Neutral Citation Number: [2008] EWHC 1903 (Pat)

Case No: HC06C02687

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 31 July 2008

Before :

THE HONOURABLE MR JUSTICE KITCHIN

- -

Between :

ELI LILLY AND COMPANY	**Claimant**
- and -	
HUMAN GENOME SCIENCES, INC.	**Defendant**

- -
- -

Mr Andrew Waugh QC and **Mr Colin Birss** (instructed by **Howrey LLP**) for the **Claimant**
Mr Simon Thorley QC and **Mr Justin Turner** (instructed by **Powell Gilbert LLP**) for the **Defendant**

Hearing dates: 7, 10-13, 17-21 December 2007, 11-12 and 15 January 2008

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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.

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THE HONOURABLE MR JUSTICE KITCHIN

MR. JUSTICE KITCHIN :

Introduction

1. In this action the claimant ("Lilly") applies to revoke European Patent (UK) 0,939,804 ("the Patent") held by the defendant ("HGS"). I also have before me an application by HGS to amend the Patent, which is opposed by Lilly. The Patent discloses the nucleotide and amino acid sequence of a novel member of the TNF ligand superfamily which it calls Neutrokine-α. The application for the Patent was filed on 25 October 1996 and it was granted on 17 August 2005. It is currently under opposition in the EPO. Oral proceedings took place before the Opposition Division in June 2008 and the Patent was revoked, apparently on the basis that the claimed invention lacked any inventive step and constituted a claim to an arbitrary member of the TNF ligand superfamily without a known function. The Opposition Division declined to provide further reasoning during the oral proceedings and a written decision is awaited. HGS intends to file an appeal and the decision of the Opposition Division will be suspended in the meantime.

2. Neutrokine-α is known by many different names including TALL-1, xTNF4, THANK, BAFF and BLyS. The reason for this is that the same protein was found by separate groups and, in various publications around 1999, each group gave it a name based on either the origin or principal apparent function of the protein.

3. Neutrokine-α is a cytokine, that is to say a protein which acts as an inter-cellular mediator in inflammation and immune responses. By 1996, in the region of 100 cytokines had been cloned, sequenced and partially characterised and it was understood that they acted via cell membrane intermediary proteins called cytokine receptors. By that date a number of these receptors had also been identified and were known to be transmembrane proteins with the ability to bind cytokines outside the cell and cause metabolic changes inside the cell. The details of how cytokines and receptors acted were not well understood, but it seemed that they often had many different activities and that those activities frequently overlapped.

4. The first TNF cytokines to be identified were TNF-α (catechin) and TNF-β (lymphotoxin), collectively "TNF". TNF was originally thought to have an anti-tumour effect (hence its name Tumour Necrosis Factor) but it was subsequently discovered that its main activity was to cause inflammation by promoting the release of prostaglandins. This discovery generated a considerable interest in scientific and pharmaceutical communities. Many diseases are associated with inflammation and some, such as osteo arthritis, rheumatoid arthritis, chronic obstructive pulmonary disease, asthma, eczema and psoriasis, are very widespread. It was hoped that TNF would prove of immense value medically. It was also believed that other TNF proteins might exist which would also prove valuable. So researchers set about finding them. By 1996, a considerable number of similar ligands had been found and the TNF superfamily had taken shape. Some, such as TNF-α, TNF-β and CD40L, had been highly studied and were known to have certain *in vivo* and *in vitro* activities. Others, such as CD27L, CD30L and 4-1BBL, were much less well understood.

5. One of the problems facing those researching into a human protein is how to obtain sufficient quantities of the protein to permit them to carry out their experiments. By the mid 1990s there was a well established way of trying to achieve this – the "wet

lab" technique. The researcher would first identify the protein with the activity of interest, partially sequence it, determine the sequence of the nucleic acid that encoded it and then use that nucleic acid sequence as a probe to clone the actual gene from a library. The cloned gene could then be used to express large quantities of the protein in some suitable host cell. It is to be noted that the starting point of this work is the protein with the activity of interest.

6. In the early 1990s, other routes of investigation began to open up, based upon the emerging science of "bioinformatics" or "computational biology". These relied upon the considerable increase in the amount of DNA and amino acid sequence data created and stored in publicly accessible databases and a parallel increase in the power of computers. As I shall elaborate, they permitted researchers to compare sequences and so identify genes and proteins of interest based upon their sequence similarity (homology) to other previously identified and characterised genes. But they suffer from the drawback that it may not be possible to determine the actual activity of the gene of interest until after it has been cloned and the protein has been subjected to *in vitro* and *in vivo* assays.

7. It was against this background that HGS found Neutrokine-α. It did so not by traditional wet lab techniques but by bioinformatics. Shortly after finding the polypeptide, it sought to protect its discovery by filing an application for patent protection which, in due course, led to the grant of the Patent. As proposed to be amended, it includes claims to the polypeptide, the nucleotide which encodes it, antibodies which specifically bind to it and corresponding claims to pharmaceutical and diagnostic compositions. The Patent identifies the polypeptide, correctly, as a member of the TNF ligand superfamily and includes a long description of its activities (which it defines as "Neutrokine-α activity") and its uses. But that description is not supported in any way by any data obtained from *in vitro* or *in vivo* studies. It is essentially a prediction based upon what was known about other members of the TNF superfamily.

8. Lilly contends that that this prediction was wholly speculative and that HGS filed its application for patent protection without knowing the biological activity or function of Neutrokine-α, the identity of any receptor, the conditions which it causes or the diseases which it might be used to treat. This gives rise to the first of the fundamental attacks on the Patent and one which has received relatively little judicial consideration in this country. Lilly says that the specification fails to disclose an invention capable of industrial application.

9. For essentially the same reasons, Lilly says that the specification does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art. It contends that the alleged invention could not be put to any practical use without undue effort. But the insufficiency attack goes wider. Lilly contends that, quite irrespective of the position in relation to Neutrokine-α itself, the claims to specific antibodies and to therapeutic and diagnostic compositions are not enabled and too broad because they encompass such products for use in relation to a vast range of diseases and conditions, and for which the teaching in the specification is wholly inadequate. It says the scope of the claims far exceeds any technical contribution which HGS may have made.

10. HGS counters that this attack flies in the case of reality. The disclosure of a new member of the TNF family was a major contribution to medicine and the disclosures of the Patent were of outstanding potential value to the pharmaceutical industry. Moreover, the invention has given rise to therapies which are undergoing clinical trials. Indeed, HGS has been collaborating with GlaxoSmithKline to carry out clinical trials of a monoclonal antibody to Neutrokine-α called Lymphostat-β for the potential treatment of rheumatoid arthritis and systemic lupus erythematosus ("SLE"). For its part, Lilly has spent about $50 million developing a monoclonal antibody to Neutrokine-α and plans to spend another $250million bringing it to the clinic.

11. The second major attack on the Patent is one of obviousness. Lilly contends the claims are obvious over two items of prior art. The first is a polynucleotide clone called the "Image clone" which is said to have been have been made available to the public before the priority date on being sent by the Lawrence Livermore National Laboratory to Washington University for sequencing. The second is a polynucleotide sequence, referred to as the "Fujiwara EST", which formed part of the GenBank library. Neither had been characterised but they both encode part of the full amino acid sequence of Neutrokine-α. Lilly contends that the application of standard bioinformatics techniques to either at the priority date would have led to Neutrokine-α and so they render the claims obvious.

12. The third attack on the Patent is one of added matter. It is made on the antibody claims and claims dependent upon them and it arises from an amendment made during the course of prosecution. Essentially it turns on a point of interpretation and I need say no more about it here.

13. I also have before me an application to amend the Patent. It is of some importance. The claims as granted are of considerable scope and HGS does not seek to defend them. They are directed not just to Neutrokine-α but also to other polypeptides encoded by polynucleotides which are homologous to the Neutrokine-α polynucleotide and which have Neutrokine-α activity. By the amendment HGS seeks to limit the claims to Neutrokine-α and to its extracellular domain. It also seeks to remove the reference to Neutrokine-α activity. Both aspects of the amendment are resisted, the first on the basis it introduces ambiguity and amounts to an attempt to redefine the invention and the second on the basis that it would extend the protection conferred by the polypeptide claims.

14. The following are therefore the principal attacks on the Patent:

    i) all the claims are invalid because the invention is not capable of industrial application, contrary to sections 1(1)(c) and 72(1)(a) of the Patents Act 1977 ("the Act");

    ii) all the claims are invalid because the specification does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art, contrary to section 72(1)(c) of the Act;

    iii) all the claims are invalid because the invention does not involve an inventive step, contrary to sections 1(1)(b), 3 and 72(1)(a) of the Act;

iv) claim 20 and dependent claims are invalid because the matter disclosed in the specification extends beyond that disclosed in the application as filed, contrary to section 72(1)(d) of the Act.

15. Lilly also argues that the proposed amendments are not allowable because they would result in the specification disclosing additional matter and an extension of the protection conferred by the claims, contrary to section 76(1)(3) of the Act.

16. For completeness, I should mention that there is an attack of lack of novelty, but it is accepted this cannot succeed against the claims as proposed to be amended.

The witnesses

17. Lilly called two expert witnesses, Professor Jeremy Saklatvala and Dr Rolf Apweiler, and one witness of fact, Dr William Heath. HGS also called two experts witnesses, Professor Randolph Noelle and Dr Andrew Martin, and one relevant witness of fact, Dr Stuart Farrow.

Professor Jeremy Saklatvala

18. In 1996, Professor Saklatvala was appointed Professor of Experimental Pathology, Imperial College Faculty of Medicine and Head of the Cell Signalling Department at the Kennedy Institute of Rheumatology. In 2002, he was appointed Deputy Head of the Institute. He is a physician by training but for most of his professional career has been involved in conducting and directing immunology research, particularly in relation to TNF and interleukin-1, another cytokine. He has been interested in the identification and characterisation of new cytokines for the past twenty years.

19. Professor Saklatvala's research into cytokines began while he was a member of the Strangeways Research Laboratory in Cambridge, first as a Senior Research Fellow and then, from 1982-1993, as Head of the Cytokine Biochemistry Department. The Strangeways Laboratory is an independent research charity which, at that time, attracted funding from bodies such as the Medical Research Council ("MRC") to conduct research on rheumatoid arthritis and other connective tissue disorders.

20. From 1993 until 1996, Professor Saklatvala headed the Cytokine Laboratory in the Department of Development and Signalling at the Babraham Institute in Cambridge. Like the Strangeways Laboratory, Babraham is a medical research charity. It is sponsored by the Biotechnology and Biological Sciences Research Council and its research is broadly focused on the mechanisms of cell signalling and gene regulation.

21. I found Professor Saklatvala to be an outstandingly good witness. He was well placed to assist me as to the state of the art at the priority date and the issues arising in relation to the allegations of lack of industrial applicability and insufficiency. He was scrupulously fair and balanced in expressing his opinions and I consider they carry considerable weight. I have found his evidence of very great assistance.

Dr Rolf Apweiler

22. Dr Apweiler is a bioinformaticist. In 1987, he joined the European Molecular Biology Laboratory ("EMBL") in Heidelberg in Germany, originally on a part time basis.

EMBL was founded to create a central computer database of DNA sequences. Initially his work at EMBL consisted of receiving nucleotide sequences submitted by a variety of laboratories, translating them into protein sequences and putting them onto the Swiss-Prot database. The size and scale of the project led to EMBL setting up the European Bioinformatics Institute ("EBI") in 1992. In 1994, the EBI, although still part of EMBL, was established in Hinxton in Cambridgeshire to share a campus with the Wellcome Trust Sanger Institute. The EBI houses the world's most comprehensive range of molecular databases and makes the data and the software needed to locate the data freely available to the research community, both commercial and academic. In its work, the EBI is funded by individual European governments, and funding agencies like the European Commission, the National Institutes of Health ("NIH") and the MRC.

23. In 1994, Dr Apweiler was asked to be head of the Swiss-Prot Group of the EBI. This group grew in scope and then became the Sequence Database Group ("SDG"), which he now leads. The SDG focuses on the production of protein sequences, protein family and nucleotide sequence databases and maintains and hosts EMBL-Bank (the European nucleotide sequence database), the UniProt protein resource, and a range of other related databases. SDG offers training and education programmes in bioinformatics to pharmaceutical and biotechnology companies.

24. It was suggested by HGS that Dr Apweiler was not a dependable witness and that his evidence was sometimes rather casual and not well thought out. I think these criticisms are unjustified. It is true he made some mistakes and that it is not easy to reconcile certain limited aspects of his evidence but, overall, I believe he was doing his best to assist the court. Moreover, I think it right to acknowledge that his experience did permit him to offer reasoned opinions as to the strategies and approaches which pharmaceutical companies take in utilising bioinformatics, including database mining, as part of their research.

Dr Richard Heath

25. Dr Heath joined Lilly as a Senior Biochemist in 1988, having completed a postdoctoral fellowship at Harvard Medical School. He has been directly involved in every Lilly antibody project since 1994. Since 2002, he has been Executive Director of Bioproduct Research and Development. He gave evidence about Lilly's attempts to develop a useful therapeutic or diagnostic antibody to Neutrokine-α. HGS made no criticism of the way Dr Heath gave his oral evidence but, it was said, his written evidence was, at best, incomplete and misleading as a result. I agree that Dr Heath's written evidence was not complete and, in my judgment, must be treated with some caution. But he gave his oral evidence clearly and fairly and it is possible, albeit with some difficulty, to piece together the principal efforts Lilly made in its Neutrokine-α programme. I deal with this later in this judgment.

Professor Randolph Noelle

26. Professor Noelle is Professor of Microbiology and Immunology in the Department of Microbiology and Immunology at the Dartmouth Medical School. He was awarded his PhD in Microbiology and Immunology from Albany Medical College of Union University in 1980. From 1980 to 1984, he was a post-doctoral fellow at the University of Texas Health Science Center at Dallas where he trained as a B cell

immunologist. In 1984, he joined the Department of Microbiology at Dartmouth Medical Center as an Assistant Professor of Microbiology and in 1990 he became an Associate Professor of Microbiology and an Adjunct Associate Professor of Biochemistry. In 1995, he was appointed Professor of Microbiology and Immunology and, since 2001, has been the Co-Director of the Immunology and Immunotherapy Program. He was Deputy Director of the Norris Cotton Cancer Center from 2002-2003, and, since 2005, has been the Director for the Immunotherapy Center at Dartmouth Medical School. Professor Noelle's laboratory at Dartmouth studies cells and molecules that govern immunity, including studying the role of members of the TNF ligand superfamily in antibody-mediated immunity. In 1991, his was one of three groups that discovered the CD40 ligand.

27. It is apparent from this summary that Professor Noelle is a highly skilled and distinguished immunologist and was at the centre of work into TNF ligand superfamily members in 1996 and in a good position to assist me in relation to the issues I have to decide. However, Lilly submitted that I should exercise considerable caution before placing reliance on Professor Noelle's opinions. Two aspects of his evidence caused me some concern. The first was his evidence that if the skilled person had wanted to confirm any of the statements contained in the Patent then he could readily have done so using methods well known at the priority date. Given the scope of the teaching of the Patent and the efforts being made, even now, to investigate the activities of Neutrokine-α, this sweeping generalisation does not accord with reality. The second was Professor Noelle's interpretation of the paper by Moore et al reporting on the work of HGS, which I discuss later in this judgment. As I explain, I do not accept that Professor Noelle's interpretation of the teaching of that paper is reasonable. Nor was it consistent with the work of HGS as shown by the underlying documents explored in the course of his cross examination. I acquit Professor Noelle of any suggestion that he intended to mislead. But these are matters which I feel I must take into account in assessing the weight to be placed on his opinions.

Dr Andrew Martin

28. Dr Martin is a Senior Lecturer in Bioinformatics in the Department of Biochemistry and Molecular Biology at University College London. He obtained his first degree in Biochemistry at the University of Oxford in 1986 and, in 1990, was awarded his D Phil in field of the molecular modelling of antibody combining sites. In 1996, Dr Martin was a post doctoral Research Fellow at University College working mostly on structural bioinformatics, analyzing and predicting the conformation of loops in proteins and, in particular, looking at the structure of antibodies. I found Dr Martin to be a fair and careful witness although I accept that his evidence was given from a stance materially more remote than that of Dr Apweiler, and this is a matter which I have had well in mind.

Dr Stuart Farrow

29. Dr Farrow is a manager in the Target Discovery Department at GlaxoSmithKline. He explained the research programme carried out by his team in seeking to identify and isolate new members of the TNF ligand superfamily in the mid 1990s. Rightly, no criticism was made of the way he gave his evidence.

Person skilled in the art

30. The Patent is directed to a team of people with about two years of post doctoral experience. It would include a molecular biologist familiar with routine techniques of cloning, expression and sequencing of genes and proteins; a biochemist to make and purify recombinant proteins; and a biologist or immunologist with experience of the TNF superfamily and with the skills necessary to generate and test antibodies. I am also satisfied that any team interested in identifying a new member of the TNF superfamily would carry out a literature search to gather as much knowledge as possible about the existing members.

31. In so far as there was a dispute between the parties it arose in relation to the role of a bioinformaticist in the team. As I have mentioned, the science of bioinformatics involves the comparison and analysis of similarities and differences in sequence data using computer software and it arose from the desire to interpret the ever increasing amount of DNA and amino acid sequence data being created and stored in databases such as GenBank and Swiss-Prot. Professor Saklatvala expressed the view that, in the case of families such as TNF, where there was an interest in identifying as many members of the family as possible, bioinformatics obviated the need for initial biochemical purification and characterisation of each cytokine and so a bioinformaticist would certainly have been part of the team. However, under cross examination he accepted that by 1996 he had not used the technique himself and he had little direct knowledge of the extent to which it was used in commercial pharmaceutical laboratories. Professor Noelle had only a peripheral awareness of bioinformatics but accepted that a team interested in finding a new member of the TNF family might consult a bioinformaticist. In addition to the experts, I also had the benefit of some evidence as to the extent to which it was used in the pharmaceutical industry at or around the priority date. Dr Farrow explained that Glaxo had a bioinformatics group at his time and that its function was to provide infrastructure for the various molecular biology research teams by up loading new versions of sequence databases and training molecular biologists in how to conduct basic homology searches. Moreover, Dr Heath at Lilly used bioinformatics to screen the Incyte database using a series of what he described as a series of degenerate screening motifs or algorithms. Finally, and as will become apparent from my discussion of the common general knowledge, it is clear that Immunex was active in the field and used bioinformatics to identify the TNF ligand, TRAIL.

32. In the light of all the evidence, I conclude that the skilled team looking for a new member of the TNF superfamily would have been aware that the science of bioinformatics could provide assistance in the search and, if a bioinformaticist was not already a member of the team, would have considered it worthwhile to consult such a person. I return to the issue of what may or may not have been obvious to the team later in this judgment.

Common general knowledge

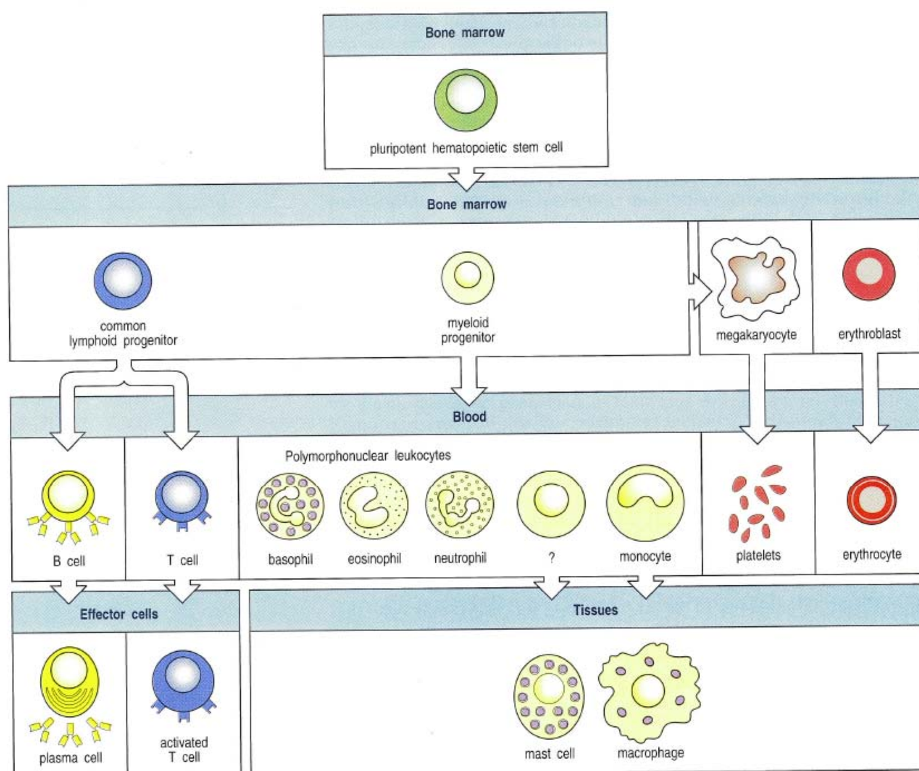
33. There are four areas of common general knowledge which have a particular bearing on this case: immunology, the TNF superfamily, biological assays and bioinformatics. I will deal with them in turn.

Immunology - general

34. Professor Noelle provided an explanation of some of the basic non contentious concepts of immunology which I have gratefully adopted, on occasion with minor modification, in paragraphs [35] to [50] of this judgment.

