.

Infringement under the Biotech Directive

550. The Directive was implemented by the United Kingdom by means of the Patents Regulations 2000, which inserted a new section 76A into the Act and two new definitions into section 130(1) of the Act. Section 76A(1) provides:

> "Any provision of, or made under, this Act is to have effect in relation to patent or an application for a patent which concerns a biotechnology invention, subject to the provisions of Schedule A2."

Schedule A2 and the new definitions in section 130(1) reproduce, either verbatim or with scarcely any alteration, most of the provisions of the Directive, including Articles 8-10.

551. As a legislative technique, this is an improvement on earlier UK intellectual property legislation, which frequently contained provisions which had been re-drafted from the European directive which was being implemented. Nevertheless, it does not alter the fact that the court is obliged to construe the domestic legislation so far as is possible in conformity with, and to achieve the result intended by, the Directive (Case C-106/89 *Marleasing SA v La Comercial Internacional de Alimentación SA* [1990] ECR I-4135 at [8]) and that the Directive must be construed in accordance not only with the wording of its individual provisions, but also its overall scheme and objectives (see e.g. Case C-482/07 *AHP Manufacturing BV v Bureau voor de Industriële Eigendom* [2009] ECR I-0000 at [27]). Accordingly, it remains necessary to refer to the Directive itself.

552. The Directive contains no less than 56 recitals, which include the following:

> "(8) Whereas legal protection of biotechnological inventions does not necessitate the creation of a separate body of law in place of the rules of national patent law; whereas the rules of national patent law remain the essential basis for the legal protection of biotechnological inventions given that they must be adapted or added to in certain specific respects in order to take adequate account of technological developments involving biological material which also fulfil the requirements for patentability;
>
> …
>
> (13) Whereas the Community's legal framework for the protection of biotechnological inventions can be limited to laying down certain principles as they apply to the patentability of biological material as such, such principles being intended in particular to determine the difference between inventions and discoveries with regard to the patentability of certain elements of human origin, to the scope of protection conferred by a patent on a biotechnological invention, to the right to use a deposit mechanism in addition to written descriptions and lastly to the option of obtaining non-exclusive compulsory licences in respect of interdependence between plant varieties and inventions, and conversely;
>
> …
>
> (46) Whereas, in view of the fact that the function of a patent is to reward the inventor for his creative efforts by granting an exclusive but time-bound right, and thereby encourage inventive activities, the holder of the patent should be entitled to prohibit the use of patented self-reproducing material in situations analogous to those where it would be permitted to prohibit the use of patented, non-self-reproducing products, that is to say the production of the patented product itself;
>
> …"

553. The Directive is divided into Chapters. Chapter I concerns "Patentability" and consists of Articles 1-7. Article 1(1) states that "Member States shall protect biotechnological inventions under national patent law". The term "biotechnological inventions" is not explicitly defined by the Directive, but it appears to be implicitly defined in Article 3(1) (emphasis added):

> "For the purposes of this Directive, inventions which are new, which involve an inventive step and which are susceptible of industrial application shall be patentable even if they *concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used*."

Indeed, the italicised wording has been adopted as the definition of "biotechnological invention" in section 130(1) of the 1977 Act.

554. Article 2(1)(a) defines "biological material" as "any material containing genetic information and capable of reproducing itself or being reproduced in a biological system". This definition is reproduced in section 130(1) of the 1977 Act.

555. Chapter II of the Directive concerns "Scope of Protection" and consists of Articles 8-11. Article 8, which is reproduced in paragraphs 7 and 8 of Schedule A2 to the 1977 Act, provides:

> "1. The protection conferred by a patent on a biological material possessing specific characteristics as a result of the invention shall extend to any biological material derived from that biological material through propagation or multiplication in an identical or divergent form and possessing those same characteristics.
>
> 2. The protection conferred by a patent on a process that enables a biological material to be produced possessing specific characteristics as a result of the invention shall extend to biological material directly obtained through that process and to any other biological material derived from the directly obtained biological material through the propagation or multiplication in an identical or divergent form and possessing those same characteristics."