35. The immune system is the body's defense mechanism against infection. The two broad classes of immune responses are antibody ("humoral") responses and cell mediated ("cellular") responses. Antibody responses involve the production of antibodies (or immunoglobulins) which are capable of binding to specific targets called antigens. Cell mediated immune responses involve the production of specialized cells that react with targets on the surface of other cells.

36. During the 1960s it was discovered that these two classes of response were mediated by different types of white blood cells, namely B cells and T cells. In mammals, B cells develop in adult bone marrow or the fetal liver and are responsible for the synthesis and secretion of antibodies, while T cells develop in the thymus and are generally responsible for cell mediated immunity. The development of the cells of the immune system, including B and T cells, is illustrated schematically below:



The general development of cells of the immune system (taken from "ImmunoBiology – The Immune System in Health and Disease" (1996) Janeway and Travers).

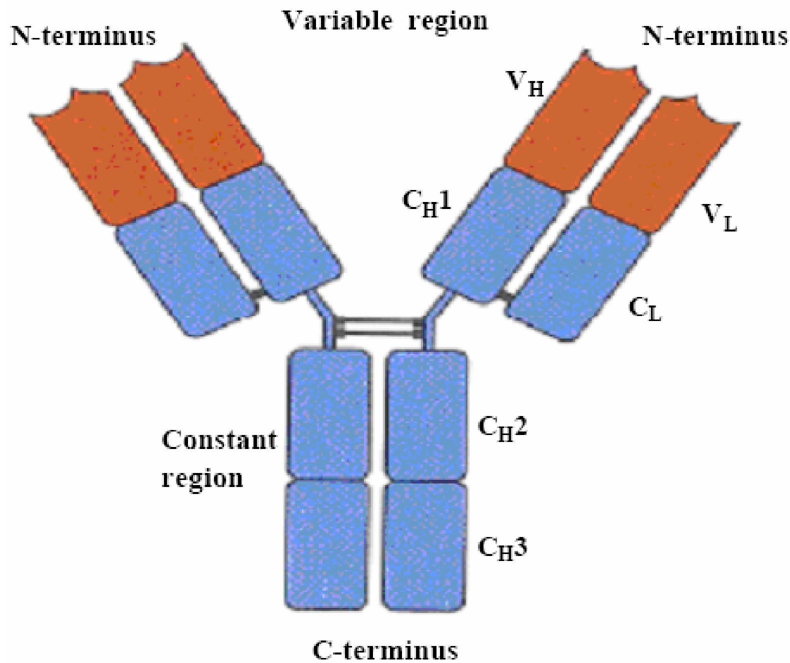
37. Generally, B cells and T cells are collectively called lymphocytes while the broader class of white blood cells, including B cells, T cells, basophils, eosinophils, neutrophils, monocytes macrophages and dendritic cells are all called leukocytes.

38. The process by which B cells produce antibodies begins when B cells are exposed to a specific antigen and become activated. Upon activation, they proliferate, differentiate and mature into immunoglobulin-secreting plasma cells which secrete antibodies having the same unique specificity to the original activating antigen. Other cells of the immune system interact with B cells, both directly and indirectly, to assist this process. A small subset of differentiated cells (called memory B cells) remains in the immune system to provide a more immediate response to subsequent exposure to antigen.

39. In general, T cells play two major roles in supporting cell mediated immune responses. First, T cells enhance the response of other lymphocytes to secrete cytokines that regulate the immune system. Second, T cells assist in destroying infected cells and tumour cells. T cells that enhance the response of other lymphocytes are called helper T cells while T cells that destroy other cells are called cytotoxic T cells.

40. Antigens are substances that are generally foreign to the body and which are recognized by antibody molecules (produced by B cells) or by T cells. Antigens contain one or more sites called antigenic determinants (or epitopes) to which antibody molecules bind in order eventually to clear the antigen from the body.

41. Thus, antibodies are synthesised in response to the presence of antigens and, in nature, will bind to the antigen that elicited their synthesis. By the priority date of the Patent, the general structure of antibodies was well known, and is shown below:



An example of the structure of an antibody (adapted from "ImmunoBiology – The Immune System in Health and Disease" (1996) Janeway and Travers).

42. They consist of two identical heavy chains and two identical light chains. The heavy chains comprise a variable region and three constant regions. The light chains comprise one constant region and one variable region. The variable regions make up the antigen binding site of the antibody and contain within them hypervariable regions (also known as complementary determining regions or CDRs) that are essential in determining its binding characteristics. The specificity of antibody binding is dependent upon the chemical and physical interaction between the antigen binding site of the antibody and its epitope at the molecular level.

43. Most antigens possess several epitopes. Consequently any particular antigen may generate the production of and be recognised by several different antibodies, each of which may recognise a unique epitope and be produced by different B cells. This is called a polyclonal antibody immune response.

44. It has been known for many years that antibodies can be generated for experimental purposes by injecting an antigen into an animal such as a mouse or rabbit, allowing the animal to raise a humoral response and then collecting the antibody rich serum (called antiserum). Just as in the natural polyclonal humoral response, this antiserum will contain a heterogeneous mixture of antibodies.

45. An antibody of interest can be separated from such a polyclonal mixture by the technique of affinity chromatography. For example, if it is known that an antiserum produced against protein X is also likely to contain many other antibodies, the antiserum can be passed through an affinity chromatography column which contains

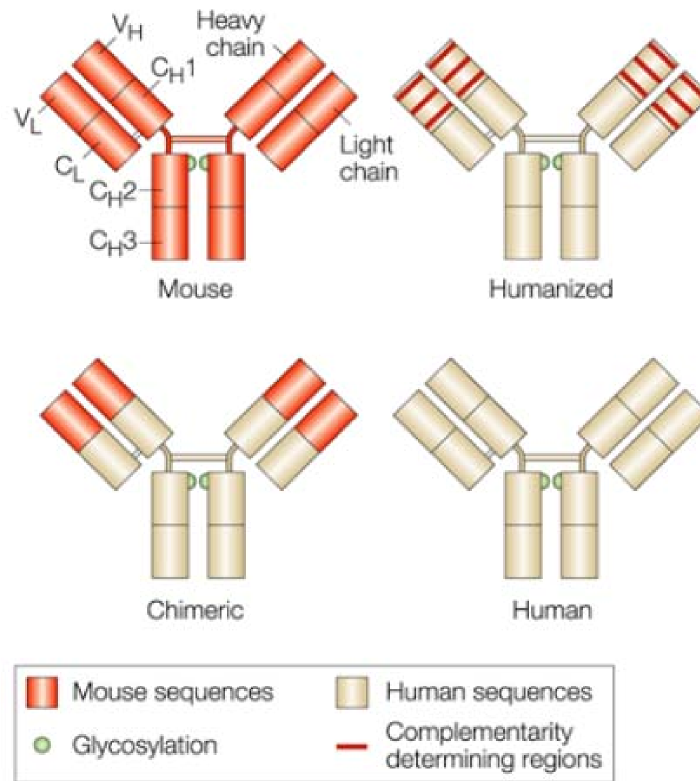
immobilized molecules of protein X. The antibodies to X will become bound to the immobilized molecules while all the other antibodies will pass through the column. The X antibodies can then be uncoupled and eluted from the column.

46. In the mid 1970s, Köhler and Milstein devised a technique for producing a homogenous population of antibodies by fusing lymphocytes from an immunized mouse to a mouse myeloma tumour cell to produce hybrid cells. The antibodies produced by such hybridoma cells are known as monoclonal antibodies since they are derived from a single B cell and produce antibodies that are identical in structure and specificity. This technology revolutionised the use of antibodies by providing a limitless supply of a single antibody.

47. The potential of these techniques to produce useful pharmaceutical products has long been recognised. However, translating that potential into practice is not necessarily straightforward. In 1996, the starting point was generally to try and find a murine monoclonal antibody which neutralised the biological activity of a particular antigen. This approach requires an understanding of the activity of the target antigen in order to design screens to filter out the potentially useful antibodies. Alternatively, the ligand receptor can be used carry out the screen, assuming of course that the receptor has been identified and is available.

48. Secondly, it requires the identification of antibodies that bind specifically to the target and not to other antigens, a matter of importance if the therapeutic antibody is to be effective and not interfere with some other biological system and cause undesirable side effects. As Professor Saklatvala explained, this requires some effort. To prove that an antibody does not react with any antigens except the one it is intended to react with is to prove a negative and there is no standard array of assays against which this can be measured.

49. Thirdly, monoclonal antibodies derived from murine sources cannot generally be used in human therapy because, upon administration to a human, they themselves are treated by the body as antigens and so tend to generate an immunogenic reaction. To try to overcome this problem recombinant DNA technology has been used to produce chimeric mouse-human antibodies and humanised antibodies which contain human sequences where possible and so attempt to disguise the residual murine elements from the human immune system. Later developments in the early 1990s involved the use of phage display technology and transgenic mice to produce fully human antibodies – but these technologies were proprietary to specialised companies such as Cambridge Antibody Technology. The general structures of mouse, chimeric, humanised and fully human antibodies are shown in this illustration produced by Professor Noelle:



A comparison of the structure of Mouse, Chimeric, Humanised and Human Antibodies.

50. A number of therapeutic monoclonal antibodies were in clinical development as early as 1980. In addition, by 1996, a number of murine, chimeric, humanised and human antibodies were also in clinical development. However, by 2007, the only available therapeutic antibodies to a TNF family member were Remicade (also known as infliximab and made by Centacor) and Humira (also known as adalimumab and made by Abbott Laboratories). A third product, Enbrel, was also available but this is a soluble receptor rather than an antibody. All three therapies relate to TNF-α. No antibody or receptor therapy has yet been marketed in relation to any other TNF family member.

The TNF superfamily

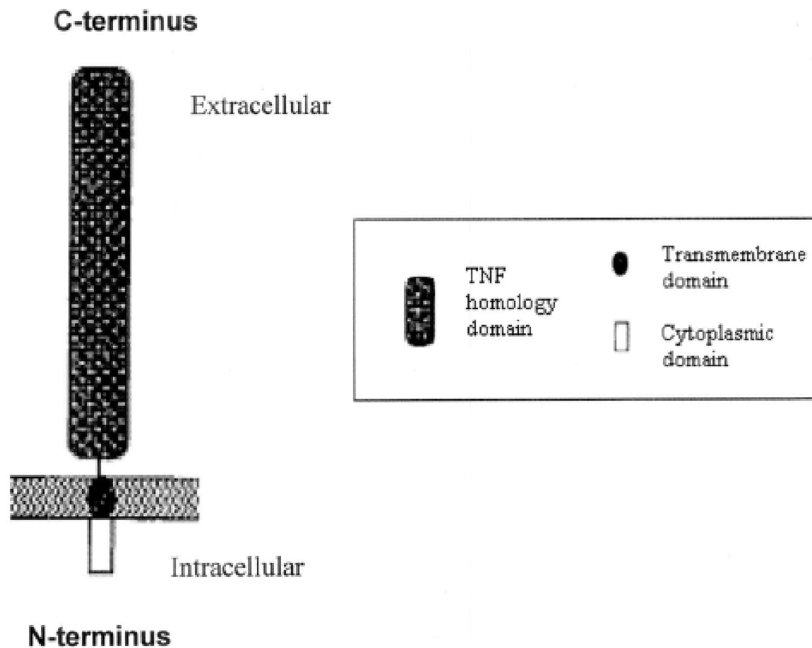
51. The founding member of the TNF ligand superfamily was TNF-α which was isolated in 1975. Its DNA sequence was determined in 1985 and its crystal structure was published in 1989. By 1996, it had long been recognised as a cytokine with a significant role in the regulation of immune cells.

52. The discovery and elucidation of the activity of TNF-α attracted a good deal of interest from immunologists who began to search for similar molecules. By 1996 at

least eight further members of the TNF ligand superfamily had been found, namely TNF-β), CD27L, CD30L, CD40L, Fas ligand (CD95L), 4-1BBL, OX40L and TRAIL.

Structural characteristics

53. Members of the ligand family were well known to be transmembrane proteins with an extracellular TNF homology domain having the general structure depicted below:



54. There was no challenge to Professor Noelle's summary of the structural characteristics of the family as including the following:

i) a type II transmembrane protein without a signal peptide and with a hydrophobic transmembrane domain;

ii) a large extracellular domain (ranging from 139-216 amino acids) with 12-36% overall homology to TNF-α;

iii) a consensus TNF ligand superfamily signature sequence within the C-terminal extracellular domain; and

iv) a small, intracellular domain (ranging from 11-82 amino acids).

55. I would simply note by way of qualification that TNF-β has been reported as being an entirely secreted protein and that several members of the TNF ligand superfamily also exist in biologically active soluble form.

56. Importantly, and as Professor Saklatvala accepted, analysis of sequence homology, in particular the conserved (consensus) domains, would permit a researcher to identify whether any candidate protein was in fact a new member of the family.

Activities

57. This is a subject of considerable importance because an understanding of the activities of a cytokine are essential to any consideration of its potential utility. By 1996, the activities of the members of the TNF ligand superfamily, and particularly TNF-α, had been the subject of a considerable amount of study. It was known that their physiological and pathological activities were mediated by binding to receptors, of which the following had been identified: OX40, 4-1BB, CD27, CD30, CD40, TNFRI, TNFRII and Fas.

58. In the course of the evidence the experts were asked about a series of publications, many of them review articles, which summarise the work carried out in relation to the TNF ligand and receptor superfamilies by the priority date.

59. The first is a book entitled *Therapeutic Modulation of Cytokines* (1996, CRC Press Inc.) edited by Henderson and Bodmer. Chapter 10 is a review by Bodmer and Foulkes of the extent to which animal models and clinical studies had shown TNF-α played a role in pathological responses. The authors referenced work suggesting it might be involved in a wide range of diseases including septic shock, rheumatoid arthritis, inflammatory bowel disease, tissue rejection, HIV infection, and some adverse drug reactions and explained that two types of TNF-α antagonists had been used in the studies: monoclonal antibodies capable of binding to and neutralising TNF-α, and molecules based on the extracellular portions of the cellular receptors. As Professor Saklatvala accepted, this work generated a considerable interest in researchers to look for other members of the family, but whether they would prove equally valuable in addressing the same clinical indications would depend upon their biological activity.

60. The second publication is an important review article by Gruss and Dower, (*Blood*, Vol 85, No 12, June 15, 1995, 3378-3404). At the outset of their discussion of biological properties, the authors explained that TNF-α and TNF-β mediate cell activity and proliferation and are functionally linked as primary mediators of immune regulation and the inflammatory response. TNF-α has a pathogenic involvement in septic shock, some autoimmune disorders, malignancies and graft versus-host disease. They then mentioned what will be seen to be a recurring theme through the publications, namely that one of the features of the members of this superfamily is that they have some overlapping functions but also many individual ones in relation to a wide variety of cell types:

> "The nine TNF-related cytokines show distinctive but overlapping cellular responses for developmental and regulatory networks involving cells of the lymphoid, hematopoietic, and other lineages, such as stromal cells and neuronal cells."

61. More specifically, Gruss and Dower continued that although the cytoplasmic domains of most TNF receptor superfamily members are divergent from each other, several biological functions, such as cytotoxic signals, induction of proliferation and differentiation, and cellular activation are shared between two or more ligands.

62. In relation to T cells, Gruss and Dower said that biological activities related to T-cell mediated immunity are a unique feature for all members of the TNF ligand superfamily. All ligands and receptors are expressed on activated T cells and all superfamily members are essential for T cell co-stimulation and activation. Based upon this description, Professor Saklatvala agreed that the skilled person would have anticipated that one of the activities of any new member would relate to T-cells and that it might play a role in regulating the immune response and in the control of tumours or malignant disease.

63. As to B cells, Gruss and Dower explained that B cell proliferation and antibody secretion is stimulated by at least TNF-α, TNF-β and CD40L. Further, several members participate in T cell dependent help for B cells. Once again, Professor Saklatvala accepted that an effect on B cell proliferation was something that would have been anticipated as a possible property of a new member of the family.

64. Gruss and Dower concluded:

> "In summary, several members of the TNF ligand and receptor superfamilies play crucial roles for lymphoid and thymic development, T-cell-mediated immune responses, T-cell-dependent help for B cells, and humoral B-cell activity. The detailed interactive network for the immune response in lymphoid differentiation mediated by the TNF-like ligands needs further evaluation."

65. Gruss wrote a further review the following year (*Int. J. Cli. Lab. Res* (1996) 26: 143-159). He reported that TNF ligands are involved in regulation of cell proliferation, cellular activation and differentiation, including control of cell survival or death by apoptosis or cytotoxicity. He again noted that biological activity related to T cell mediated immunity is a common feature of all members of the family and all are expressed on the surface of T cells and co-stimulate T cell proliferation. Overall, he said the interaction of the TNF receptor and ligand superfamilies is involved during lymphoid or thymic development, T cell mediated immune responses, T cell dependent help for B cells or humoral B cell activity. In addition, several have been involved with distinct human diseases. In the course of his cross examination, Professor Saklatvala agreed that anybody beginning research into a new member of the TNF ligand superfamily would have expected that it would have the same roles, to some degree, as these.

66. However, Gruss also contained a great deal of detail, from which it is apparent that the picture was recognised to be extremely complex. He explained the ligands had been shown to be expressed in different tissues. He reiterated the point made in Gruss and Dower that it had also been found that some properties are shared by all ligands, some properties are shared by only some ligands and other properties are unique to particular ligands. Even more confusingly, the response to any particular ligand can be stimulatory or inhibitory. As he elaborated in a significant passage at page 146 (references deleted):

> "Shared biological activities of the TNF-like ligands

NGFR p75, CD40, CD95, CD120a and CD120b are expressed in many tissues, while CD 27, CD30, 4-1BB, and OX40 are almost completely restricted to the hematopoietic system. In general, members of the TNF ligand super-family have distinctive but also overlapping cellular activities. It is of particular interest that all members of the TNF receptor and ligand superfamilies are expressed on activated T cells and involved in costimulation of T cells, but differences in the distribution, kinetics of induction, and requirements for induction indicate a defined role of each ligand for T cell-dependent immune responses. Biological involvement for cell-cell interactions, particularly between T cells and B cells, T cells and monocytes, and T cells and T cells, have been identified and can be reciprocal with signalling through both the ligand and/or the receptor (Fig.1). Overall, the biological response can be stimulatory or inhibitory, depending on the cell type or activation stage. Additional stimulatory signals are induced by stimulation of cytokine secretion, upregulation of adhesion, activation, and costimulatory molecules to amplify the cellular activation process. One negative regulatory mechanism to limit the stimulatory cellular activation includes the shedding of the receptors after ligand binding. The induction of cytotoxicity, proliferation, cellular activation, or differentiation is shared between several TNF ligands. For example, TNF, LT-α and CD40L have been shown to take part in the T cell-dependent help for B cells required for B cell proliferation, immunoglobulin secretion, and accessory molecule expression. TNF, LT-α, CD30L, and CD40L are capable of inducing cellular aggregation and upregulation of adhesion molecules. CD30L and CD40L are also able to induce/upregulate CD8 (B7-1) and CD86 (B7-2) expression. In addition, some of the TNF ligands, including TNF, CD30L, and 4-1 BBL, are abundantly expressed by activated monocytes/macrophages. The ability to induce cell death (necrosis and/or apoptosis) is another unique biological feature of this ligand family and is presently established for TNF, LT-α, CD30L, 4-1BBL, CD95L, and TRAIL. For example, CD95 and CD120a/CD120b are expressed broadly and transduce both stimulatory or inhibitory signals. TNF is able to induce cell death by necrosis or apoptosis, while CD95 mediates mainly apoptotic (programmed) cell death, including the activation-induced cell death of T cells required for T cell repertoire formation and tolerance. CD30L and 4-1BBL show distinct cytotoxic activities for selected biological targets, including large cell anaplastic lymphomas or activated T cells. Further studies are needed to identify unique versus redundant biological and physiological functions for each of the TNF superfamily ligands."

67. The fourth paper is by Shanebeck et al., (*Eur. J Immunol.* 1995. 25:2147-2153). In the introduction the authors noted that all the members of the TNF ligand superfamily had been reported to be expressed on activated T cells and all had been shown to co-stimulate T cell proliferation, but that the effects on B cells had not been well characterised. The aim of their study was to investigate the recently discovered ligand CD30. They concluded it is a potent mediator of B cell growth and differentiation *in vitro*.

68. Cosman published another review of the TNF ligand superfamily in 1994: (*Stem Cells* 1994; 12, 440-455). After reviewing the literature in relation to the various ligands, he concluded that the discovery of the family had opened an important area of research. He observed that in view of the diverse and redundant biological activities of the ligands in vitro, the construction of genetically modified mice in which receptor genes had been disrupted (so called "knock out" mice) would be essential in understanding the role of each family member. It was obvious that all the receptors and ligands were expressed on activated T cells and all shared the property of costimulation of T cell proliferation, which suggested redundancy of function. However, even the limited studies conducted to date suggested the receptors and ligands would be found on different lymphocyte or monocyte subpopulations, would have different requirements for induction and would be induced and expressed with different kinetics. There was also a good possibility that synergistic interactions would take effect between different ligands. He suggested that understanding the complexity of the signalling pathways would be a challenge for years to come. When asked about this paper, Professor Saklatvala again accepted that a researcher who found a new family member would have been looking for and expected to find that it was expressed on activated T cells and was a costimulant of T cell proliferation.