556. Article 9, which is reproduced in paragraph 9 of Schedule A2 to the 1977 Act, provides:

> "The protection conferred by a patent on a product containing or consisting of genetic information shall extend to all material, save as provided in Article 5(1), in which the product is incorporated and in which the genetic information is contained and performs its function."

557. Articles 8 and 9 of the Directive have been the subject of consideration in two cases before the Court of Justice of the European Communities. In the first, Case C-377/98 *Kingdom of the Netherlands v European Parliament and Council of the European Union* [2001] ECR I-7079, the Netherlands sought annulment of the Directive on various grounds. One of these was that the Directive was in breach of the principle of legal certainty. One of the arguments advanced in support of this contention was that there was an inconsistency between Article 4(1)(a) on the one hand and Articles 8 and 9 on the other hand. This argument was rejected by the Court of Justice.

558. During the course of his opinion on this point, Advocate General Jacobs observed (footnotes omitted):

> "121. A patent for a product normally gives the holder the exclusive right to manufacture that product (subject to compliance with

> applicable laws and regulations). In the case of patented material which is capable of reproducing itself, the value of the patent would clearly be eroded if it did not extend to future generations of such material. For example, if the purchaser of patented seeds were able to use the seeds produced by the crop grown from the purchased seeds, the value of that patent would be much reduced. Article 8(1) accordingly states that in such cases the protection conferred by the original patent extends to future generations of biological material derived through propagation or multiplication. Recital 46 expresses that principle in terms of the patent-holder's entitlement 'to prohibit the use of patented self-reproducing material in situations analogous to those where it would be permitted to prohibit the use of patented, non-self-reproducing products, that is to say the production of the patented product itself'. (With regard to seeds, as discussed above Article 11(1) derogates from that protection in prescribed circumstances and for a fee.)
>
> 122. Article 8(2) similarly adapts a well-known principle of traditional patent law to the exigencies of biotechnological inventions. Where the subject-matter of a patent is a process, the protection conferred by the patent extends to the products directly obtained by such a process. That principle has been incorporated in international patent legislation since at least 1958, when Article 5 *quater* was inserted into the Paris Convention. It finds expression in Article 64(2) of the European Patent Convention, which provides:
>
> > 'If the subject-matter of a European patent is a process, the protection conferred by the patent shall extend to products directly obtained by such process.'
>
> 123. If the products so obtained are themselves capable of replication, the problem discussed in paragraph 121 will arise. For example, a patented process may result in the production of a micro-organism which can be cloned. If such material could be freely propagated by a purchaser, the value of the process patent would be nullified. Article 8(2) accordingly makes it clear that the protection conferred on biological material directly obtained by a patented process extends to future generations of that material."

559. Case C-428/08 *Monsanto Technology LLC v Cefetra BV* [2010] ECR I-0000 concerned the same European patent that was in issue in *Monsanto v Cargill* and a very similar allegation of infringement. The Rechtsbank s'Gravenhage (District Court of the Hague) referred four questions concerning the interpretation of Article 9 of the Directive to the ECJ. The first and second questions concerned the effect of Article 9 on the scope of protection conferred by the patent in suit. The third question, which concerned the applicability of the Directive to patents granted prior to 30 July 2000

(the date by which Article 15(1) of the Directive required Member States, if necessary, to adjust their national patent law to take account of the provisions of the Directive). The fourth question concerned the effect of Articles 27 and 30 of TRIPS. It is convenient to consider the Court's answer to these questions in reverse order.

560. The Court's answer to the fourth question was that Articles 27 and 30 of TRIPS did not affect the interpretation of Article 9 it had arrived at in answering the first question.

561. The Court's answer to the third question was that the Directive did apply to patents granted before 30 July 2000. Accordingly, MedImmune does not dispute that it is capable of applying to the Patents.

562. The second question was whether Article 9 effected an exhaustive harmonisation of the protection conferred by patents falling within it, with the result that it precluded national patent legislation from offering wider protection. The Court held at [51]-[63] that Article 9 of the Directive did effect an exhaustive harmonisation. Novartis contends, and MedImmune does not dispute, that by parity of reasoning Article 8(2) must also be regarded as effecting an exhaustive harmonisation.