69. The sixth paper in the series is by Wiley at al (*Immunity*, Vol 3, 673-682, December 1995). This reported work at Immunex and the identification, cloning and characterisation of a new member of the TNF family, TRAIL, which the authors found rapidly induced apoptosis of a wide range of cell lines. It was found by using bioinformatics to conduct a search of the National Center for Biotechnology Information EST database using a consensus sequence based upon the most conserved region of the TNF family.

70. The final paper is by Maini et al of the Kennedy Institute (*Immunological Reviews* 1995, No.144). This described the investigation and use of the Remicade monoclonal antibody to treat rheumatoid arthritis. These researchers followed what Professor Saklatvala described as the standard route of performing experiments *in vitro* (in this case on rheumatoid arthritis synovial tissue) and then *in vivo* in animal models. Having gathered evidence of an important role for TNF-α, the concept was then tested in human trials. It was their working hypothesis that the antibody had two major effects. First, it interrupted the cytokine cascade. Secondly, there was substantial evidence that it had a major effect on the recruitment and trafficking of blood cells to the joint. This was confirmed by Professor Saklatvala who considered that an explanation for its therapeutic effect in rheumatoid arthritis is that it prevents leukocyte traffic across the vascular endothelium and this is due in part to a direct effect on the endothelium.

71. Pulling these various strands together, I derive the following conclusions. I have no doubt that the details of all these publications did not form part of the common

general knowledge of the ordinary skilled person in 1996. However, as the experts accepted, they would have been found by any researcher setting out to find or investigate the properties of a new member of the TNF ligand superfamily. Upon reading the publications any such researcher would have appreciated that the activities of the members of the superfamily are extremely complex and had been the subject of extensive research, as reflected in the forest of papers they reference. But some general points about the TNF ligand superfamily members would have emerged:

i) They were all expressed by activated T cells and some by other cells such as activated monocytes and macrophages.

ii) Their activities were mediated by binding to receptors, of which a number had been identified.

iii) They were known to have pleiotropic actions, that is to say a multitude of different effects on different cell types, driving multiple biological processes. Some of those activities were understood to be unique to particular TNF ligands and others were understood to be shared by some or all the other TNF ligands.

iv) They all played a role in the regulation of T cell proliferation and T cell mediated immune responses.

v) Some of the ligands played a role in the regulation of B-cell proliferation and antibody secretion and some took part in T cell dependent regulation of B cells.

vi) Some of the ligands had an ability to induce cell death by necrosis or apoptosis.

vii) TNF-α and TNF-β were functionally linked as primary mediators of immune regulation and inflammatory response.

viii) It had been suggested that various ligands were associated with a very wide range of particular disease states such as septic shock, rheumatoid arthritis, inflammatory bowel disease, tissue rejection, HIV infection, and some adverse drug reactions. But no disease had been identified in which all the ligands were involved.

ix) TNF-α was the only ligand shown to have a therapeutic application; that being for the treatment of rheumatoid arthritis through the use of a specific monoclonal antibody. It was believed to operate in a particular way, namely by interrupting the cytokine cascade and by controlling the recruitment and trafficking of blood cells to the joint.

72. Moreover, it was appreciated that further studies were both needed and desirable to identify further ligands in the TNF superfamily and, in relation to each ligand, to seek to identify its unique and redundant biological functions. There was undoubtedly an incentive to do so, because of their apparent roles in the regulation of the immune system and inflammatory response, their possible involvement in various different

diseases and so also, in due course, their potential as therapeutic agents. The rewards were potentially very great. As Professor Saklatvala accepted at Day 2, page 203:

> "Q. Again, a very general question, but can I suggest to you that the data in this paper [Maini] are such as to provide a real incentive to anybody to investigate the properties of a new member of the TNF family to see whether that is going to be as good as or even possibly better than TNF alpha?
>
> A Yes, I agree with that."

73. And again a little later on Day 2 at 209-210:

> Q. ……..What is it that causes you to try and identify a particular new molecule?
>
> A. Well, I think if it belongs to, if, say, there is a group or family of proteins and you think there may be missing members and you would seek to find missing members because they have biological activity in an area which is your interest or which may have practical application.
>
> Q. So when you go to your head of research to justify the expenditure on the project, it is because you are able to say there is a reasonable expectation of activity and hence utility?
>
> A. Yes. I mean, I do not know how pharmaceutical companies decided on setting up projects in particular areas in terms of their disease interests, disease focus. Obviously we are just talking about this example here is we would have – be thinking of considering a plan to hunt for new members of the TNF family and we would be doing that because we were interested in TNF and because we knew that blocking TNF in rheumatoid had been successful; so that is one particular example. So I think that would be quite a strong case for going ahead and looking for members of this family which could be useful."

74. This was a reflection of the reality that pharmaceutical companies and academic institutions were indeed looking for further members of the TNF ligand and receptor superfamilies and seeking to elucidate their various biological functions and roles in disease states, ultimately with a view to developing a therapeutic or diagnostic product, if possible.

Biological assays

75. Assays are essential to determine the activities and functions of a cytokine. They are also necessary to determine whether any putative therapeutic is effective. It was undoubtedly the case that many assays had been performed in relation to members of the TNF ligand and receptor superfamilies. A good number of them are described in the publications to which I have referred and many are referred to in the Patent, to which I will shortly turn. However, for obvious reasons, none had been described in

relation to Neutrokine-α. It was not suggested by Lilly that the actual assays necessary to assess the activity of Neutrokine-α were common general knowledge but it was put to Professor Saklatvala that, based upon the teaching in the Patent and the common general knowledge, one would anticipate activity on T cells and B cells and design an assay accordingly. He did not accept this would be straightforward (Day 2 at pages 228-230):

> "Q. Right, and because of the knowledge that you have and we have been through Gruss and Dower and all those sort of things, you would anticipate activity on T cells and B cells?
>
> A. Yes, I would try to get activity on T cells and B cells. I would also try to get activity on connective tissue cells.
>
> Q. Right and you would devise a specific assay for B cells which would probably involve some form of well-known costimulant for B cells?
>
> A. I think this is a research project rather than carrying out a straightforward assay. This document does not give me the activity. It just says here is a sequence, it is related to the TNF superfamily. It does not tell me anything about its activity that I could not get from reading, for instance, Gruss and Dower.
>
> Q. Right, so ---
>
> A. So I do not think that -- I was not persuaded when I read this document that these people had done any experiments on the biological properties of this molecule at all.
>
> Q. That is, as far as we are concerned ----
>
> A. ---- they are simply saying it is a member of a superfamily. It is just a sequence and it is a member of a superfamily
>
> Q. If that were the case ----
>
> A. So then they do not know its function. They cannot know its function just because they know it belongs to a superfamily.
>
> Q. What they can do is to predict function, or as you would put it, make an educated guess as to function, is that fair?
>
> A. Yes.
>
> Q. And the educated guess is something that can be made because of the established data in relation to members of the TNF ligand superfamily?
>
> A. Yes.

> Q. So they are drawing upon that to make their, you would say prediction, because you say have not done the work. What I am getting at now is ---
>
> A. You say it is prediction, I would say it is speculation
>
> Q. We can all argue about the English language. The reasonable expectation, would you go that far?
>
> A. Expectation, yes."

76. Professor Noelle was of the view that it would be relatively straightforward to devise and conduct assays and suggested that a good many were routinely conducted in his laboratory. By way of illustration, he considered the position in relation to T cells and explained that only a limited number of T cell costimulation assays existed and that such an assay could be conducted in four to five days. However, he accepted that faced with what was believed be a new TNF ligand, a researcher would prioritise and order them based upon his own personal interests.

77. The evidence by the two experts is apparently inconsistent but I believe the difference between them was largely attributable to their different view points. In my judgment the skilled person would indeed have been able to identify or develop from his common general knowledge some assays with which to begin the study of the new ligand and start to assess at least some of its possible activities. But I am not satisfied that such studies would have produced informative results and I have no doubt that to carry out a comprehensive screening programme so as to identify the role of the ligand in the biology of any particular cell type would be an altogether more complex task, and one properly characterised as a research programme. This is a topic to which I return in considering the work actually done in relation to Neutrokine-α.

Bioinformatics

78. Much of the background was not in dispute and I have drawn the discussion which follows largely from the reports of Dr Apweiler and Dr Martin.

DNA, RNA, cDNA and ESTs

79. DNA is the molecule of inheritance in prokaryotic and eukaryotic cells and in some viruses. It comprises a long linear chain of units called bases or nucleotides which are linked together with a backbone of sugar phosphates to form a polynucleotide. There are four DNA bases and they pair together in a specific way which allows two complementary strands of DNA to interact with each other and form the well known double helix structure.

80. DNA has two essential functions. One is to allow replication of the genetic code. The other is to encode functional molecules, most importantly proteins. To achieve this latter function the DNA acts as a template to encode a related molecule called RNA. The process of copying DNA to form RNA is known as transcription and the regions of DNA which are transcribed are called genes. Within a gene only one strand of the DNA, the coding strand, is transcribed and the process involves reading the gene in a particular direction (5' to 3').

81. Chemically RNA is very similar to DNA. The particular kind of RNA of relevance to these proceedings is called messenger RNA or simply mRNA. It is first produced in the form of a primary transcript which, in the case of eukaryotic cells, includes non coding regions of the gene called introns. These are spliced out of the molecule and a tail and cap (called UTRs or untranslated regions) are added to produce the mature transcript.

82. Thus the mature mRNA molecule contains the coding regions of a gene copied from the DNA together with the UTRs. The genetic code uses contiguous groups of three bases read along the mRNA (equivalent to the coding strand of the DNA) to encode each amino acid. A group of three bases is known as a codon. Since there are four types of base, there are 4^3 (i.e. 64) possible codons. Three of the codons act as 'stop' signals to indicate the end of translation. Since there are 61 other codons to encode the standard 20 amino acids, there is redundancy in the code. The result of the translation process is a linear strand of amino acids which folds up to form the functional protein.

83. The benefit for scientists of looking at mRNA rather than DNA is that it represents those parts of the genome which code for proteins. However, it is unstable outside the cell so it cannot be sequenced directly. Instead, it is copied in the laboratory to produce the more stable complementary DNA (cDNA) using an enzyme called reverse transcriptase.

84. Expressed Sequence Tags ("ESTs") are small pieces of DNA sequence generated by sequencing the end of a cDNA. They are usually 200 to 500 nucleotides long and represent 20-30% of the cDNA. Either strand of the cDNA can be sequenced to generate an EST which therefore represents either the 5' end of the mRNA or its reverse complement at the 3'end. The 5' EST usually codes for protein but the 3'EST usually contains the non-coding 3' UTR in addition to a coding region.

85. This summarises the ideal position. But it was well understood by 1996 that most cDNAs did not encompass the entire sequence of the original mRNA because the synthesis of the first cDNA strand was incomplete. It was also well known that cloning artefacts could occur resulting in the production of artificial and inaccurate sequences. Moreover, ESTs themselves were sequenced in high-throughput, single pass, sequencing experiments with the result that the quality of the data was low and often included errors.

Computer translation of coding sequences

86. Given a cDNA sequence for the coding region of a protein, it is in principle straightforward to translate the DNA sequence into a protein sequence using the genetic code. However, in order to perform a correct translation, it is necessary to know the 'reading frame' in which the sequence should be interpreted. This may not be possible to determine, not least because of errors in the sequence data. A further problem arises because it may not be obvious which DNA strand is the coding strand. So one can also derive the complementary strand and perform translations on that strand. The safe course is therefore to take 3 forward and 3 reverse reading frames in what is known as a '6-frame translation'.

87. Sequence errors within the EST sequence also cause problems within the correct reading frame. For example, an error in reading a DNA base can cause the DNA

sequence to encode either an incorrect amino acid residue or a premature stop codon, thus truncating the protein sequence. In addition, sequencing errors resulting in an erroneous insertion or deletion of either one or two DNA bases causes a 'frameshift', and the resulting amino acid sequence will be incorrect from that point. Sequencing errors such as these mean that the selection of the longest open reading frame from a six-frame translation of an EST will not necessarily result in the biologically relevant peptide being identified.

The available information

88. By 1996, various types of DNA data were being produced and made available. First, there were the full sequences of genes which had been studied in depth. Second, DNA sequence data were being generated on a large scale as part of the Human Genome Project. The project was officially launched, and the National Center for Human Genome Research was established in the US, in October 1990, with the aim of sequencing the entire human genome. It generated genomic, EST and cDNA data. It is fair to say that progress was initially slow but it speeded up substantially in about 1998 when faced with competition from Craig Venter of Celera Genomics. The first completed draft of the human genome was announced in June 2000 but it suffered from considerable errors and lack of coverage.

89. GenBank is the NIH's genetic sequence database, an annotated collection of all publicly available DNA sequences maintained by the National Center for Biotechnology Information ("NCBI"). GenBank is part of an international collaboration with the DNA DataBank of Japan and EMBL in Europe.

90. Sequence data is deposited daily and is available to the public in the form of a "daily update file", which can be downloaded from GenBank as a single file or as a cumulative file (i.e. the entirety of GenBank up to that day's deposit, or solely that day's deposit). GenBank has always operated in this way, the only difference being the amount of data deposited each day now is significantly more than it was in, for example, 1996.

91. Each GenBank entry includes, so far as known, a concise description of the sequence, the scientific name and taxonomy of the source organism and a table of features that identifies coding regions and other sites of biological significance such as transcription units, repeats and sites of mutations or modifications, and repeats. Protein translations for identified coding regions are included in a feature table.

92. Over the years the number of genetic sequences in public databases has grown exponentially. In 1996 there were approximately 2 million sequences in GenBank. By 2005, the figure had grown to about 56 million.

93. In addition to the DNA databases, there were three main protein sequence databases available in 1996: Genpept, PIR and Swiss-Prot. Of these, Swiss-Prot provided a high level of annotation and cross-referencing and was often the first choice for the analysis of protein sequence data. Swiss-Prot was a collaboration of EMBL, the EBI and the Swiss Institute of Bioinformatics. Its purpose was to provide the scientific community with a single, centralised, freely-accessible and authoritative resource for protein sequences and functional information. Swiss-Prot version 33 was available in early 1996 and contained some 52,000 entries. Swiss-Prot version 34 contained some

59,000 entries. There is an issue as to when it became available, to which I shall return.

Data analysis and searching techniques

94. It had been appreciated for a number of years prior to 1996 that the comparison of different protein and DNA sequences can reveal a good deal about their ancestry and function. This is particularly so in the case of protein sequences because the statistical significance of matches between amino acids is that much greater than it is for matches between bases. To carry out such a comparison the sequences must be aligned. One approach is to use an algorithm which tries to find the optimum alignment between the whole of one sequence and the whole of another. Another is to use what is known as the Smith Waterman alignment algorithm which finds the optimal match between regions of the two sequences.

95. By 1996, standard sequence alignment software was available and included SSEARCH, BLAST, FASTA and CLUSTAL.

96. SSEARCH is very sensitive and it performs a full Smith Waterman alignment against every sequence in a database. But is only able to perform protein/protein or DNA/DNA comparisons. It is therefore necessary first to perform 6-frame translations of the DNA sequence if one wishes to search against a protein database.

97. FASTA is a much faster, but less sensitive, program. It comprises a suite of different programs which allow searches of a protein sequence against a protein database and a DNA sequence against a DNA database (FASTA), a protein sequence against a DNA database (TFASTA) or a DNA sequence against a protein database (FASTX).

98. BLAST, like FASTA, emphasises speed over accuracy and is less sensitive than FASTA. Although mentioned in some papers and in the evidence, it was not used by Lilly in its experiments and I need say no more about it.

99. Finally, I must mention CLUSTAL. This is different to the programs described above in that it is a multiple sequence alignment program, that is to say it aligns three or more sequences together. It was used in the experiments but does not affect my conclusions.

The Patent

100. The Patent is drafted in an apparently conventional way and it is convenient to identify material aspects of it by reference to the sections in which they appear.

Field of invention

101. The specification begins with a description of the "Field of the Invention" which is said to relate to a novel cytokine expressed by neutrophils and which it calls Neutrokine-α.

Related art

102. Paragraphs [0002]-[0019] contain a description of the "Related Art". The inventors explain that TNF (a mixture of TNF-α and TNF-β) was originally discovered as a

result of its anti-tumour activity but is now recognised as a pleiotropic cytokine capable of numerous biological activities including apoptosis of some transformed cell lines, mediation of cell activation and proliferation and also as playing important roles in immune regulation and inflammation.

103. It explains that nine members of the superfamily have been found and that they share a certain degree of homology. It refers to Gruss and Dower as a general review which it incorporates in its entirety by reference. It suggests the proteins are involved in regulation of cell proliferation, activation and differentiation, including control of cell survival or death by apoptosis or cytotoxicity.

104. This theme is elaborated in the following paragraphs which contain a vast range of possible activities and conditions in which TNF is thought to be involved. Paragraph [0006] suggests they include inhibition of lipoprotein lipase synthesis; activation of polymorphonuclear leukocytes; inhibition of cell growth or stimulation of cell growth; cytotoxic action on certain transformed cell types; antiviral activity; stimulation of bone resorption; stimulation of collagenase and prostaglandin E2 production; immunoregulatory actions, including activation of T cells, B cells, monocytes and thymocytes (T cell precursors) and, finally, stimulation of the cell-surface expression of major histocompatibility complex (MHC) class I and class II molecules.

105. Paragraph [0007] suggests it has pro-inflammatory actions which result in tissue injury, such as induction of procoagulant activity on vascular endothelial cells; increased adherence of neutrophils and lymphocytes; and stimulation of the release of platelet activating factor from macrophages, neutrophils and vascular endothelial cells.

106. Paragraph [0008] states that recent evidence implicates TNF in the pathogenesis of many infections, immune disorders, neoplastic pathology (such as cachexia – wasting resulting from cancer or malnutrition) and in autoimmune pathologies and graft-versus host pathology.

107. Paragraph [0009] continues that TNF is thought to play a role in the pathophysiological consequences of gram-negative sepsis and endotoxic shock including fever, malaise, anorexia, and cachexia.

108. Paragraphs [0010]-[0013] contain a summary of efforts of various workers to develop neutralising sera or antibodies to TNF in an attempt to diagnose or treat a variety of conditions. But the inventors explain at [0011]:

> "However, these studies do not provide a basis for producing TNF neutralizing antibodies that can be used for *in vivo* diagnostic or therapeutic uses in humans, due to immunogenicity, lack of specificity and/or pharmaceutical suitability."

109. Similarly, in paragraph [0013] the inventors state:

> "To date, experience with anti-TNF mAb therapy has been limited but shows beneficial therapeutic results, eg, in arthritis and sepsis."

110. After referring to work on the fas ligand, which said to mediate apoptosis and to be involved in the depletion of T cells, the inventors identify the technical problem at paragraph [0019] as being:

> "….a need to provide cytokines similar to TNF that are involved in pathological conditions. Such novel cytokines could be used to make novel antibodies or other antagonists that bind these TNF-like cytokines for therapy for disorders related to TNF-like cytokines."

Summary of the invention

111. The invention provides the full length nucleic acid and amino acid sequences of Neutrokine-α which is said to be:

> "… structurally similar to TNF and related cytokines and is believed to have similar properties and activities."

112. It is encoded by the cDNA clone deposited on 22 October 1996 assigned ATCC number 97768. It has an open reading frame encoding a complete polypeptide of 285 amino acids. Figure 1 of the Patent sets out the nucleic acid (SEQ ID No:1) and amino acid (SEQ ID No:2) sequences.

113. The inventors also describe nucleic acid sequences having various degrees of homology to the deposited sequence and which encode polypeptides which have "Neutrokine-α activity", an expression introduced for the first time in paragraph [0022].

114. Paragraphs [0026] and [0027] explain that the invention also provides antibodies that bind specifically to the disclosed polypeptides, and that these antibodies are useful diagnostically and therapeutically. But no description of any particular antibody is provided.

115. Paragraph [0028] continues that the invention provides therapeutic compositions comprising Neutrokine-α polypeptides and explains these may be used to treat an extensive range of diseases and conditions including tumour and tumour metastasis, infections by bacteria, viruses and other parasites, immunodeficiencies, inflammatory diseases, lymphadenopathy (diseases of the lymph nodes), autoimmune diseases, graft versus host disease and to stimulate peripheral tolerance, destroy some transformed cell lines, mediate cell activation and proliferation, and are functionally linked as primary mediators of immune regulation and inflammatory responses. Despite the breadth of this range, no composition is described.

116. Paragraphs [0029] to [0031] describe yet further aspects of the invention involving compositions for administration to cells; a screening method for identifying compounds capable of enhancing or inhibiting a cellular response induced by Neutrokine-α; and a method for identifying Neutrokine-α receptors. Once again, no specific composition or method is identified yet the specification suggests antagonists may be employed to prevent septic shock, inflammation, cerebral malaria, activation of the HIV virus, graft-host rejection, bone resorption, rheumatoid arthritis and cachexia.

117. Paragraph [0032] provides a list of tissues in which the inventors claim to have discovered that Neutrokine-α is expressed. These merit recital:

> “The present inventors have discovered that Neutrokine-α is expressed not only in neutrophils, but also in kidney, lung, peripheral leukocyte, bone marrow, T cell lymphoma, B cell lymphoma, activated T cells, stomach cancer, smooth muscle, macrophages, and cord blood tissue. For a number of disorders of these tissues and cells, such as tumor and tumor metastasis, infection of bacteria, viruses and other parasites, immunodeficiencies, septic shock, inflammation, cerebral malaria, activation of the HIV virus, graft-host rejection, bone resorption, rheumatoid arthritis and cachexia (wasting or malnutrition, it is believed that significantly higher or lower levels of Neutrokine-α gene expression can be detected in certain tissues (e.g., bone marrow) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" Neutrokine-α gene expression level, i.e., the Neutrokine-α expression level in tissue or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a disorder, which involves: (a) assaying Neutrokine-α gene expression level in cells or body fluid of an individual; (b) comparing the Neutrokine-α gene expression level with a standard Neutrokine-α gene expression level, whereby an increase or decrease in the assayed Neutrokine-α gene expression level compared to the standard expression level is indicative of a disorder.”

118. These claims are significant for they reveal the importance of the identification of the tissues where Neutrokine-α is expressed, the tissues where it acts, the nature of its biological activity and how that profile varies in any particular disease state. However, no data is provided to support these claims. Further, Professor Saklatvala considered the variety of conditions for which the described method is said to be useful to be puzzlingly wide and, as I elaborate in considering the allegation of insufficiency, the method itself impossible to operate in the absence of any information as to the standard level of Neutrokine-α expressed in each of these tissues in normal conditions.

Detailed description

119. The specification then proceeds to describe the detail of the invention. Having referred to the nucleic acid molecules encoding Neutrokine-α, it turns to consider variant nucleotides and, in that connection, describes the activity of Neutrokine-α in three important paragraphs.

120. Paragraph [0061] purports to define Neutrokine-α activity:

> “…. By "a polypeptide having Neutrokine α activity" is intended polypeptides exhibiting activity similar, but not

> necessarily identical, to an activity of the extracellular domain or of the full-length Neutrokine-α protein of the invention, as measured in a particular biological assay. For example, the Neutrokine-α protein of the present invention modulates cell proliferation, cytotoxicity and cell death. An in vitro cell proliferation, cytotoxicity and cell death assay for measuring the effect of a protein on certain cells can be performed by using reagents well known and commonly available in the art for detecting cell replication and/or death. For instance, numerous such assays for TNF-related protein activities are described in the various references in the Background section of this disclosure, above. Briefly, such an assay involves collecting human or animal (e.g., mouse) cells and mixing with (I) transfected host cell-supernatant containing Neutrokine-α protein (or a candidate polypeptide) or (2) nontransfected host cell-supernatant control, and measuring the effect on cell numbers or viability after incubation of certain period of time. Such cell proliferation modulation activities as can be measured in this type of assay are useful for treating tumor, tumor metastasis, infections, autoimmune diseases inflammation and other immune-related diseases."

121. The difficulty facing the reader is that a large number of assays were known and many were referred to in the papers cited in paragraphs [0006]-[0009] of the Patent. Some 24 of them were identified by Professor Saklatvala in paragraph 10.11 of his first report as being of potential use for assessing a wide range of different activities. Yet no particular assay is specified, nor any cell type, nor the conditions under which it must be conducted. Professor Saklatvala said, and I accept, that the description is so vague as to be almost meaningless. Despite this lack of guidance it is said that the cell proliferation modulation activities that can be measured in such assays are useful for treating tumour, tumour metastasis, infections, autoimmune diseases inflammation and other immune-related diseases. These are apparently all characteristic of Neutrokine-α activity.

122. Paragraph [62] suggests that Neutrokine-α modulates cell proliferation and differentiation in a dose dependent manner in the "above described assay" – whatever that might be.

123. Paragraph [63] then provides yet further elaboration, explaining that Neutrokine-α has an activity on leukocytes:

> "Like other members of TNF family, Neutrokine-α exhibits activity on leukocytes including for example monocytes, lymphocytes and neutrophils. For this reason Neutrokine-α is active in directing the proliferation, differentiation and migration of these cell types. Such activity is useful for immune enhancement or suppression, myeloprotection, stem cell mobilization, acute and chronic inflammatory control and treatment of leukemia. Assays for measuring such activity are known in the art …[references cited]."

124. So Neutrokine-α apparently has an activity in relation to all white blood cell types which can be assessed using standard assays although, as Professor Saklatvala points out in his first report, the references cited are to colony stimulating factor assays.

125. The Patent returns to the theme of diagnosis of immune system disorders in paragraphs [0102]-[0112]. At [0102] it says:

> " The present inventors have discovered that Neutrokine-α is expressed in various tissues and particularly in neutrophils. For a number of immune system-related disorders, substantially altered (increased or decreased) levels of Neutrokine-α gene expression can be detected in immune system tissue or other cells or bodily fluids (e.g., sera, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" Neutrokine-α gene expression level, that is, the Neutrokine-α expression level in immune system tissues or bodily fluids from an individual not having the immune system disorder. Thus, the invention provides a diagnostic method useful during diagnosis of an system disorder, which involves measuring the expression level of the gene encoding the Neutrokine-α protein in immune system tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard Neutrokine-α gene expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of an immune system disorder"

126. The absence of any detail reveals the inventors had no idea which tissues should be examined for expression or what the normal or abnormal levels of expression might be.

127. Nevertheless, paragraph [0108] explains that the invention is useful for the diagnosis or treatment of various immune system related disorders, including:

i) tumours and tumour metastasis,

ii) infections by bacteria, viruses and other parasites,

iii) immunodeficiencies,

iv) inflammatory diseases,

v) lymphadenopathy,

vi) autoimmune diseases, and

vii) graft versus host disease.

128. A section on antibodies follows from paragraphs [0113] to [0119] but, once again, no details are given of any specific antibody that has been made, let alone what its useful properties were.

129. Treatment of immune system disorders is addressed from paragraphs [0120] to [0123]. The Patent suggests that substantially increased or decreased levels of expression of Neutrokine-α compared to the standard level may produce pathological conditions and that administration of compositions containing or producing Neutrokine-α can be used to treat patients suffering from a deficiency.

130. Paragraph [0123] then identifies a series of conditions and actions for which Neutrokine-α might be useful, which were summarised by Lilly, without any material criticism from HGS, as follows:

i) to modulate angiogenesis;

ii) to inhibit immune cell functions and hence have a wide range of anti-inflammatory activities;

iii) to act as an anti-neovascularizing agent to treat solid tumours and other non-cancer indications where blood vessel proliferation is not wanted;

iv) to enhance host defences against resistant chronic and acute infections, for example, myobacterial infections via the attraction and activation of microbiocidal leukocytes;

v) to inhibit T-cell proliferation by the inhibition of IL-2 biosynthesis for the treatment of T-cell mediated auto-immune diseases and lymphocytic leukaemias;

vi) to stimulate wound healing, both via the recruitment of debris clearing and connective tissue promoting inflammatory cells;

vii) to treat other fibrotic disorders, including liver cirrhosis, osteoarthritis and pulmonary fibrosis.

viii) to increase the presence of eosinophils which have the distinctive function of killing the larvae of parasites that invade tissues, as in schistosomiasis, trichinosis and ascariasis;

ix) to regulate hematopoiesis, by regulating the activation and differentiation of various hematopoietic progenitor cells, for example, to release mature leukocytes from the bone marrow following chemotherapy, i.e., in stem cell mobilization; and

x) to treat sepsis.

131. Conversely, it then explains in paragraph [0143] that antagonists (such as neutralising antibodies) might have an equally wide range of activities and uses:

i) the inhibition of Neutrokine-α;

ii) to inhibit the chemotaxis and activation of macrophages and their precursors, neutrophils, basophils, B lymphocytes and some T-cell subsets, eg activated and CD8 cytotoxic T cells and natural killer cells;

iii) in certain auto-immune and chronic inflammatory and infective diseases: examples of auto-immune diseases including multiple sclerosis and insulin-dependent diabetes; infectious diseases including silicosis, sarcoidosis, idiopathic pulmonary fibrosis;

iv) to treat idiopathic hyper-eosinophilic syndrome by preventing oesinophil production and migration;

v) to treat endotoxic shock by preventing the migration of macrophages;

vi) to treat atherosclerosis by preventing monocyte infiltration in the artery wall;

vii) to treat histamine-mediated allergic reactions and immunological disorders including late phase allergic reactions, chronic urticaria, and atopic dermatitis;

viii) to treat IgE-mediated allergic reactions such as allergic asthma, rhinitis, and eczema;

ix) to treat chronic and acute inflammation chronic and acute inflammatory pulmonary diseases;

x) to treat rheumatoid arthritis by preventing the attraction of monocytes into synovial fluid;

xi) to treat degenerative and inflammatory arthropathies;

xii) to prevent inflammation;

xiii) to inhibit prostaglandin-independent fever induced by chemokines;

xiv) to treat cases of bone marrow failure;

xv) to treat asthma and allergy by preventing oesinophil accumulation in the lung.

132. These very long lists are again not supported by any data or *in vitro* or *in vivo* studies.

133. Finally the Patent contains various examples which primarily relate to the expression of Neutrokine-α.

Conclusion as to the teaching of the Patent

134. Overall, the Patent contains extravagant and sometimes contradictory claims. By way of illustration, it suggests in paragraph [0123] that Neutrokine-α inhibits immune cell function and in paragraph [0143] that antagonists of Neutrokine-α also inhibit immune cell function. There is nothing by way of experimental evidence to support the claims made and I accept Professor Saklatvala's evidence that the idea that Neutrokine-α and antagonists to Neutrokine–α could be used to treat the extraordinary range of diseases identified was fanciful. He found it hard to believe that anyone could seriously suggest on the basis of no experimental data at all that that Neutrokine-α was the answer to so many conditions, from treating cancer to treating worms. In my judgment the skilled person would come to the conclusion that the inventors had no idea as to the activity of Neutrokine-α when drafting the Patent. It

teaches the skilled person nothing useful about its activity other than that Neutrokine-α is another member of the TNF ligand superfamily.

Points of construction

135. The claims as granted and as proposed to be amended are set out in Annex A to this judgment. It will be noted that the proposed amendments dramatically reduce the scope of the monopoly by excluding nucleotide fragments and homologous nucleotide sequences which encode polypeptides having what is described as Neutrokine-α activity. This is an important limitation and it cuts away one of the major attacks of insufficiency and the attack of lack of novelty based on the Image clone. However, a few points of interpretation remain and I address them in turn.

Claim 1: "isolated"

136. This originally appeared to be a point of contention, but it fell away during the trial. The specification explains the term *isolated* has its conventional meaning of being taken out of its normal environment.

Claim 1: "having Neutrokine-α activity"

137. This expression is a feature of claim 1 as originally granted and is the subject of considerable criticism by Lilly. It says HGS listed as many activities as it could think of and described them collectively as Neutrokine-α activity because it had no idea what the functions of the protein actually were. In effect, the expression means no more than "whatever activities this protein may ultimately be found to have". I accept this submission and the expression presented a considerable difficulty, forming as it did an important functional limitation on the scope of the monopoly. However, the difficulty has been removed by the proposed amendment to claim 1. The claim is now limited to an isolated nucleic acid molecule comprising one of two sequences which are specifically disclosed and are not defined by reference to their activity.

Claim 15 (as proposed to be amended):"Neutrokine-α portion"

138. Claim 15 as proposed to be amended (original claim 20) is directed to an isolated antibody or *portion* thereof that binds specifically to the *Neutrokine-α portion* of a *Neutrokine-α polypeptide* having the amino acid sequence encoded by the nucleic acid molecule of claim 1 or the *Neutrokine-α portion* of a *Neutrokine-α polypeptide* of claim 11. In these circumstances, Lilly asks: What is the Neutrokine-α portion of a Neutrokine-α polypeptide to which the claim refers? As it fairly points out, the reference to "portion" was added during the course of prosecution. Hence it gives rise to an added matter objection because the concept of such a portion is not explicitly disclosed in the application as filed.

139. I consider the answer to this question lies in the wording of claim 1 in its original form. This, it will be seen, extended not just to the disclosed polynucleotide sequences but also to other homologous sequences, and it defined a Neutrokine-α polypeptide as a polypeptide encoded by any of them. The examining division of the EPO expressed concern, inter alia, that antibodies that bind to such polypeptides might bind to parts not derived from the disclosed sequences, in which case they would have nothing to do with the invention. A limitation was therefore required and duly accepted by the

examiner. Original claim 20 therefore only extended to antibodies which bound to the Neutrokine-α portion of the encoded polypeptides.

140. Claim 1 as proposed to be amended now limits the expression Neutrokine-α polypeptide to those polypeptides encoded by the two disclosed sequences (a) and (b). These encode, respectively, the whole Neutrokine-α polypeptide and its extracellular domain. Accordingly, the antibodies of proposed claim 15 cannot bind to anything else. It is no longer necessary to exclude from proposed claim 15 antibodies which bind to other polypeptide sequences and the words "Neutrokine-α portion" are no longer a limitation on the claim. In my judgment this would be clear to the skilled person but to avoid ambiguity, and if the Patent were otherwise valid, I would direct that proposed claim 15 be further amended to delete these words.

Subsequent work on Neutrokine-α

141. I heard a good deal of evidence about the work carried on Neutrokine-α after 1996. Lilly argued it confirmed that the therapeutic applications suggested in the Patent were speculative. HGS contended exactly the opposite and that it confirmed the predictions made in the Patent were reasonable. Both sides focussed primarily on B cells and T cells. I will take them in turn, and then consider the ligand's other activities.

B cells - HGS

142. I begin by considering the work done by HGS. No witness from HGS gave evidence but a number of internal documents were produced on disclosure and these were explored through the cross examination of Professor Noelle. The following key points emerged.

143. In March 1997, some six months after it had filed its application for the Patent, HGS established what it described as a one year research plan with the objectives of determining, inter alia, the function, receptor-ligand pair and therapeutic and diagnostic potential for TNF superfamily members and monoclonal antibodies – including Neutrokine-α (which it called TL 7 in its internal documents); and to submit at least two therapeutic protein candidates.

144. The rationale behind the plan was that HGS had identified and obtained at least seven full length TNF ligands, eight TNF receptors and a variety of other related proteins and had established over ten collaborations in different areas for TNF superfamily members. So it thought it had a unique opportunity to characterise the biological functions of what it described as "these potentially therapeutic proteins" noting that "thus far very little is known about these novel genes".

145. The plan itself involved, inter alia, preparing the gene constructs and proteins, preparing assays and monoclonal antibodies and, importantly, carrying out functional screening assays for family members and monoclonal antibodies and examining their therapeutic potential in models for autoimmune diseases, inflammatory diseases and transplantation. It reported that screening assays would be designed on the basis of the major potential functions, of which 24 were identified. Therapeutic potential was to be assessed in 15 different animal models in respect of no fewer than 16 different disease states or conditions.

146. Work apparently continued through 1997 and 1998. Progress reports from May to June 1988 show that screening assays were conducted throughout this period and a picture emerges of an appreciation that the primary activity of Neutrokine-α lay in relation to B cells, although it was not known whether it stimulated B cell production in the absence of a co-stimulatory signal.

147. HGS published the results of its work in 1999 in a paper by Moore et al (*Science*, Vol 285, 9 July 1999, 260-263) – a publication of some significance. They called the Neutrokine-α ligand "BLyS" (B lymphocyte stimulator) and reported that it was expressed on human monocytes and functioned as a potent B cell growth stimulation factor in co-stimulation assays. Its biological profile suggested it was involved in monocyte driven B cell activation.

148. The authors also reported they had found BLyS mRNA expressed in peripheral blood mononuclear cells, spleen, lymph node and bone marrow, and lower expression in various other tissues. Expression was not detected on T cells.

149. As to its activity, the authors wrote (references deleted):

> "Purified recombinant BLyS (rBLyS) was assessed for its ability to induce activation, proliferation, differentiation, or death in numerous cell-based assays involving B cells, T cells, monocytes, natural killer (NK) cells, hematopoietic progenitors, and a variety of cell types of endothelial and epithelial origin. A biological response to BLyS was observed only among B cells in a standard costimulatory proliferation assay in which purified tonsillar B cells were cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human immunoglobulin M (IgM) as priming agents. The rBLyS induced a concentration-dependent proliferation of tonsillar B cells similar to that of recombinant IL-2 (rIL-2) (Fig. 2A). BLyS also induced B cell proliferation when cultured with cells costimulated with graded doses of anti-IgM (Fig. 2B). A concentration-dependent response was readily observed as the amount of cross-linking agent increased in the presence of a fixed concentration of either IL-2 or rBLyS."

150. In my judgment this passage is clear. The skilled person would understand that Moore and his co-workers had carried out numerous assays involving different cell types and found a biological response only among B cells. However, Professor Noelle refused to accept this. He maintained the authors meant no more than that in the *co-stimulation* assay only B cells were activated. In the light of the cross examination I have reached the conclusion this was not a reasonable interpretation of the passage either on its own or in the context of the paper as a whole and it did him no credit to maintain the position he did.

151. The paper concludes (references deleted):

> "Here, we define BLyS as a member of the TNF superfamily that induces both in vivo and in vitro B cell proliferation and

> differentiation. BLyS is distinguished from other B cell growth and differentiation factors such as IL-2, IL-4, IL-5, IL-6, IL-7, IL-13, IL-15, CD40L, or CD27L (CD70) by its monocyte-specific gene and protein expression pattern and its specific receptor distribution and biological activity on B lymphocytes. BLyS is likely involved in the exchange of signals between B cells and monocytes or their differentiated progeny. Although all B cells may use this mode of signalling, the restricted expression patterns of BLyS receptor and ligand suggest that BLyS may function as a regulator of T cell-independent responses in a manner analogous to that of CD40 and CD40L in T cell-dependent antigen activation. As such, BLyS, its receptor, or related antagonists may find medical utility in the treatment of B cell disorders associated with autoimmunity, neoplasia, or immunodeficiency syndromes."

152. Importantly, the authors distinguished BLyS from other B cell growth and differentiation factors on the basis of its expression pattern and its specific receptor distribution and biological activity on B lymphocytes. This, they suggested, indicated that BLyS might function as a regulator of T cell independent responses and *as such* might find medical utility in the treatment of B cell disorders of particular kinds.

B cells - Biogen

153. In June 1999 Schneider and co-workers at Biogen and the University of Lausanne (*J. Exp. Med.,* Vol 189. No 11, June 7, 1999, 1747-1756) reported what they described as a novel member of the TNF family which they designated BAFF (for B cell activating factor belonging to the TNF family). As I have said, this was in fact Neutrokine-α. In their paper they sought to characterise the structural and functional properties of BAFF. They described their efforts to identify where BAFF was expressed, where its receptors were expressed and what its activities appeared to be. In summary, they found that BAFF was expressed by T cells and dendritic cells, and that the BAFF receptor was expressed on B cells but apparently not in cell lines of T cell, fibroblastic, epithelial or endothelial origin. In this respect it was considered to be rather different to other receptors with a wider expression pattern such as CD40, CD30 and the TNF receptors. This led them to speculate that BAFF might uniquely affect B cells.

154. The difference between BAFF and CD40 was, to these workers, the subject of particular note. They observed that the biological responses induced in B cells by BAFF were distinct from those of CD40 and that BAFF did not react with any of 16 recombinant receptors of the TNF family tested. They concluded (references deleted):

> "Several obscure zones remain in our understanding of an immune response. For instance, little is known about the mechanisms governing the differentiation of a B cell into a plasma cell versus a germinal center B cell. Similarly, aside from the possible involvement of the CD40 pathway shown in vitro, we have very little information about the signals deciding the differentiation of a germinal center B cell into a memory B cell or a plasma cell. It will be very interesting to investigate

> whether or not BAFF has any unique role to play in these critical checkpoint decisions."

155. The implication is that much work was still to be done. And it is notable there is no suggestion here of any therapeutic or diagnostic utility.

156. Later in the same year, Mackay and other workers at Biogen and the University of Lausanne published the results of further studies on BAFF (*J. Exp. Med.,* Vol 189. No 11, December 6, 1999, 1697-1710). They found that transgenic mice which overexpressed BAFF had vastly increased numbers of mature B and effector T cells, and developed autoimmune-like manifestations such as the presence of high levels of rheumatoid factors, circulating immune complexes, anti-DNA auto-antibodies and immunoglobulin deposition in the kidneys. They noted that this phenotype was reminiscent of certain autoimmune disorders and suggested "dysregulation" of BAFF expression might be a critical element in the chain of events leading to auto immunity. They also speculated that overexpression might suppress the protective effects of dendritic cells against the emergence of autoreactive T cells. They concluded:

> "These experiments demonstrate that ectopic overexpression of BAFF was sufficient to initiate the expansion of the mature B cell compartment, resulting in lupus-like autoimmune manifestations. This transgenic mouse model potentially brings new insight into the etiology of autoimmune disorders, provides a novel framework for the investigation of autoreactivity, and potentially opens the door to new therapeutic strategies both for the treatment of some autoimmune disorders and the stimulation of humoral responses."

157. To my mind this is another significant publication. It reveals a basis for supposing the Neutrokine-α has an effect on B cells and that this in turn might result in particular physiological changes with implications for various disease states and the possibility of a therapeutic application.

B cells - Lilly

158. The efforts made by Lilly to investigate and develop a therapeutic product based upon Neutrokine-α (which it called LP-40) were explained by Dr Heath.