563. The first question was in essence whether Article 9 was to be interpreted as conferring patent protection in circumstances such as those involved in the main proceedings. The Court considered this question at [33]-[50] and its answer at [50] was in the negative:

> "Accordingly, the answer to the first question is that Article 9 of the Directive must be interpreted as not conferring patent right protection in circumstances such as those of the case in the main proceedings, in which the patented product is contained in the soy meal, where it does not perform the function for which it was patented, but did perform that function previously in the soy plant, of which the meal is a processed product, or would possibly again be able to perform that function after it had been extracted from the soy meal and inserted into the cell of a living organism."

564. The Court's reasoning in summary was that Article 9 makes the protection for which it provides subject to the condition that the genetic information contained in the patented product or constituting that product "performs" its function in the "material … in which" that information is contained. It followed that the protection conferred by Article is not available when the genetic information has ceased to perform the function it performed in the initial material from which the material in question is derived. Furthermore, since it was clear from recitals 23 and 24 and Article 5(3) of the Directive that the patentability of a DNA sequence was subject to indication of the function it performs, the Directive must be regarded as not according any protection to a patented DNA sequence which is not able to perform the specific function for which it was patented. It followed that Article 9 did not accord protection to a patented DNA sequence which was not able to perform its function, as was the case with a DNA sequence such as that in issue when it was incorporated in a dead material such as soy meal.

565. Turning to the present case, it is common ground that the Patents concern biotechnological inventions and are thus within the scope of the Directive as a whole. As counsel for MedImmune submitted, however, it does not necessarily follow that the Patents are caught by all the provisions of the Directive and in particular those in Chapter II. Novartis contends that (i) the Patents are within the scope of Article 8(2) and (ii) the effect of Article 8(2) is to circumscribe the protection conferred by the Patents, with the result that (even if they would otherwise infringe by virtue of section 60(1)), Novartis' acts in relation to Lucentis do not infringe. MedImmune disputes this.

566. It is convenient to begin with two preliminary points raised by counsel for MedImmune. First, he submitted that Chapter II of the Directive did not comprehensively regulate the protection conferred by patents for biotechnological inventions. In support of this submission, he pointed out that each of Articles 8(1), 8(2) and 9 concerns a specific type of patent and that those did not encompass all possible biotechnological inventions. In addition he relied on recitals (8), (13) and (46). In my view counsel for MedImmune may be correct about this, but it is unnecessary for me to decide whether he is or not since Novartis' argument is squarely based on Article 8(2).

567. Secondly, he submitted that, although Articles 8 and 9 of the Directive refer to "The protection conferred by a patent …", this can only be ascertained by reference to the individual claims in accordance with Article 69 EPC and the Protocol on Interpretation. Thus Articles 8 and 9 only apply to claims within a patent which have the specified characteristics. Counsel for Novartis did not accept this, but did not advance any coherent argument to the contrary. I note that in *Monsanto v Cefetra* neither the Advocate General in his opinion nor the Court in its judgment referred to the claims of the patent in suit, but it appears to me that the explanation for this is that the claim in the underlying proceedings was for infringement of the product claims. As a matter of principle, I consider that the submission made by counsel for MedImmune is correct and I therefore accept it. It follows that the key question to be decided is whether either claim 8 of 511 or claim 1 of 777 is caught by Article 8(2).

568. Counsel for Novartis submitted that each of these claims is a claim to a "process that enables a biological material to be produced possessing specific characteristics as a result of the invention" within Article 8(2). In the case of Claim 1 of 777, this is because:

i) it enables (indeed, it requires) the production of filamentous bacteriophage, which is a biological material; and

ii) such phage have specific characteristics as a result of the invention in that (a) they display a binding molecule which is specific for a particular target and (b) they contain recombinant nucleic acid that encodes the binding molecule as a fusion protein.

569. Similarly, in the case of claim 8 of 511, which is dependent on claim 5, the claim requires the production of phagemids having specific characteristics as a result of the invention. Phagemids are biological materials since they are capable of being reproduced in a biological system (i.e. with the assistance of helper phage).