159. In 1997, scientists at Lilly were using bioinformatics to identify new sequences of interest. Specifically they used what they described as a series of degenerate screening motifs or algorithms to look for proteins of known sequences. That year they identified a sequence which they believed at least partially encoded a new member of the TNF ligand family. They called it "Trail-like2". Dr Heath stated in his statement that Lilly cloned the full length sequence in August 1998. That was not in fact correct. Lilly only obtained the full length sequence in 1999. Moreover, the original Lilly sequence data appears to have contained errors. Be that as it may, Lilly scientists believe it was a genuine TNF gene because ultimately they found it did have some activity upon expression. However, at that time they found they could only express it recombinantly at very low levels which made purification very difficult.

160. From a date which is not clear, Lilly scientists set about trying to determine its biological activity and its role in physiology and pathophysiology although they deduced from the fact that it was a member of the TNF superfamily that it likely played a role in the regulation of immune and inflammatory responses and in apoptosis.

161. Initial tissue expression studies indicated that Trail-like2 was ubiquitously expressed, so that gave no clues as to its particular function. In his statement, Dr Heath explained they also expended substantial efforts in developing assays. The initial efforts to develop any kind of *in vitro* assay failed. Part of these efforts involved studies to determine whether Trail-like2 bound to any of the known TNF receptors. But they failed to find any positive receptor binding activity. Further, without some type of assay known to assess a positive function of the protein, they were not sure they were expressing and purifying a biologically active or relevant form of the protein. When they encountered a negative result in a particular assay, they did not know whether that was because they had failed to express and purify an active protein or whether it was due to some other aspect of the assay.

162. In the light of these difficulties, Lilly turned to transgenic animals to try and gather preliminary information about the protein's function. This was an area of research where Lilly had some experience and expertise. However, as Dr Heath explained, the transgenic animal project for Trail-like2 was also not straightforward. They microinjected the gene and founders were born, but they were unable to detect elevated levels of Trail-like2. They finally saw the first phenotypic changes in the animals nine months later as they displayed increased spleen weights and an increase in white blood cells. Those changes by themselves were fairly meaningless. It was not until the animals were approximately a year old that they displayed elevated serum Trail-like2 levels. Additional analysis and pathology studies were then carried out, and, at a precise date which was not made clear, these gave Lilly a real indication as to a general function of Trail-like2 involving the proliferation of certain types of B-cells.

163. In July 1999, Lilly became aware of the Moore publication and its scientists appreciated that Trail-like2 and BLyS were the same, that is to say Neutrokine-α. They also realised that at least three other groups had recently published on the same protein but had each given it a different name. This publication made it clear to them that it was a potent inducer of B cell proliferation and that, unlike other cytokines that could activate B cells, its receptor, which had not been identified, was uniquely expressed on B cells. From about this point they began to refer to Neutrokine-α variously as Trail-like2, BAFF and BLyS.

164. In August 1999, Lilly scientists recorded that the activity of Neutrokine-α as a potent B cell activator made it a potentially important therapeutic target. At this time they had large scale transient expression systems underway and began to set up in vitro assays to try and confirm the published reports on the function of Neutrokine-α and to contemplate assays for screening antibodies which they proposed to develop using the Cambridge Antibody Technology ("CAT") technology, to which they had access under licence. The aim was to generate single chain antibodies capable of blocking Neutrokine-α from binding to its receptor.

165. In the summer of 2000, Lilly also began to try and develop a therapeutic antibody. In the light of the risk of immunogenicity associated with the injection of foreign antibodies into a human, Lilly entered into a collaboration with a company called Medarex to develop a fully human Neutrokine-α antibody. Medarex had developed a technology that allowed the development in mice of human-like or fully human antibodies with a view to bypassing the immunogenicity problem. It was seen, as Dr Heath said, as being potentially very powerful. A sample of Neutrokine-α was sent off to Medarex to allow the work to begin.

166. At the same time Lilly found a number of related products being sold commercially. One was a polyclonal antibody to Neutrokine-α being sold by a company called MoBiTec. Lilly bought it in to see if it had any use. As Dr Heath pointed out, simply having the antibody is not sufficient. It might recognise denatured protein and be useful in a Western blot but not an ELISA assay. Lilly also found some form of E Coli expressed Neutrokine-α being sold by a company called Jackson ImmunoResearch. Both were regarded by Lilly as potentially useful for research purposes.

167. Through the remainder of 2000, work at Medarex continued. At the end of the year Medarex had identified an antibody which appeared to neutralise Neutrokine-α and, by early 2001, it was described as a "lead". In order to carry out the assessment of this or any other antibody, Lilly had to develop suitable assays. Dr Heath estimated this involved one to two years work. Eventually they developed an *in vitro* co-stimulation assay that proved successful. They also used their transgenic mice which expressed human Neutrokine-α to screen for *in vivo* neutralising activity. The lead antibody was then subjected to animal toxicology and animal pharmacology studies.

168. It is not easy to extract a completely clear picture of the work carried out by Lilly from the cross examination and the statement of Dr Heath. However, I believe the following general conclusions can be drawn. Lilly recognised from 1997 that Trail-like2 was another member of the TNF ligand superfamily and that, as such, it might be involved in regulation of immune and inflammatory responses and in apoptosis. Over the following two years Lilly workers continued to carry out bioinformatics work in the hope of finding out more about the activities of the protein. But they found its ubiquitous expression pattern revealed little about its activities. Their work was also hampered by the low levels of expression they were able to secure and the difficulties they had in developing any suitable assays. With a view to addressing these problems, they also carried out work with their own transgenic mice. In 1999, this work and the Moore paper revealed the activity of Neutrokine-α in relation to B cells and Lilly then appreciated its importance as a potential therapeutic target. From about this time Lilly devoted real effort to developing screens and assays, using, inter alia, CAT technology. In 2000 it began its collaboration with Medarex with a view to finding a neutralising monoclonal antibody and, within a relatively short period of time, a lead antibody was identified.

T cells

169. The position in relation to T cells can be summarised quite shortly. Schneider reported that BAFF was expressed by T cells in his 1999 paper to which I have referred. However it was another two years before co-stimulation of T cells was reported in a paper by Huard et al. (*J. Immunol.* 2001; 167;6225-6231). This and a later paper by

the same researchers were the subject of a wide ranging review by Susan Kalled et al (*Curr Dir Autoimmun*. Basel, Karger, 2005, Vol 8, 206-242). She summarised the position at 226 (references deleted):

> "A 2001 report was the first to describe T cell costimulation by BAFF. In those experiments, recombinant BAFF added to cultures of human T cells, which were suboptimally stimulated with anti-CD3, resulted in proliferation of $CD4^+$, but not $CD8^+$, T cells. Both T cell populations, however, were costimulated by BAFF to produce type I and II cytokines and increase CD25 expression. Interestingly, this BAFF-mediated activity could only be obtained when BAFF was coated onto plates, it was not observed when soluble BAFF was used. This same group of investigators more recently reported that endogenously produced BAFF from T cells is enough to costimulate proliferation, albeit at a lower level than when exogenous BAFF is added. How physiologically relevant this activity is in vivo needs to be further investigated. In addition, it will be important to get confirmation of BAFF mediated T cell activity from other laboratories since our own attempts with our recombinant, trimeric BAFF have not been successful. Indeed, the differences observed between laboratories may be due to the different sources of BAFF protein."

170. As she explained, the physiological significance of these results would require further investigation. She concluded at 235:

> "The BAFF and APRIL pathways are inherently complex due to the numerous receptors, cell types expressing the receptors, and potential downstream signaling events that are involved. While the B cell survival function of BAFF is not disputed, its role in B cell differentiation and T cell biology, as well as its functional structure remain debated among investigators. Clearly, additional experimentation will help to resolve these issues as well as to clarify functions for BAFF outside of B cell survival. The APRIL story is still unfolding within the realm of immunology and oncology, and with time the conflicting data will surely be resolved. BAFF and APRIL remain interesting and exciting molecules to investigate, and continued examination of these pathways will further advance our understanding of the immunological processes that lead to both health and disease. "

171. So, even in 2005, additional experimentation was necessary to elucidate the role of BAFF beyond B cell survival.

Other activities

172. Professor Saklatvala maintained there was no evidence that Neutrokine-α had any effect on leukocytes other than promoting the proliferation and differentiation of lymphocytes, and specifically B cells. He did not accept that it had any effect on

monocytes and neutrophils, or on cell migration or angiogenesis. I found his evidence persuasive on all these issues.

173. Professor Saklatvala was also asked about B cell malignancies and agreed that once it was established that Neutrokine-α was a B cell cytokine then a candidate area of therapeutic application would be B cell malignancies such as myeloma, lymphoma and chronic lymphatic leukaemia. In the course of his cross examination he was taken to a series of papers published in the period from 2004 to 2006 which clearly established that researchers were exploring this potential. I need only refer to two by way of example.

174. Novak et al (*Blood*, 15 October 2004, Vol 104, No.8, 2247-2253) found evidence that Neutrokine-α was expressed in tumours from patients with non-Hodgkin lymphoma and that the levels of Neutrokine-α increased as the tumours became more aggressive. They considered that Neutrokine-α and its receptors represented a potentially important therapeutic target in B cell lymphoma.

175. Tai et al (*Cancer Res*., 2006; 66: (13), July 1, 2006, 6675-6682) carried out studies into the role of Neutrokine-α in myeloma cells. The abstract to the paper concludes:

> "These studies establish a role for BAFF in localization and survival of multiple myeloma cells in the bone marrow microenvironment and strongly support novel therapeutics, targeting the interaction between BAFF and its receptors in multiple myeloma."

Summary

176. The papers and work to which I have referred represent only a very small fraction of the work carried out on Neutrokine-α. Nevertheless, I believe the following general conclusions can be drawn from them and the expert evidence. From 1999 it became increasingly clear that Neutrokine-α is expressed by peripheral blood leukocytes, and in the spleen and lymph nodes. From that time it also became apparent that Neutrokine-α plays a significant and particular role in the proliferation and differentiation of B cells. Subsequently it has also been shown to play a part in the regulation of T cell proliferation and activation. As the activities of Neutrokine-α have gradually been elucidated, and particularly those relating to B cells, it has become increasingly recognised as a potential therapeutic target for diseases that are specifically associated with altered B cell function. Notable amongst these are autoimmune diseases such as rheumatoid arthritis and SLE and B cell malignancies such as lymphoma. Neutrokine-α has now been shown to have an important role in the development of autoimmune disease and B cell cancers; but, at the same time, much of its biology remains unclear and is the subject of continuing study by many different research centres. In my judgment the nature and extent of all this research work, the limited conclusions ultimately drawn and the amount of work that remains to be done point strongly to the conclusion that the therapeutic and diagnostic applications suggested in the Patent were indeed speculative.

Industrial application

177. Lilly alleges that the subject matter of the Patent is not a patentable invention because it is not capable of industrial application. It contends the specification consists simply of sequence information for a polypeptide with broad, unspecific and inherently speculative statements about its biological activity. Further, it fails properly to characterise the polypeptide, is function or any therapeutic or diagnostic utility for it. This is a major attack on the Patent. If the allegation is a good one then all the claims are invalid.

Industrial application- the law

Introduction

178. It is a requirement of patentability that the claimed invention is susceptible of industrial application. This is derived from Article 52 of the EPC which provides, in relevant part:

> "(1) European patents shall be granted for any inventions, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of industrial application."

179. Article 57 defines industrial application:

> "An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture."

180. Essentially this requirement is directed at ensuring the invention has a real practical application. There must be some use for which it can be employed. In the case of most inventions, including inventions involving new chemical entities, the use will be clear from the nature of the invention. It may or may be difficult to carry it into practice, in which case it may be objectionable on other grounds, such as insufficiency, but at least its utility will be apparent. But in the case of biotechnology inventions the position is often not so straightforward. These may be concerned with biological material, including gene sequences and proteins found in nature. A gene or protein sequence, once identified and isolated, may be relatively easy to reproduce. It may also be supposed that since it is a sequence from a living organism it will have a function. However, it is quite possible that although the sequence is known, its function is not – or is at least not well understood. This was increasingly the case from the early 1990s with the commencement of the Human Genome Project and the development of a number of different databases of DNA and protein sequences whose biological functions were not known. As I have explained in addressing the common general knowledge, as computers became more powerful, it became possible to search these databases for sequences with a degree of homology to genes or proteins of known function. Claims to inventions based upon such sequences raise acutely the question of what is necessary to satisfy the requirement of industrial applicability.

181. The UK has recognised for many years that biological material may be patented but different approaches in some other Member States led to a desire for harmonisation and ultimately the adoption, in 1998, of Directive 98/44/EC ("the Directive"). Articles 1 to 11 of the Directive were implemented in this country by the Patents Regulations 2000 which came into force on 28 July 2000. As such they do not strictly apply to this

case, relating as it does to an application filed in 1996. However, both sides agreed that they make no fundamental change to UK patent law. The Directive confirms that, in principle, biotechnology inventions are patentable. Importantly for present purposes, the Directive also addresses the question of industrial applicability.

182. Recitals 23 and 24 read:

> "23. Whereas a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention;
>
> 24. Whereas, in order to comply with the industrial application criterion it is necessary in cases where a sequence or partial sequence of a gene is used to produce a protein or part of a protein, to specify which protein or part of a protein is produced or what function it performs;"

183. And Article 5 provides:

> "1. The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.
>
> 2. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.
>
> 3. The industrial application of a sequence or partial sequence of a gene must be disclosed in the patent application."

184. So also the EPO considers that biotechnological inventions are, in principle, patentable under the EPC. For such inventions the relevant provisions of the EPC are to be applied and interpreted in accordance with Chapter V of the Implementing Regulations (Rules 26 to 34) and the Directive is to be used as a supplementary means of interpretation. The requirements of Article 5 of the Directive are now directly reflected in EPC Rule 29. I should also refer to Rule 42(1)(f) which reads:

> "(1) The description shall:
>
> …….
>
> (f) indicate explicitly, where it is not obvious from the description or nature of the invention, the way in which the invention is industrially applicable."

185. This then is the framework. In a nutshell, the industrial application of a gene must be disclosed in the application. If it encodes a protein then the protein or its function must be specified.

The UK cases

186. There is very little authority from this jurisdiction on the scope of the requirement. The Court of Appeal considered it briefly in *Chiron Corporation v Murex and Ors.* [1996] RPC 535. The patentee had discovered the HCV virus but included in its patent a claim to polypeptides which might have nothing to do with the HCV virus and were useless for any known purpose. The Court found the claim invalid, observing at 607-608:

> "We accept that the polypeptides claimed in the second part of claim 11 can be made, for as will become apparent from the section of our judgment dealing with insufficiency, it is a routine task to see whether one polynucleotide will hybridise with another. But the sections require that the invention can be made or used "in any kind of industry" so as to be "capable" or "susceptible of industrial application". The connotation is that of trade or manufacture in its widest sense and whether or not for profit. But industry does not exist in that sense to make or use that which is useless for any known purpose.
>
> On this point we prefer the submissions for the appellants. We think that they more accurately reflect the true meaning of sections 1(1)(c) and 4 and the manifest intention of Patents Act 1977 and the European Patent Convention that monopoly rights should be confined to that which has some useful purpose. We think that the judge fell into error by giving the sections too literal a construction and in considering what can be made and used by industry rather than what can be made and used in any kind of industry."

187. The only other case to which I was referred was a decision of Mr Back, the Divisional Director acting for the Comptroller, in *Aeomica's Application* BL O/286/05, dated 25 October 2005. The application related to the human ZZAP1 protein. It was identified using bioinformatics techniques and the application explained that the similarities between this and other known proteins, described as V-ATPases, implied a role in protein-protein interactions, aberrant expression of which was likely to be associated with the development of certain types of cancer and other diseases. In considering whether the invention was capable of industrial application the hearing officer applied the "specific, substantial and credible" test introduced by the United States Patent and Trademark Office (USPTO), to which I shall return in considering the position in the US and the requirement there that an invention be "useful" imposed by section 101 of the United States Code, Title 35 ("35 USC"). I hope I fairly summarise the elements of the test as follows:

    i) *Specific*: A particular utility must be disclosed. So, a general statement of diagnostic or therapeutic utility will not suffice. There must be a disclosure of a particular condition that can be diagnosed or treated. Nor will a claim to a probe be specific unless a target has been identified.

ii) *Substantial*: A "real world" use must be described. If further research is necessary to confirm a use it is not substantial. Similarly, research into the product itself is not substantial.

iii) *Credible*: The utility asserted must be credible to the ordinary skilled person who would accept that the invention is currently available for the described use.

iv) The utility must be apparent from the specification alone or taken together with the knowledge of the person skilled in the art.

188. Applying this test, the hearing officer rejected the application. He considered the applicant did not know for certain what the role of the claimed ZZAP1 protein was. Further research was necessary to verify its suggested function. In these circumstances the proposed industrial application was not substantial. Further, the VTPase family of proteins to which the ZZAP1 protein was said to be related had a variety of functions of a diverse nature and so it was not possible to identify the role of the protein in its natural environment sufficiently precisely. Consequently the proposed use was not specific.

The EPO cases

189. The approach adopted in the EPO has developed through a number of decisions. I will deal with them in chronological order. The first is that of the Opposition Division in *ICOS Corporation* (2001), [2002] O.J. EPO 293, a case of some importance as revealed by its publication in the Official Journal. The specification disclosed a V28 protein (V28) which was predicted to function as a receptor (of a kind known as 7TM), and a method of verifying that function. The prediction was based upon various structural elements in the deduced amino acid sequence and homology to known 7TM receptors but the specification disclosed no ligand. It was thought the receptor had immunological properties and played a role in inflammation. The patent included claims to the receptor and to antibodies specific to the receptor. The opponents argued the patent did not solve any problem and was invalid for obviousness, insufficiency and for lack of any industrial application.

190. The Opposition Division decided the claims to the receptor were not inventive (paragraphs 3(iv) and (vi)) and were insufficient (paragraph 5(iv)). The absence of a ligand made the task of establishing that V28 was a receptor unduly burdensome. It also found the antibody claims insufficient. No specific antibody was disclosed and the generation of specific antibodies could not be considered routine because of the effort needed to exclude those which were cross reactive. It would be even harder to find antibodies suitable for use in therapy, as the Opposition Division explained at paragraph [6]:

> "6. The subject-matter of **claims 16–21** relates to an antibody substance specific for V28 protein.
>
> (i) The specification does not disclose any antibody substance which specifically recognises V28 protein. Although it is conceivable that a number of antibodies (including known antibodies) recognise and bind to V28 protein, an antibody that

> specifically recognises V28 protein, is not disclosed. Furthermore, the assertion of the patentee that generation of such antibodies is routine matter in the art is not followed by the opposition division. An antibody that specifically recognises V28 is understood to mean an antibody that does not recognise any other protein. The generation of such antibodies is not considered a routine matter given the labour intensive exclusion of cross reactivity of the candidate specific antibody with any other protein.
>
> (ii) As discussed above, antibody substances which specifically recognise V28 protein are not enabled by the disclosure of the specification. Even more remote from the disclosure of specific antibodies is the disclosure of specific antibodies for V28 protein which are suitable for treating inflammation in a mammal. The involvement of V28 protein in inflammation is not demonstrated in the specification. Therefore, the identification of specific antibodies suitable for counteracting a speculative activity of V28 protein (ie induction of inflammation) is not enabled by the disclosure of the specification.
>
> (iii) Antibodies suitable for use in a method for modulation of binding of a ligand/antiligand to V28 are also antibodies possessing special properties (for example, spatially hindering or enhancing the binding of a ligand to V28 protein). No such antibodies are disclosed in the specification. The identification of such antibodies necessitates prior identification of the ligand/antiligand molecules or the binding site of said molecules. None of these is disclosed nor enabled by the disclosure of the specification."

191. The Opposition Division also considered the question of industrial application. The patentee argued the requirement for industrial application was satisfied because the specification showed how the receptor could be made and its involvement in immunological and inflammatory events in vivo. The Opposition Division disagreed, concluding the potential uses described in the specification were speculative. In assessing this question it considered whether the described uses were specific, substantial and credible (at paragraph [9]):

> "(i) Potential uses of the invention are disclosed in the specification (p. 3.4) which however are based on a proposed function of the V28 protein as a receptor which is not sufficiently disclosed in the specification (see section 5 above). Thus, the potential uses disclosed in the application are speculative, ie are not specific, substantial and credible and as such are not considered industrial applications.
>
> In more detail: The specification states that host cells expressing products of V28 7TM gene are useful in methods for the large scale production of V28 7TM protein (p. 3). Since

> the V28 protein is not disclosed to have any function (eg biological which would implicate a therapeutic use nor as a marker which would implicate a diagnostic use), it cannot be seen why it would be useful to produce said protein on a large scale in industry.
>
> The specification states that antibody substances specifically reactive with V28 7TM protein are useful in complexes for immunisation to generate anti-idiotypic antibodies, for purifying V28 peptides and for identifying cells producing the V28 polypeptides (p. 4). Specific antibodies are not disclosed in the specification and may not even be possible to be generated due to high sequence identity shared by a large number of proteins (see Table 1 of specification and above section 6(i)). Therefore, these proposed users are directed to a substance that has not been disclosed and can only be considered as speculative.
>
> The specification further asserts that antibodies, agonists or antagonists of V28 protein are manifestly useful in modulating ligand/receptor binding and/or inflammatory events in vivo. (p. 4). As discussed above (section 6(iii)), antibodies suitable for modulating ligand/receptor binding represent a special type of antibody which has not been exemplified in the specification. Furthermore, the involvement of V28 protein in immunological and/or inflammatory events in vivo has not been demonstrated either. The proposed use thus is directed to a potential interference of a speculative activity of V28 protein with a substance which has not been shown to be possible to prepare. Such a use lacks credibility."

192. In *Multimeric Receptors / Salk Institute* (2002) T 0338/00 the Board of Appeal was concerned with a claim to a heterodimeric receptor comprising one member selected from the isoforms of RXR (retinoic acid receptor) and one different member of the steroid/thyroid receptor superfamily. In considering whether the invention was susceptible of industrial application, the Board examined (at paragraph [2]) whether a capability of exploitation in industry could be derived from the description or whether what was described was merely an interesting research result that might yield a yet to be identified industrial application.

193. The Board agreed with the patentee that the application disclosed not only the presence of heterodimeric receptors but also evidence of their use for modulating expression systems. It therefore concluded (at paragraph [3]) that the activities and products disclosed in the application were not aimed at an abstract or intellectual character but at a direct technical result that might clearly be applied in an industrial activity namely, modulation of the expression of a gene/product of interest in a particular expression system and the screening of products with specific pharmacological activity.

194. In *BDP1 Phosphatase/Max-Plank* (2005) T 0870/04 the Board further elaborated the nature of the Article 52 objection. The application disclosed a polypeptide called

Brain Derived Phosphatase 1(BDP-1) which was one of a class of enzymes called protein tyrosine phosphatases (PTPases). It suggested that PTPases were involved in the regulation of signal transduction pathways and in the control of cellular differentiation and proliferation processes. It also stated that PTPases could down regulate the activity of certain enzymes involved in cellular proliferation and so were possible “candidate anti-cancer proteins”. It also disclosed that BDP-1 was expressed in most tissues and cell lines at a basal level but was expressed in high levels in epithelium origin cell lines and in cancer cell lines. It also described BDP-1 as having certain structural features which suggested it was a member of the PTPase-PEST family which were thought to play an important role in what it described as “housekeeping” cellular functions.

195. Before expressing its conclusions, the Board took the opportunity to give some general guidance in relation to biotechnology inventions. It observed that the notion of industry had to be interpreted broadly (at paragraph [3]):

> “The case law indicates that the notion of "industry" has to be interpreted broadly to include all manufacturing, extracting and processing activities of enterprises that are carried out continuously, independently and for financial (commercial) gains (cf. e.g. T 144/83 OJ EPO 1986, 301, see point 5 of the reasons).”

196. Nevertheless, a practical application of the invention had to be disclosed (paragraph [4]):

> “The requirement of Article 57 EPC that **the invention** "can be made or used" in at least one field of industrial activity emphasizes that a "practical" application of the invention has to be disclosed. Merely because a substance (here: a polypeptide) could be produced in some ways does not necessarily mean that this requirement is fulfilled, unless there is also some profitable use for which the substance can be employed.”

197. It then contrasted two categories of case. If a substance is disclosed and its function is known to be essential for human health, then the identification of the substance having that function will immediately suggest a practical application (at paragraph [5]):

> “Biotechnological inventions are quite often concerned with substances found in nature (e.g. a protein, a DNA sequence, etc.). In cases where the structure and function of the substance is elucidated and means are provided for extracting it or producing it in large amounts, industrial applicability exists in relation to the possibility to exploit the information and technical means disclosed in order to manufacture the substance and use it for some function related to its natural one or for some other previously unknown (now disclosed) function or as a starting material for making useful analogs or derivatives with some improved features. If a function is well known to be essential for human health, then the identification

> of the substance having this function will immediately suggest a practical application in the case of a disease or condition caused by a deficiency, as was the case, for example, for insulin, human growth hormone or erythropoietin. In such cases, an adequate description will ensure in accordance with the requirements of Article 57 EPC that "**the invention** can be made or used in industry" (emphasis added)."

198. If, on the other hand, the function of a naturally occurring substance is not understood and no other practical application is suggested then the position is very different (paragraph [6]):

> "In cases where a substance, naturally occurring in the human body, is identified, and possibly also structurally characterised and made available through some method, but either its function is not known or it is complex and incompletely understood, and no disease or condition has yet been identified as being attributable to an excess or deficiency of the substance, and no other practical use is suggested for the substance, then industrial applicability cannot be acknowledged. While the jurisprudence has tended to be generous to applicants, there must be a borderline between what can be accepted, and what can only be categorized as an interesting research result which per se does not yet allow a practical industrial application to be identified. Even though research results may be a scientific achievement of considerable merit, they are not necessarily an invention which can be applied industrially."

199. Turning to the disclosure, the Board noted that the application suggested various possible roles for BDP-1 but did not adequately identify any specific activity, for example as a tumour suppressor; nor did it provide any evidence as to what its particular role in cancer might be. Similarly, the specification did not attribute clear functions to PTPases as a class. In these circumstances the burden lay on the reader to guess or find a way to exploit the disclosure in industry. It was not enough that the application disclosed a polypeptide of interest to researchers (at paragraph [21]):

> "In the board's judgment, although the present application describes a product (a polypeptide), means and methods for making it, and its prospective use thereof for basic science activities, it identifies no practical way of exploiting it in at least one field of industrial activity. In this respect, it is considered that a vague and speculative indication of possible objectives that might or might not be achievable by carrying out further research with the tool as described is not sufficient for fulfilment of the requirement of industrial applicability. The purpose of granting a patent is not to reserve an unexplored field of research for an applicant."

200. Nor was it enough that the polypeptide could be used to find out more about its function (at paragraph [23]):

> "This contrasts with the present case where the only practicable use suggested is to use what is claimed to find out more about the natural functions of what is claimed itself. This is not in itself an industrial application, but rather research undertaken either for its own sake or with the mere hope that some useful application will be identified."

201. It therefore dismissed the applicant's appeal.

202. The following year saw two further significant cases. *PF4A receptors/Genentech* (2006) T 0604/04 concerned a patent which disclosed polypeptides believed to be receptors for members of the PF4A family of cytokines to which IL-8 belonged. There could be no certainty because no ligand had been identified, but the structural features of the polypeptides, including their homology to the IL-8 receptor, suggested this was, at least, plausible. The patent included claims to the polypeptides and to monoclonal antibodies capable of specifically binding to them. The patent was opposed on the basis, inter alia, that the claims lacked industrial applicability and were insufficient.

203. In addressing the issue of industrial applicability, the Board of Appeal expressly agreed with the criteria identified in *BDP1 Phosphatase/Max-Plank* and observed that, taken in isolation, the teaching in the specification fell short of fulfilling them, there being no evidence of which ligands the polypeptides bound to. Nevertheless, it was also important to take into account the common general knowledge and at the priority date and it was known that the PF-4 related proteins were attractive targets for the development of new therapeutic agents, that inhibition of their activity might provide an effective anti-inflammatory activity and that promoting their activity might enhance wound healing and tissue repair. The molecules and antibodies to them were therefore important to the pharmaceutical industry and they satisfied the requirement of industrial applicability.

204. Turning to insufficiency, the Board considered that the polypeptides could be made without undue difficulty but the same could not be said of the claims to monoclonal antibodies for use in therapy. There was evidence that PF4 related polypeptides had some overlapping activities as mediators of the inflammatory response. Hence it was not the case that blocking a receptor for one specific cytokine would necessarily result in a therapeutic effect and the disclosure was not sufficient. The patentee suggested that such a conclusion would be inconsistent with the finding of industrial applicability, as to which the Board said at paragraph [27]:

> "However, the board's decision to accept industrial applicability was not made on the above mentioned basis but on the basis that at the priority date, the person skilled in the art perceived chemokines and any molecules capable of interfering with their activity as of great interest to the pharmaceutical industry if only to investigate their potential as targets for drug development, irrespective of what the end result might be ….. The conclusion cannot be drawn from this reasoning that monoclonal antibodies to the polypeptides of Figures 4 or 5 could necessarily be of use in therapy or as a pharmaceutical composition."

205. Later the same year the Board of Appeal decided another case upon which HGS placed particular reliance: *Hematopoietic cytokine receptor/Zymogenetics* (2006) T 0898/05. This was an appeal by the applicant against a decision by the examining division refusing an application disclosing the nucleotide sequence and the encoded amino acid sequence of the human trans-membrane receptor Zcytor1. The application contained claims to the nucleotide, the polypeptide and to antibodies which specifically bound to the polypeptide.

206. In considering industrial applicability, the Board made some general observations at the outset. It noted at paragraph [4] it was enough that it could be expected the patent would lead to financial or commercial benefit:

> "….patents being an incentive to innovation and economic success, the criterion of "industrial applicability" requires that a patent application describes its subject invention in sufficiently meaningful technical terms that it can be expected that the exclusive rights resulting from the grant of a patent will lead to some financial or other commercial benefit."

207. At paragraph [5] it enquired whether there was a sound and concrete basis for recognising that the contribution could lead to practical exploitation in industry:

> "… the invention claimed must have such a sound and concrete technical basis that the skilled person can recognise that its contribution to the art could lead to practical exploitation in industry. It would be at odds with the purpose of the patent system to grant exclusive rights to prevent the commercial activities of others on the basis of a purely theoretical or speculative patent application. This would amount to granting a monopoly over an unexplored technical field."

208. The Board then elaborated its approach in an important passage at paragraphs [6]-[8] which emphasises the closely related requirements of Articles 56 (inventive step), 57 (industrial application) and 83 (sufficiency of description) of the EPC:

> "6. The board takes the view that, in the present context, the concept of "profit" should be seen in its wider sense of benefit instead of its narrower sense of financial reward. Accordingly, the expression "profitable use" should be understood more in the sense of "immediate concrete benefit". This conveys, in the words "concrete benefit", the need to disclose in definite technical terms the purpose of the invention and how it can be used in industrial practice to solve a given technical problem, this being the actual benefit or advantage of exploiting the invention. The essence of the requirement is that there must be at least a prospect of a real as opposed to a purely theoretical possibility of exploitation. Further, the use of the word "immediate" conveys the need for this to be derivable directly from the description, if it is not already obvious from the nature of the invention or from the background art. It should not be left to the skilled reader to find out how to exploit the

> invention by carrying out a research programme. Not only is this the essence of the requirements of Rules 23e(3) and 27(1)(f) EPC, it also corresponds to the requirements of Articles 56 (the need to provide a non-obvious solution to a technical problem), 57 (the need to indicate how to exploit the invention), and 83 EPC (the need to provide a sufficient disclosure of the claimed invention). All those provisions reflect the basic principle of the patent system that exclusive rights can only be granted in exchange for a full disclosure of the invention.
>
> 7. Accordingly, a product whose structure is given (e.g. a nucleic acid sequence) but whose function is undetermined or obscure or only vaguely indicated might not fulfil the above criteria, in spite of the fact that the structure of the product per se can be reproduced (made) (cf. case of T 870/04, point 10 *infra*). If a patent is granted therefor, it might prevent further research in that area, and/or give the patentee unjustified control over others who are actively investigating in that area and who might eventually find actual ways to exploit it.
>
> 8. On the other hand, a product which is definitely described and plausibly shown to be usable, e.g. to cure a rare or orphan disease, might be considered to have a profitable use or concrete benefit, irrespective of whether it is actually intended for the pursuit of any trade at all. Thus, although no particular economic profit might be expected in the development of such products, nevertheless there is no doubt that it might be considered to display immediate concrete benefits."

209. The Board noted that the application identified various structural features of the Zcytor1 receptor based upon computer assisted sequence homology studies and disclosed studies of the tissues in which the receptor was expressed. These data indicated the receptor was a putative member of the hematopoietin receptor family and played a role in the proliferation, differentiation and activation of immune cells and, specifically, in early thymocyte development and regulation of the immune response. This "educated guess" was proved correct by subsequent data.

210. The Board expressed its conclusion in paragraph [31]:

> "In the present case, the suggested role of the Zcytorl receptor corresponds to the level of the biological function and the practical applications or the concrete technical benefits derived therefrom are clearly disclosed in the present application, namely the stimulation of cell-mediated immunity and of lymphocyte proliferation by agonist ligands of Zcytorl and the suppression of the immune system by antagonists of the Zcytorl receptor (cf. page 20, lines 5 to 18). Although the details of the biochemical activity and the cellular function of the Zcytorl receptor have not been elucidated in the application, the

> (therapeutic) treatments directly derivable from the biological function identified by the computer-assisted method cannot be considered to be so "vaguely defined" that they do not suggest any therapeutic or diagnostic use. On the contrary, the treatments referred to in the application are specifically in relation to the function plausibly attributed to the molecule, and are in the areas of rheumatoid arthritis, multiple sclerosis, diabetes mellitus, etc. In this respect, this case differs from that of decision T870/04 (supra) where no clear role for the claimed molecule was identified (cf. point 10 supra). The Zcytorl receptor, and more particularly the products related thereto, such as the extracellular Zcytorl fragment, cannot be seen as a mere tool for research undertaken for its own sake or in the quest to provide industrially applicable matter, but rather as a product with a plausible application in an industrial (medico-pharmaceutical) activity. Thus, on this issue, the board cannot concur with the conclusion arrived at by the first instance "

211. In all the circumstances the Board concluded that although the details of the biochemical activity and the cellular function of the receptor had not been elucidated, therapeutic applications derivable from the biological function had been adequately disclosed and included the treatment of diseases such as rheumatoid arthritis and multiple sclerosis. The receptor was therefore not merely a tool for use in research but had a plausible industrial application. The requirements of Article 57 were therefore satisfied and the Board remitted the case for further prosecution and so as to examine the application for sufficiency of disclosure and inventive step.

212. Finally I must refer to two decisions in 2007. In *Serine Protease/Bayer* (2007) T 1452/06 the invention related to a polynucleotide and encoded polypeptide said to be related to epithin, a type II membrane serine protease. The application stated the polypeptide was expected to be useful for the same purposes as previously identified serine proteases, in particular for identifying new drugs for treating cancer and inflammatory diseases. The applicant particularly relied on one example showing an anti proliferative effect on colon cancer cells and another showing an expression profile suggesting a broad tissue distribution. It also relied upon a later publication suggesting the predictions made in the application were sound.

213. The Board of Appeal dismissed the appeal and rejected the application. The polynucleotide was only a partial sequence of an epithin like gene and the there was no evidence the encoded polypeptide had serine protease activity. Further, not all members of the serine protease family had the same biological functions. Applying *Zymogenetics* and *BDP1 Phosphatase/Max-Plank* the application must indicate how to exploit the invention and that indication must have a sound and concrete technical basis. A speculative indication of possible objectives that might or might not be achievable by carrying out further research was not sufficient.

214. The last case in the series is *Schering's Application* (2007) T 1165/06 in which the Board of Appeal allowed an appeal against the refusal of an application by the examiners for lack of inventive step. The subject matter of the application was the disclosure of a polypeptide said to be a new member of the IL17 family of cytokines. The Board considered that this solved a technical problem which was not obvious.

Moreover the requirement of industrial applicability was satisfied because it was plausible that the polypeptide was a member of the family and would have biological properties similar to those of the other family members known at the filing date.

215. I was also referred to the guidelines issued by the EPO. These set out the practice and procedure to be followed in the various aspects of the examination of European applications and patents in accordance with the EPC. They are addressed primarily to the staff in the EPO but are also intended to be of assistance to litigants. In relation to industrial applicability they state, at EPO C-IV 5.1:

> "Industry should be understood in its broad sense as including any physical activity of "technical character" …. i.e. an activity which belongs to the useful and practical arts as distinct from aesthetic arts; … Thus, Article 57 excludes from patentability very few "inventions" which are not already excluded by the list in Article 52(2)."

216. And specifically in relation to genes, at C-IV 5.4:

> "In general it is required that the description of a European patent application should, where this is not self-evident, indicate the way in which the invention is capable of exploitation in industry. In relation to sequences and partial sequences of genes, this general requirement is given specific form in that the industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application. A mere nucleic acid sequence without indication of a function is not a patentable invention (EU Dir. 98/44/EC, rec. 23). In cases where a sequence or partial sequence of a gene is used to produce a protein or a part of a protein, it is necessary to specify which protein or part of a protein is produced and what function this protein or part of a protein performs. Alternatively, when a nucleotide sequence is not used to produce a protein or part of a protein, the function to be indicated could e.g. be that the sequence exhibits a certain transcription promoter activity.

217. They are, I think, entirely consistent with the case law I have summarised.

The US position

218. US law does not contain a requirement of industrial applicability as such. However, as I have mentioned, it does contain a similar requirement of "utility". This is contained in section 101 of 35 USC, which reads:

> "Whoever invents… any new and useful ….composition of matter …. may obtain a patent therefore…."

219. The Supreme Court considered the scope of this requirement in *Brenner v Manson* 383 U.S. 519 (1966), stating at 534-535:

> "The basic quid pro quo contemplated by the Constitution and by Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point – where specific benefit exists in currently available form – there is insufficient justification for permitting an applicant to engross what may be a broad field."

220. Here one sees the origin of the specific and substantial utility test that informed the decision of the Opposition Division of the EPO in *ICOS Corporation* and the decision of the hearing officer in *Aeomica.*

221. The scope of the requirement was considered further in the context of a biotechnology invention by the US Court of Appeals for the Federal Circuit in *Fisher v Lalgudi* (2005) 04-1465, 09/619,643. The claimed invention related to five purified nucleic acid sequences (ESTs) encoding proteins and protein fragments in maize plants. At the time of filing Fisher did not know the precise structure or function of either the genes or the proteins they encoded. In addressing the objection of lack of utility, the court first considered the meaning of "specific" and "substantial" (at 10-11):

> "The Supreme Court has not defined what the terms "specific" and "substantial" mean per se. Nevertheless, together with the Court of Customs and Patent Appeals, we have offered guidance as to the uses which would meet the utility standard of § 101. From this, we can discern the kind of disclosure an application must contain to establish a specific and substantial utility for the claimed invention.
>
> Courts have used the labels "practical utility" and "real world" utility interchangeably in determining whether an invention offers a "substantial" utility. Indeed, the Court of Customs and Patent Appeals stated that " '[p]ractical utility is a shorthand way of attributing 'real-world' value to claimed subject matter. In other words, one skilled person in the art can use a claimed discovery in a manner which provides some <u>immediate benefit to the public</u>." <u>Nelson</u>, 626 F.2d at 856 (emphasis added). [f.n. In Cross, this court considered the phrase "practical utility" to be synonymous with the phrase "substantial utility." 753 F.2d at 1047, n.13.] It is thus clear that an application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the "substantial" utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public.
>
> Turning to the "specific" utility requirement, an application must disclose a use which is not so vague as to be meaningless. Indeed, one of our predecessor courts has observed "that the nebulous expressions 'biological activity' or 'biological properties' appearing in the specification convey no more

> explicit indication of the usefulness of the compounds and how to use them than did the equally obscure expression 'useful for technical and pharmaceutical purposes' unsuccessfully relied upon by the appellant in In re Diedrich." In re Kirk, 376 F.2d 936, 941 (C.C.P.A 1967). Thus, in addition to providing a "substantial" utility, an asserted use must also show that that claimed invention can be used to provide a well-defined and particular benefit to the public."

222. So the application must show that the invention is useful to the public as disclosed, not at some future date after further research. The utility must be significant and presently available. It must also disclose a use which is well defined and not so vague as to be meaningless.

223. Applying these principles in the context of the case before it, the court concluded:

> "That the Kirk [376 F.2d 936] and Joly [376 F.2d 906] decisions involved chemical compounds, while the present case involves biological entities, does not distinguish these decisions. The rationale presented herein, having been drawn from principles set forth by the Supreme Court in Brenner, applies with equal force in the fields of chemistry and biology as well as in any scientific discipline. In Brenner, the Supreme Court was primarily concerned with creating an unwarranted monopoly to the detriment of the public:
>
> > "Whatever weight is attached to the value of encouraging disclosure and of inhibiting secrecy, we believe a more compelling consideration is that a process patent in the chemical field, which has not been developed and pointed to the degree of specific utility, creates a monopoly of knowledge which should be granted only if clearly commanded by the statute. Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development, without compensating benefit to the public….This is not to say that we mean to disparage the importance of contributions to the fund of scientific information short of the invention of something "useful", or that we are blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. [A] patent system must be related to the world of commerce rather than to the realm of philosophy."
>
> Brenner, 383 U.S. at 535-36 (citations, quotation, and footnote omitted). Here, granting a patent to Fisher for its five claimed

> ESTs would amount to a hunting license because the claimed ESTs can be used only to gain further information about underlying genes and the proteins encoded for by those genes. The claimed ESTs themselves are not an end of Fisher's research effort, but only tools to be used along the way in the search for a practical utility. Thus, while Fisher's claimed ESTs may add a noteworthy contribution to biotechnology research, our precedent dictates that the '643 application does not meet the utility requirement of § 101 because Fisher does not identify the function for the underlying protein-encoding genes. Absent such identification, we hold that the claimed ESTs have not been researched and understood to the point of providing an immediate, well-defined, real world benefit to the public meriting the grant of a patent."

224. This conclusion contains a powerful citation from the decision of the Supreme Court in *Brenner*. In return from his monopoly the patentee must disclose how his invention can be used. A patent is not a hunting licence to find a use for the claimed product. It is a reward for the successful conclusion of the search.