570. Counsel for MedImmune accepted that phage and phagemids are biological materials within the meaning of Article 2(1)(a). Nevertheless, he submitted that neither claim 8 of 511 nor claim 1 of 777 fell within Article 8(2) because:

i) The two claims are for methods of producing "a binding molecule specific for a particular target epitope or antigen" (claim 8, 511) and "a molecule with binding specificity for a particular target" (claim 1, 777). The binding molecules produced are not "biological materials" within Article 2(1)(a). Therefore neither of these processes enables the production of biological material. Although the methods involve biological materials, they are not ultimately directed at the production of biological material.

ii) Alternatively, even if the methods could be said to enable the production of biological materials, for example the phage particles, those products do not possess specific characteristics as a result of the invention. They may be altered, damaged or destroyed during the removal of the nucleic acid encoding the binding molecule. Only the binding molecule (which is not biological material) has specific characteristics as a result of the invention.

571. It is convenient to deal first with MedImmune's alternative argument, which was not strongly pressed. In my judgment it is clear that, to the extent that claim 8 of 511 and claim 1 of 777 do enable the production of biological materials, namely phage and phagemids, those materials do possess specific characteristics as a result of the invention. Thus they contain nucleic acid encoding the binding molecules displayed at their surface and so on.

572. The question, therefore, is whether the processes claimed by claim 8 of 511 and claim 1 of 777 are processes that enable a biological material to be produced. In my judgment MedImmune is correct to say that they are not for the following reasons.

573. First, as I have said, I consider that the correct approach is to consider the protection conferred by the relevant claim. As counsel for MedImmune submitted, both claim 8 of 511 and claim 1 of 777 are claims to processes for the production of binding molecules. The binding molecules are not biological materials. It is immaterial that the processes involve biological materials.

574. Secondly, as counsel for MedImmune also submitted, if Article 8(2) did apply to claims such as these, it would have surprising consequences. Novartis contends that, just as the ECJ interpreted Article 9 in *Monsanto v Cefetra* as restricting the scope of protection conferred by the patent in suit in that case, by parity of reasoning the protection conferred by Article 8(2) is restricted to "biological material directly obtained through that process and to any other biological material derived from the directly obtained biological material through propagation or multiplication in an identical or divergent form and possessing those same characteristics". Novartis says that such protection cannot extend to ranibizumab since, as is common ground, it is not a "biological material" within the definition in Article 2(1)(a).

575. Counsel for MedImmune did not in the end seriously dispute that, if Article 8(2) applied at all to claim 8 of 511 and claim 1 of 777, its effect would be to circumscribe the protection conferred by the claims in this way. Rather, he argued that this

confirmed that Article 8(2) cannot apply to these claims. As he pointed out, the consequence would be that it would be difficult, if not impossible, to obtain patent protection for recombinant methods of producing proteins, since proteins are not "biological materials" within the definition in Article 2(1)(a), yet recombinant methods of producing them involve the production of biological materials.

576. Thirdly, it appears from Advocate General Jacobs' analysis in *Netherlands v European Parliament* that the purpose of Article 8(2) is not to limit the protection conferred by process claims in patents for biotechnological inventions, but, if anything, to extend it.

577. For these reasons, I conclude that Article 8(2) does not provide Novartis with a defence to the claim for infringement of these claims if they are otherwise infringed.

Summary of conclusions

578. For the reasons given above I conclude that:

i) None of claims 5-8 of 511 and claim 1 of 777 is entitled to priority from PD3. As MedImmune concedes, it follows that both Patents are invalid.

ii) If the claims were entitled to priority from PD3, the claimed inventions would not be obvious in the light of Parmley & Smith, but would be obvious in the light of Professor Smith's talk at the Banbury Conference.

iii) Neither claim 8 of 511 nor claim 1 of 777 is invalid on the ground of insufficiency.

iv) Neither claim 5 of 511 nor claim 1 of 777 is invalid on the ground of added matter.

v) Ranibizumab was not produced by a process falling within either claims 5-8 of 511 or claim 1 of 777. Accordingly, Novartis has not infringed either of the Patents even if they are valid.

vi) If ranibizumab was produced by a process falling within claim 8 of 511 and claim 1 of 777, then it was a product obtained directly by means of those claims within section 60(1)(c). This conclusion is not affected by Article 8(2) of the Biotech Directive. On that hypothesis, Novartis would have infringed both Patents if valid.