The law - conclusions

225. At the outset I would reiterate that it is the duty of this court to construe section 1 of the Act so that, so far as possible, it has the same effect as Article 52 of the EPC. Moreover, it is clearly of the utmost importance that the interpretation given by this court to section 1 of the Act and the interpretation given by the EPO to Article 52 should be the same. Accordingly, I must have regard to the decisions of the EPO, as explained in many cases, including *Merrell Dow Pharmaceuticals Inc. v H. N. Norton &Co. Ltd.* [1996] RPC 76 and *Kirin-Amgen Inc. v Hoechst Marion Roussel Ltd.* [2005] RPC 9. Decisions of the Boards of Appeal and the Enlarged Board of Appeal are of great persuasive authority.

226. With that in mind I believe the following important principles emerge from the cases to which I have referred:

i) The notion of industry must be construed broadly. It includes all manufacturing, extracting and processing activities of enterprises that are carried out continuously, independently and for commercial gain (*BDP1 Phosphatase/Max-Plank*). However, it need not necessarily be conducted for profit (*Chiron*) and a product which is shown to be useful to cure a rare or orphan disease may be considered capable of industrial application even if it is not intended for use in any trade at all (*Hematopoietic cytokine receptor/Zymogenetics*).

ii) The capability of industrial exploitation must be derivable by the skilled person from the description read with the benefit of the common general knowledge (*PF4A receptors/Genentech*).

iii) The description, so read, must disclose a practical way of exploiting the invention in at least one field of industrial activity (*BDP1 Phosphatase/Max-Plank; Multimeric Receptors/Salk Institute*).

iv) More recently, this has been re-formulated as an enquiry as to whether there is a sound and concrete basis for recognising that the contribution could lead to practical application in industry. Nevertheless, there remains a need to disclose in definite technical terms the purpose of the invention and how it can be used to solve a given technical problem. Moreover, there must be a real prospect of exploitation which is derivable directly from the specification, if not already obvious from the nature of the invention or the background art (*Hematopoietic cytokine receptor/Zymogenetics*; *Serine Protease/Bayer*).

v) Conversely, the requirement will not be satisfied if what is described is merely an interesting research result that might yield a yet to be identified industrial application (*Multimeric Receptors/Salk Institute*). A speculative indication of possible objectives that might or might not be achievable by carrying out research is not sufficient (*BDP1 Phosphatase/Max-Plank*). Similarly, it should not be left to the skilled reader to find out how to exploit the invention by carrying out a research programme (*Hematopoietic cytokine receptor/Zymogenetics*).

vi) It follows that the purpose of granting a patent is not to reserve an unexplored field of research for the applicant (*BDP1 Phosphatase/Max-Plank*) nor to give the patentee unjustified control over others who are actively investigating in that area and who might eventually find ways actually to exploit it (*Hematopoietic cytokine receptor/Zymogenetics*).

vii) If a substance is disclosed and its function is essential for human health then the identification of the substance having that function will immediately suggest a practical application. If, on the other hand, the function of that substance is not known or is incompletely understood, and no disease has been identified which is attributable to an excess or a deficiency of it, and no other practical use is suggested for it, then the requirement of industrial applicability is not satisfied. This will be so even though the disclosure may be a scientific achievement of considerable merit (*BDP1 Phosphatase/Max-Plank*).

viii) Using the claimed invention to find out more about its own activities is not in itself an industrial application (*BDP1 Phosphatase/Max-Plank*).

ix) Finally, it is no bar to patentability that the invention has been found by homology studies using bioinformatics techniques (*Hematopoietic cytokine receptor/Zymogenetics*) although this may have a bearing on how the skilled person would understand the disclosure.

227. I believe these principles are consistent with the Directive and with the approach adopted by the US courts in considering the requirement for utility imposed by section 101 of 35 U.S.C. Underlying that provision is the same policy consideration that in return for his monopoly the patentee must make a full disclosure of his invention, including a practical use to which it can be put. It not a hunting licence to find such a use. The “specific, substantial and credible” test is a convenient way of approaching the issue which has to be decided. But the approach adopted by the Boards of Appeal of the EPO is another. In my judgment the principles I have summarised in the immediately preceding paragraph are those this court should apply in considering the objection of lack of industrial application.

Industrial application - application to the facts

228. HGS submits that as at the date of the application, members of the TNF ligand superfamily had proved to have industrial applicability, indeed some were in the process of clinical trials. Further, in the light of the common general knowledge, any skilled person reading the Patent and accepting the identification of Neutrokine-α as being a new member of the TNF ligand superfamily, would appreciate that both the protein sequence and antibodies raised to it would have the potential for commercial exploitation. The invention resides in the identification not only of the sequence but of its properties as being a member of the family. That is enough in law.

229. HGS also submits that utility is amply demonstrated in the present case by reason of the fact that by 2000 commercial products making use of the invention were on the market. So far as the protein is concerned, recombinant Neutrokine-α was available commercially from Research Diagnostics Inc and anti Neutrokine-α antibodies were available from MoBiTec.

230. I accept that the contribution made by HGS was to find Neutrokine-α and to identify it as a member of the TNF ligand superfamily. However it is clear from the cases to which I have referred that simply identifying a protein is not necessarily sufficient to confer industrial utility upon it. *Multimeric Receptors/Salk Institute* is just one example. It may be sufficient if the identification of the protein will immediately suggest a practical application, such as was the case with insulin, human growth hormone and erythropoietin. But if the function of the protein is not known or is incompletely understood and if no disease has been attributed to a deficiency or excess of it, then the position may well be different. In these cases the industrial utility must be identified in some other way.

231. In this case I am quite satisfied that the skilled person would consider the Patent does not of itself identify any industrial application other than by way of speculation. As is apparent from my review in paragraphs [100]-[134] of this judgment, it contains an astonishing range of diseases and conditions which Neutrokine-α and antibodies to Neutrokine-α may be used to diagnose and treat and there is no data of any kind to support the claims made. The skilled person would consider it totally far-fetched that Neutrokine-α could be used in relation to them all and, as I have found, would be driven to the conclusion that the authors had no clear idea what the activities of the protein were and so included every possibility. To have included such a range of applications was no better than to have included none at all.

232. But that is not the end of the matter because the disclosure must be considered in the light of the common general knowledge which I have considered in paragraphs [34]-[77] of this judgment. The skilled person would have known that TNF was involved as a primary mediator in immune regulation and the inflammatory response and had an involvement in a wide range of diseases as septic shock, rheumatoid arthritis, inflammatory bowel disease, tissue rejection, HIV infection, and some adverse drug reactions. He would have known that all the members of the TNF ligand superfamily identified hitherto were expressed by T cells and played a role in the regulation of T cell proliferation and T cell mediated responses. Further, as Professor Saklatvala accepted, the skilled person would anticipate that the activities of Neutrokine-α might relate to T cells and, in particular, be expressed on T cells and be a co-stimulant of B cell production; that it might play a role in the immune response and in the control of

tumours and malignant disease; that it might have an effect on B cell proliferation; and that it would have the same roles, to some degree, as those described in the Gruss paper.

233. On the other hand, the skilled person would have also known that the members of the family had pleiotropic actions; that some of those activities were unique to particular TNF ligands and others were shared by some or all the other TNF ligands and that no disease had been identified in which they were all involved. Moreover, as explained in the Maini publication, the therapeutic application of TNF-α monoclonal antibody for the treatment of rheumatoid arthritis was believed to operate by interrupting the cytokine cascade and by controlling the recruitment and trafficking of blood cells to the joint – a rather specific activity.

234. Does that common general knowledge, taken as a whole, disclose a practical way of exploiting Neutrokine-α? Or does it provide a sound and concrete basis for recognising that Neutrokine-α could lead to practical application in industry? In my judgment it does not. The fact that Neutrokine-α might be expected to play a role in regulating the activities of B cells and T cells and play an unspecified role in regulating the immune and inflammatory response did not reveal how it could be used to solve any particular problem. Neither the Patent nor the common general knowledge identified any disease or condition which Neutrokine-α could be used to diagnose or treat. Its functions were, at best, a matter of expectation and then at far too high a level of generality to constitute a sound or concrete basis for anything except a research project.

235. I believe this conclusion is confirmed by the activities of those in the pharmaceutical industry in the years following the filing of the application. HGS, Lilly and Biogen (and possibly others too) carried out research programmes to try and find out where Neutrokine-α was expressed, where its receptors were expressed and what its activities appeared to be. They carried out *in vitro* assays and animal studies and determined that it appeared to have an activity in relation to B lymphocytes with a particular biological profile. On the basis of this work they recognised that it was an important therapeutic target – some two to three years after the application for the Patent had been filed. It is significant that in so doing they considered that its utility might lie in the treatment of B cell disorders of particular kinds.

236. I must also deal with the submission that industrial utility is established by the fact that by 2000 (and possibly earlier) recombinant Neutrokine-α was available commercially from Research Diagnostics Inc and anti Neutrokine-α antibodies were available from MoBiTec. I have no doubt that these products were being sold for research purposes and to enable those in the field to further investigate Neutrokine-α. But using the invention as a tool to carry out research into its activities does not constitute a relevant industrial application and in my judgment the position is not improved because the tool is made and sold by third parties for such research purposes.

237. In conclusion, I am satisfied that this is a case where the claimed inventions were not susceptible of industrial application at the date of the Patent. It is no answer to say that subsequent research has shown they may be useful to treat diseases associated with particular B cell disorders. There is no basis for distinguishing between the

claims to polynucleotides, polypeptides, antibodies and pharmaceutical and diagnostic compositions. They are all invalid.

Insufficiency

Introduction

238. Lilly alleges that the specification does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art. Since HGS does not suggest the Patent as granted is valid, I need only consider the objections to the proposed amended claims. In substance they are:

i) *The sequence claims* (*claim 1 and all claims dependent on claim 1*). These had no known function and consequently made no technical contribution. Moreover, in referring to *Neutrokine-α polypeptide* they necessarily refer to a protein having *Neutrokine-α activity* and it was not possible for the skilled person to determine what this is.

ii) *The antibody claims* (*proposed claim 15 and all claims dependent on claim 15*). Here the objections are threefold:

a) They refer to the *Neutrokine-α portion* of a *Neutrokine-α polypeptide* and it is not possible for the skilled person to determine what this is.

b) They call for antibodies which bind *specifically* to the *Neutrokine-α portion* of a *Neutrokine-α polypeptide*, and such antibodies could not be identified without undue effort

c) The promise of the Patent is to produce antibodies which are therapeutically and diagnostically useful. No such antibodies are disclosed and they could not be produced without undue effort, and *a fortiori* could not be produced without undue effort across the whole scope of the claims.

iii) *The pharmaceutical and diagnostic composition claims* (*proposed claims 20 and 21*). These claims encompass polynucleotides, polypeptides and antibodies and no such compositions are disclosed or enabled. Still less are the claims enabled across their width.

Insufficiency - the law

239. The specification must disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. The key elements of this requirement which bear on the present case are these:

i) the first step is to identify the invention and that is to be done by reading and construing the claims;

ii) in the case of a product claim that means making or otherwise obtaining the product;

iii) in the case of a process claim, it means working the process;

iv) sufficiency of the disclosure must be assessed on the basis of the specification as a whole including the description and the claims;

v) the disclosure is aimed at the skilled person who may use his common general knowledge to supplement the information contained in the specification;

vi) the specification must be sufficient to allow the invention to be performed over the whole scope of the claim;

vii) the specification must be sufficient to allow the invention to be so performed without undue burden.

240. Elements vi) and vii) merit a little elaboration. It has long been a principle of patent law that the specification must enable the invention to be performed to the full extent of the monopoly claimed. If the invention discloses a principle of general application, the claims may be in correspondingly general terms. But 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: *Genentech I/Polypeptide expression* T 292/85 [1989] OJEPO 275; *Biogen v Medeva* [1997] RPC 1 at [48].

241. The question whether a burden is undue must be sensitive to the nature of the invention, the abilities of the skilled person and the art in which the invention has been made. The court must consider whether the effort required of the skilled person is undue having regard to the fact that the specification should explain to him how the invention can be performed. Each case must be decided on its own facts. Nevertheless, helpful guidance is to be found in the decision of the Court of Appeal in *Mentor v Hollister* [1993] RPC 7. Lloyd LJ explained at 13-14:

> "…..if a working definition is required then one cannot do better than that proposed by Buckley LJ in giving the judgment of the Court of Appeal in *Valensi v. British Radio Corporation* [1973] R.P.C. 337. After referring to a number of earlier authorities, including *Edison & Swan v. Holland*, he said:
>
> > "We think that the effect of these cases as a whole is to show that the hypothetical addressee is not a person of exceptional skill and knowledge, that he is not to be expected to exercise any invention nor any prolonged research, inquiry or experiment. He must, however, be prepared to display a reasonable degree of skill and common knowledge of the art in making trials and to correct *obvious* errors in the specification if a means of correcting them can readily be found."
>
> Then a little later:
>
> > "Further, we are of the opinion that it is not only inventive steps that cannot be required of the addressee. While the addressee must be taken as a person with a will to make the instructions work, he is not to be called upon to make a prolonged study of matters which present some initial

> difficulty: and, in particular, if there are actual errors in the specification -- if the apparatus really will not work without departing from what is described -- then, unless both the existence of the error and the way to correct it can quickly be discovered by an addressee of the degree of skill and knowledge which we envisage, the description is insufficient."

In that case there was a mistake in the specification. But Buckley LJ's language is equally apt to cover an omission.

…….

Before leaving the authorities, I should mention *No-Fume Ltd. v. Frank Pitchford & Co. Ltd.* (1935) 52 R.P.C. 231. Quoting from the judgment of Romer L.J. in that case, Buckley LJ in *Valensi* is reported as saying:

> "The test to be applied for the purpose of ascertaining whether a man skilled in the art can readily correct the mistakes or readily supply the omissions, has been stated to be this: Can he rectify the mistakes and supply the omissions with the exercise of any inventive faculty? If he can, then the description of the specification is sufficient. If he cannot, the patent will be void for insufficiency."'

"With" in that quotation must be a misprint for "without". I turn to the judge's conclusion on the law. What he said was this:

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

> I have already quoted the remainder of that paragraph.
>
> I can find no vestige of error in that statement of the law. It was at first argued that the skilled man should not have to carry out any research, enquiry or experiment at all, whether prolonged or otherwise. But Mr. Thorley subsequently retreated from that extreme position. There is no support for setting so high a standard of disclosure, whether in *Valensi* itself or in any of the previous authorities, save possibly the judgment of Lindley LJ in *Edison & Swan v. Holland*. When, a little later, Aldous J came to apply the law to the facts of this case, he refers to "routine trials" and "normal routine matters that the skilled man would seek to do and would be able to do". Mr. Thorley criticises the use of the word "routine". To require the performance of routine trials is, he said, to ask too much of the addressee. I do not agree. "Routine" is just the word I would have chosen myself to describe the sort of trial and error which has always been regarded as acceptable; and "routine trials" has the further advantage that it is a positive concept, which is easily understood and applied. In practice, therefore, it may provide a surer test of what is meant by "clearly enough and completely enough" in section 72(1) of the Act than the negative test proposed in *Valensi*, namely the absence of prolonged research, enquiry and experiment. If the trials are unusually arduous or prolonged, they would hardly be described as routine."

242. A little later (at page 17, lines 4-14) the court accepted the requirement was not to produce a successful commercial product but rather a workable prototype. This is an important point and one which must be kept well in mind in assessing inventions in the pharmaceutical field as much as any other.

243. The case law of the EPO is, I believe, entirely consistent. Even though a reasonable amount of trial and error is permissible, when it comes to sufficiency of disclosure, for example in an unexplored field or where there are many technical difficulties, the skilled person has to have at his disposal, either in the specification or on the basis of his common general knowledge, adequate information leading necessarily and directly towards success through the evaluation of initial failures: see eg *Unilever* (1987) T 226/85.

Insufficiency - application to the facts

The sequence claims (claim 1 and all claims dependent on claim 1)

244. There are two points and they can be dealt with shortly. The first, that the sequences had no known function, is the same as that underpinning the allegation of lack of industrial applicability and HGS accepts it stands or falls with that allegation. It applies to all the claims, including the antibody claims.

245. The second is that the claims depend upon knowledge of what Neutrokine-α activity is. I have addressed this at [137] in considering the proper interpretation of the claims.

For the reasons I have given, I believe the allegation is misconceived. In the proposed amended claims, the Neutrokine-α polypeptide must be encoded by one of the two identified polynucleotide sequences of amended claim 1. It is therefore precisely defined. There is no suggestion that the skilled person would have any difficulty obtaining the defined sequences or expressing them and this allegation of insufficiency therefore fails.

The antibody claims (claim 15 and all claims dependent on claim 15)

246. The first objection is another point of interpretation and I have addressed it in paragraphs [138] to [140] above. For the reasons I have given, it does not amount to an insufficiency.

247. The second objection raises an issue of fact. Lilly says it required undue effort to identify antibodies which bind *specifically* to Neutrokine-α. It is to be noted this is not an allegation that the specification failed sufficiently to identify a function for the claimed antibodies. Nor is it an allegation that it required undue effort to make antibodies which are useful in therapy or as diagnostics. I address both of these further allegations below.

248. "Specific" in the context of an antibody means that the antibody binds to one antigen and not another. Professor Saklatvala did not suggest that raising polyclonal or monoclonal antibodies to a known antigen was other than routine. However, he maintained in his reports that to prove that an antibody does not react with any antigens except the one it is intended to react with is extremely difficult. It is to prove a negative and there is no standard array of antigens against which this can be measured. Indeed, he suggested that cross-reactivity with other proteins *in vivo*, and therefore any unwanted side effects, can only be assessed once the antibody has been administered to a human. In cross examination, Professor Saklatvala adopted a somewhat softer line. He accepted that the most likely reaction would be with highly related molecules and so the skilled person would carry out *in vitro* studies to see if there was any cross reaction and he described such work as conventional.

249. Professor Noelle explained in his reports that techniques for generating antibodies were well known in the art and that the specificity of an antibody could be determined at the date of the Patent by routine techniques involving suitably controlled immunoassays, in other words by *in vitro* studies. Under cross examination he accepted there was no standard array of antigens but said one could test the specificity of a particular antigen of interest in monkeys to see to see if it cross-reacted with any monkey tissue antigens, of which there would be many millions. Assuming there was no cross reactivity, one would be encouraged that the specificity of the antigen was quite precise.

250. In the light of all this evidence I am satisfied that it did not require undue effort to make and identify specific antibodies to Neutrokine-α at the priority date. This particular allegation of insufficiency therefore fails.

251. The final allegation is that the Patent promises antibodies which are therapeutically and diagnostically useful and that such antibodies could not be produced without undue effort. It is to be noted that proposed claim 15 is not directed to diagnostic or therapeutic antibodies. It simply claims antibodies which bind specifically to

Neutrokine-α. This allegation therefore adds nothing to the attack that the invention is not susceptible of industrial application and the general allegation of insufficiency to which this gives rise.

The pharmaceutical and diagnostic composition claims (claims 20 and 21)

252. The allegation that these claims are insufficient is important. Attention was focused particularly on such compositions containing antibodies and the importance for this purpose of *neutralising* antibodies was a recurring theme through the evidence and, indeed, is emphasised in the Patent itself in the passages cited in paragraphs [108] – [110] of this judgment.

253. Professor Saklatvala was clear it was a major undertaking to make a pharmaceutically useful antibody at the priority date and, indeed, remains so today. I have already touched on what is required in considering the common general knowledge but some aspects require a little elaboration. Professor Saklatvala explained in his reports that a therapeutic antibody to counteract the effect of over production of Neutrokine-*α* in disease needs to be a neutralising antibody. But it is not possible to identify the antibodies that neutralise the activity of a protein unless the activity of the protein is known. As he put it, if the skilled man does not know the activity of a protein, then how is he to know he has neutralised it?

254. Similarly, the Patent provides no data concerning the tissue distribution of expression, nor of protein levels in tissues or body fluids, nor the standard expression level of Neutrokine-*α* in humans. It is not possible to use antibodies to a protein to diagnose an over- or under-expression of that protein unless it is known how an over- or under-expression of that protein correlates with particular disease states. Nor is it possible to use antibodies to a protein to diagnose an over- or under-expression of that protein unless it is known what a standard level of expression of that protein is and in which tissues that standard level is to be found. It was Professor Saklatvala's opinion that the contribution of the Patent is the identification of a DNA sequence which is similar to that of TNF-*α.* But that this was only the starting point for research programs of enormous length and breadth which might or might not ultimately lead to something which is of therapeutic or diagnostic utility.

255. Under cross examination, Professor Saklatvala maintained his opinions save that he acknowledged that another route to obtaining neutralising antibodies is to carry out a screen using a receptor. However, finding the receptor for TNF- *α* proved problematic, as Professor Noelle accepted. It was not until April 2000 that details of the first receptors TACI and BCMA were published in *Nature* by workers at Zymogenetics. Even then Professor Saklatvala thought it would take about another year to identify a lead candidate.

256. Professor Noelle maintained in his reports that the skilled person would have been able to make monoclonal antibodies to Neutrokine-*α* and to identify therapeutic and diagnostic candidates for development using techniques that were well known in the art. In support of this he referred to the review articles I have discussed earlier in this judgment and to the teaching of the Patent itself. In cross examination, however, he agreed with Professor Saklatvala that to produce a therapeutic antibody to a protein ligand it was necessary to know the activity of the ligand *in vivo*; and to identify a diagnostic antibody to a protein one would need to understand how and which tissues

and fluids it manifests itself in particular disease states. This, he suggested, was "part of the business at the time". However, he also accepted that the skilled person reading the Patent would know the spectrum of activities that TNF family members have and would prioritise them based upon his knowledge and interests. For his part, Professor Noelle was particularly interested in B cells and so thought he would gravitate towards B cell proliferation and differentiation. But he recognised that the interests of another reader might lie elsewhere, for example in T cells. Either would have involved a research programme and the latter would have taken very many years, as illustrated by the papers to which I have referred in paragraphs [169]-[170] of this judgment. The position remained uncertain even in 2005. Much the same picture emerges in relation other therapeutic applications such as the treatment of B cell malignancies. In paragraphs [173]-[175] I have mentioned just two papers published by researchers investigating such diseases in the period 2004-2006. In summary, it has taken years of research to investigate only a portion of the activities and applications identified as useful in the Patent.

257. Overall I was left with the clear impression from the expert evidence that anyone seeking to develop a candidate antibody to Neutrokine-*α* for any therapeutic or diagnostic application based upon the teaching of the Patent would have been faced with a substantial research programme with an uncertain outcome. Depending upon his particular interests, the skilled person might choose to follow up an aspect of the teaching which would involve years of research or, even worse, lead him into a blind alley. Even today, the full range of activities of Neutrokine-*α* is still the subject of study.

258. The position is, I believe, confirmed by the evidence I heard relating to the efforts of HGS, Biogen and Lilly which I have summarised in paragraphs [142]-[168]. The work conducted by HGS after the priority date was extensive and constituted fundamental research to try and identify the activities of Neutrokine-*α*. Likewise Biogen conducted a range of studies to try and find where the protein was expressed, where its receptors were expressed and how the two interacted to produce a biological response. Again, this was a precursor to the research necessary to begin to find a diagnostic or therapeutic application. The story at Lilly is less clear but again is, I believe, broadly consistent. Lilly workers also tried to develop assays but, without any idea of the function of the protein, they could not determine the reason for their failure to identify activity. It was only in 1999 and with the benefit of their work with transgenic animals and having read the Moore paper that they appreciated that Neutrokine-*α* induced B cell proliferation and was a potentially important therapeutic target. Ultimately they developed a lead candidate relatively quickly but they did so by using the Medarex mice, which was seen as a powerful technology and one which was not established to be generally available to anyone who was prepared to pay for it.

259. In the light of all these matters I have reached the conclusion that it would have required a research programme and been far from routine for the skilled person to produce a candidate pharmaceutical or diagnostic composition comprising an antibody to Neutrokine-*α*, that is to say the pharmaceutical or diagnostic equivalent of a workable prototype, on the basis of the information contained in the Patent and the common general knowledge. Indeed, such a project may have failed altogether

depending on the route the skilled person chose to take. In my judgment proposed claims 20 and 21 are therefore insufficient.

260. I would add that although both claims are directed to a composition they are extremely broad because the application of the composition is not specified. They extend to compositions for treating or diagnosing any of the many different conditions discussed in the specification. It follows from my findings that the specification is wholly insufficient to allow the inventions of these claims to be performed over their whole scope.

Anticipation

261. I can deal with this attack very shortly because it must fail if I allow the proposed amendments to the claims, and because HGS does not contend the claims as granted are valid. However, it forms a convenient way of introducing the Image clone.

262. The Image clone consisted of a bacterial host into which had been inserted a fragment of human cDNA comprising 456 nucleotides which encode the C terminal end of Neutrokine-α, specifically amino acids 162-285 of Seq ID No:2 of the Patent. This falls within the scope of unamended claim 1(c).

263. On 2 July 1996, the Image clone was one of 9176 clones sent by the Lawrence Livermore National Laboratory to Washington University for sequencing. It was carried on a well plate with 384 wells, that is to say with 383 other cDNA clones. It is common ground that Washington University duly carried out the sequencing and that the sequence was published on GenBank after the priority date as accession number AA682496.

264. Lilly accepts that, as proposed to be amended, claim 1 is novel over the Image clone since the claim requires the full amino acid sequence of Neutrokine-α (claim1(a)) or amino acids 73-285 (claim 1 (b)). Accordingly, I need say no more about it in this context.

Obviousness

265. As I have mentioned, there are two separate attacks of obviousness. One is a conventional attack, that the claims are obvious over the Fujiwara EST and the Image clone. The other is that the claims make no contribution to the art. I will deal with them in turn but first must consider the correct approach in law.

266. In *Pozzoli v BDMO SA* [2007] EWCA Civ 588, [2007] FSR 37, the Court of Appeal explained that obviousness is conveniently addressed using the following structured approach:

i) (a) Identify the notional "person skilled in the art"

(b) Identify the relevant common general knowledge of that person;

ii) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

iii) 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 claim as construed;

iv) Ask whether, viewed without any knowledge of the alleged invention as claimed, those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

267. Since *Pozzoli*, the House of Lords has considered the question of obviousness in *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49. In that case the claimed invention was for a taxol coated stent and the teaching of the specification was that such a stent would prevent or treat restenosis. However, the specification said very little by way of detail about how or why taxol would be efficacious in that application. It saw the solution for restenosis in terms of preventing angiogenesis but offered no proof that this was right. The trial judge, Pumfrey J, held the claim to be obvious on the basis that, in these circumstances, it was legitimate to ask whether the invention was obvious to try *without* any expectation of success. The Court of Appeal upheld his decision and Angiotech appealed to the House of Lords.

268. Their Lordships allowed the appeal explaining the Pumfrey J had erred in law. If the specification passes the threshold test of disclosing enough to make the invention plausible, the question of obviousness is not to be subject to a different test according to the amount of evidence the patentee has presented to justify his conclusion that his patent will work. The correct question is whether it was obvious to use a taxol-coated stent to prevent restenosis, and it could be inferred that had Pumfrey J asked this question, he would have upheld the patent.

269. In arriving at this conclusion, Lord Hoffmann explained that in the case of many product claims there may be nothing inventive in discovering how to make the product. In these cases the invention lies in disclosing that the product has a particular quality. As he said at [17]:

> "… In the present case, the invention specified in claim 12 was a stent coated with taxol. There was no dispute that this was a new product. The question should therefore simply have been whether it involved an inventive step. As in the case of many product claims, there was nothing inventive in discovering how to make the product. The alleged inventiveness lay in the claim that the product would have a particular property, namely, to prevent or treat restenosis. (Compare *Pharmacia Corp v Merck & Co Inc* [2002] RPC 775). So the question of obviousness was whether it was obvious to use a taxol-coated stent for this purpose. And this, as I have said, was the question to which the experts addressed themselves.

270. However, the invention is not to be watered down by alleged inadequacies in the disclosure as to the extent of testing that has been performed. Thus Lord Hoffmann continued at [19]:

> "In my opinion, however, the invention is the product specified in a claim and the patentee is entitled to have the question of

> obviousness determined by reference to his claim and not to some vague paraphrase based upon the extent of his disclosure in the description. There is no requirement in the EPC or the statute that the specification must demonstrate by experiment that the invention will work or explain why it will work…."

271. After referring to the facts, Lord Hoffmann confirmed that a patent will not be granted for an idea which is mere speculation and summarised the line of EPO cases to the effect that product claims which have no evident utility provide no technical contribution, solve no technical problem and hence are obvious. This forms the heart of the second allegation of obviousness advanced by Lilly in the present case and it is therefore convenient to set out the material paragraphs of Lord Hoffmann's opinion which address this issue:

> "31. In this case, however, the patent had been granted by the EPO and article 84 was therefore no longer in issue. There is also a line of authority in the EPO in which claims to broad classes of chemical compounds alleged to have some common technical effect have been rejected under article 56 (obviousness) when there was nothing to show that they would all have that technical effect. The leading case is *AGREVO,* Case No T 0939/92, which was a product claim for a class of chemical compounds alleged to be useful as herbicides. But there was nothing in the description to justify the assertion that all the compounds in the class would have herbicidal properties. The Board of Appeal decided that the claims were not insufficient (the skilled man would have been able to make all the compounds claimed) but failed for lack of an inventive step because there was nothing inventive in simply making the compounds. The invention, if any, would lie in the discovery that they were herbicides. The Board of Appeal said (at paragraph 2.5.4):
>
> > "… [A] technical effect which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by substantially all the selected compounds …"
>
> 32. At paragraph 2.6.2 the Board acknowledged that a patentee does not have to have tested every compound to see whether it has the claimed effect: "reasonable predictions of relations between chemical structure and biological activity are in principle possible, but that there is a limit beyond which no such prediction can be validly made."
>
> 33. The case of *Johns Hopkins University School of Medicine* Case No T 1329/04 deals with the question of whether the use which may be made of the claimed product (ie that which may constitute the inventive step) must be stated in the specification or can be proved by later evidence. The claim was to a DNA sequence encoding a protein "having GDF-9 activity". Again,

as in AGREVO, there was nothing inventive in simply making the DNA sequence. The inventive step, if any, would lie in a disclosure that it coded for a useful protein. But the specification disclosed no more than speculation about how GDF-9 activity might be useful. The examining division rejected the application on the ground that such speculation did not go beyond what was obvious and refused to take into account subsequently published material showing specific properties of GDF-9.

34. The Board of Appeal pointed out (at paragraph 10) that in the specification various effects were "tentatively and presumptively" attributed to GDF-9. It went on:

> "[T]he issue here is … how much weight can be given to speculations in the application in the framework of assessing inventive step, which assessment requires that facts be established before starting the relevant reasoning. In the board's judgment, enumerating any and all putative functions of a given compound is not the same as providing technical evidence as regard a specific one … [T]here is not enough evidence in the application to make at least plausible that a solution was found to the problem which was purportedly solved."

35. The Board then went on to consider whether this deficiency could be remedied by evidence coming into existence after the application:

> "12. The appellant filed post-published evidence … establishing that GDF-9 was indeed a growth differentiation factor. This cannot be regarded as supportive of an evidence which would have been given in the application as filed since there was not any. The said post-published documents are indeed the first disclosures going beyond speculation. For this reason, the post-published evidence may not be considered at all. Indeed, to do otherwise would imply that the recognition of a claimed subject-matter as a solution to a particular problem could vary as time went by. Here, for example, had the issue been examined before the publication date of the earliest relevant post-published document, GDF-9 would not have been seen as a plausible solution to the problem … and inventive step would have had to be denied whereas, when examined thereafter, GDF-9 would have to be acknowledged as one such member. This approach would be in contradiction with the principle that inventive step, as all other criteria for patentability, must be ascertained as from the effective date of the patent. The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in

> the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve."
>
> 36. These cases are in my opinion far from the facts of this case. The specification did claim that a taxol coated stent would prevent restenosis and Conor did not suggest that this claim was not plausible. That would have been inconsistent with the evidence of its experts that taxol was just the thing to try. It is therefore not surprising that implausibility was neither pleaded nor argued. The same was true of the proceedings in the Netherlands (see paragraph 4.17 of the judgment)."

272. Finally, their Lordships confirmed that it may be permissible to enquire whether the invention was obvious to try. As Lord Hoffmann said 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 in which there was a fair expectation of success. How much of an expectation would be needed depended upon the particular facts of the case. As Kitchin J said in *Generics (UK) Ltd v H Lundbeck A/S* [2007] RPC 32, para 72:
>
> > "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."

273. In considering the conventional obviousness case I must therefore apply the *Pozzoli* test, subject to this. The invention is to be identified by reference to the claims and the question is simply whether it was obvious to make a product falling within their scope.

274. The further obviousness case, that the invention provides no technical contribution, is to be determined by considering whether the invention lies in making the products of the claim or rather whether, as in the *Johns Hopkins* case, it must lie in a disclosure that the DNA products of claim 1 code for useful proteins and, if so, whether the specification does no more than speculate as to what those uses might be. Any

deficiency cannot be remedied by evidence coming into existence after the application.

Obviousness – Fujiwara EST and Image clone

Fujiwara EST

Introduction

275. The Fujiwara EST encodes the sequence of 63 amino acids of Neutrokine-α running from 222 to the C terminus at 285 in SEQ ID No:2 of the Patent. There is no dispute that it was accessible to the public on the GenBank database at the priority date but it had not been characterised or identified as a sequence having anything to do with TNF. It was one of 390,000 ESTs among a total of some 1,021,000 sequences on that database, the majority of which were not annotated and so carried no indication of their function based upon biology or homology to other sequences.

276. Lilly's argument is, in summary, as follows. As a matter of law, the Fujiwara EST must be deemed to be put in front of the skilled person, in this case a team looking for new members of the TNF family. To such a team it would have been obvious to seek to characterise the EST and for this purpose they would have approached a bioinformaticist (if not already a member of the team) and asked if it represented a protein with some sequence similarity to TNF proteins. In order to answer that question, the bioinformaticist would have carried out a computer search against the Swiss-Prot protein database. Lilly has adduced experimental evidence from Dr Apweiler which, it says, shows that such a search would have revealed the EST to be related to the TNF family. Thereafter it would have been obvious to obtain the full length gene and produce products within each of the claims.

277. As an alternative, Lilly argues it was obvious to set up an automated system or "pipeline" in order to "mine" the available public databases. ESTs were being placed on these databases on a daily basis and it was obvious to undertake searches automatically on the data as it became available. The kind of searches a team interested in TNF would have undertaken would have picked up the Fujiwara EST as a candidate for further study.

278. HGS responds that Lilly's argument fails at a number of levels. First, it is wrong in law to treat the Fujiwara EST as being put in front of the skilled team. It is only with the benefit of hindsight that this particular EST can be identified as a suitable starting point. Moreover, database mining of the kind postulated was neither common general knowledge nor an obvious strategy to adopt.

279. Second, on the assumption the skilled person chose to pursue a bioinformatics route he would start with the family of TNFs and perform searches against ESTs, not the other way around.

280. Third, the experiments conducted by Lilly are flawed because they were carried out on version 34 of Swiss-Prot which was not available at the priority date. Moreover, it is not possible to draw any conclusions from the limited search that Lilly did in fact conduct.

Question (i) – the skilled person and the common general knowledge

281. I have identified the person skilled in the art earlier in this judgment. Materially, I have accepted in paragraphs [31]-[32] that it is a team including or with access to a bioinformaticist. I have also discussed many aspects of the common general knowledge. However, in the context of this part of the case, the following matters are of particular importance.

282. First, I am satisfied that those in the art knew the TNF family had diverse but overlapping functions. They also thought it worthwhile to seek out other putative members of the family which might be relatively diverse in their sequences.

283. Second, ESTs were known to represent human gene products and were created in order to be characterised. But it must be remembered that the number of ESTs on databanks such as GenBank increased rapidly through the 1990s, and many of them were uncharacterised. So it does not necessarily follow it was obvious to pick out one EST rather than another and carry out a series of specific tests in relation to it. This is a matter to which I return in a moment.

284. Third, the concept of comparing a sequence against other sequences in one of the databanks was well known, as were the programs which permitted this to be performed automatically, as discussed in paragraphs [78]-[99]. As Lilly submits, an EST allows the question to be asked: what does this EST resemble? And databases such as Swiss-Prot allows such questions to be answered by providing catalogues of known proteins against which it can be compared.

285. Fourth, when two sequences are aligned with one another, a sequence identity or score can be calculated. This then needs to be assessed to determine if the sequence identity is sufficiently high to suggest the database hit is likely to be a homologue of the probe sequence. A variety of different ways of assessing the score were known. Of these the most informative was considered to be the "e-value" which represents the number of times one can expect to see at least a given score occur in the database by chance. The lower the e-value, the greater the chance that the two sequences are indeed homologues. By way of example, an e-value of 0.01 means that, on average, for every 99 true hits indicating homology, one would expect one false non-homologous hit. I am not satisfied that it was a matter of common general knowledge simply to consider "top hits" as an appropriate way to proceed, as Lilly appeared to suggest. However, I do accept that it might have been obvious to take this into account, depending on the circumstances.

286. Fifth, I am satisfied that it was common general knowledge to search ESTs against protein databases, such as Swiss-Prot. However, Lilly goes further and suggests it was common general knowledge to use ESTs en masse in a bioinformatics context to search or "mine" for new genes and new members of a protein family. This is essentially a difference is scale, but an important one all the same. Dr Apweiler suggested in his report that in the three months from September to December 1996, 120,000 new sequences were added to GenBank, of which about one third would have been sequences of human DNA. It was therefore feasible to download all the sequence data uploaded each day onto GenBank and to search it on a daily basis against Swiss-Prot in a "pipeline". I will return to consider whether this was an obvious strategy to adopt, but for the moment confine myself to a consideration of

whether it was a technique which formed part of the common general knowledge. I am satisfied it was not. This was Dr Martin's view and Dr Apweiler was not aware of any companies that carried out such searches in the hope that something might turn up. Nor was it a technique foreshadowed in any of the published art, save in relation to attempts to annotate a small population of ESTs.

Question (ii) – the inventive concept of claim 1 as proposed to be amended

287. Lilly suggests that care must be taken in attributing too much by way of function to the subject matter of claim 1 in the light of the difficulties of identifying the meaning of the expression "Neutrokine α activity". But it must be borne in mind this expression does not appear in the claims as proposed to be amended. I propose to address the question of obviousness on the basis that the invention of claim 1 is a novel polynucleotide which, as the specification explains, encodes a novel member of the TNF ligand superfamily.

Question (iii) – the differences

288. The Fujiwara EST is about 20% of the whole protein coding sequence and about 33% of the extracellular domain of Neutrokine-α. The difference between the EST and the polynucleotides of proposed amended claim 1 is therefore the length of the sequence.

Question (iv) – Does the difference constitute a step which would have been obvious?

289. Lilly's arguments proceed on the assumption that the Fujiwara EST was made available to the public at the priority date and so formed part of the state of the art both on its own and in the context of the of the GenBank database as a whole. HGS disputes that the Fujiwara EST was ever made available to the public on its own but does accept it was made available to the public as part of the whole database.

290. In developing its position that the Fujiwara EST did not form part of the state of the art on its own, HGS did not advance any argument to the effect that nothing about the clone (or its sequence) revealed its nature and hence did not place any reliance upon the decision of the House of Lords in *Merrell Dow Pharmaceuticals v H N Norton* [1996] RPC 76. It accepts that if it was obvious to make a sequence in the claim then the claim is invalid. Instead, it relied on the decision of the EPO Board of Appeal in case T307/87 *Biogen/Recombinant DNA* [1990] EPOR 190 concerning an invention relating to DNA sequences encoding a polypeptide of IFN-α (interferon) type. There the Board rejected a lack of novelty attack based upon hybrid phages contained in Lawn's gene bank, a public collection of 240,000 fetal human chromosomes. It reasoned that the skilled person would have had no idea whether the Lawn gene bank contained a clone containing DNA sequences coding for an interferon type polypeptide and it would have required undue effort to find out. Although any vial containing the phage was a separate entity, it was impossible to get to the vial without working through tens of thousands of samples using a biochemical process. The position was analagous to the isolation of a bacterium from the soil where, until it is found, it exists in admixture with other useless materials.

291. The Board's decision appears to include two interwoven stands of reasoning, namely first, whether any individual clone formed part of the state of the art and second, whether the disclosure was enabling. As the House of Lords made clear in *Synthon v*

SmithKline Beecham [2005] UKHL 59, these are separate requirements and both must be satisfied if an invention is to be deprived of novelty. However, underpinning both of them was the view of the Board that the skilled person would not have known whether any clone encoded a polypeptide of the interferon type. That, as I have indicated, is an argument which HGS has not advanced in this case.

292. Here the Fujiwara EST had been sequenced and it formed part of the public database. It could be searched for and reproduced without difficulty. In my judgment it formed part of the state of the art both as a sequence and as part of the database.

293. Lilly then contends as follows. The public are entitled to do whatever is obvious over the prior art. A skilled person presented with the Fujiwara EST would have sought to characterise it. Such a characterisation would have been carried out by searching it against a protein database such as Swiss-Prot and results of the kind shown in Annex 1, tables 1A and 1B of Lilly's Notice of Experiments would have been obtained. These were produced by using the Fujiwara EST to search against version 34 of Swiss-Prot using, respectively, FASTA and SSEARCH. Lilly argues the skilled person would have seen multiple hits to members of the TNF family in the default top 20 list and so would have passed the EST on to the wet biologist to be cloned and expressed. The results would not have allowed the skilled person to conclude definitively that the EST is a member of the TNF family. But it would have provided him with a reasonable degree of confidence that the EST represented a gene which should be investigated as a member of the TNF family, and that is enough.

294. In the alternative, Lilly submits that an automated pipeline search strategy was also obvious. It says that on the evidence a pipeline programmed to flag ESTs which hit multiple TNF family members would have been likely to produce only a handful of results, comparable to those obtained using the Fujiwara EST.

295. I am unable to accept either of these submissions. In my judgment the first is a wholly artificial approach and it is not one which the law requires. I accept that the skilled person must be deemed to consider any piece of prior art properly and in that sense with interest. This emerges clearly from the decision of the Court of Appeal in *Asahi Medical Co Ltd v Macopharma (UK) Ltd* [2002] EWCA Civ 466 and is necessary to prevent a patent from depriving the public of their right or make or do anything which is merely an obvious modification of what has been done or published before. But the law does not deem the skilled person to assume the prior art has any relevance to the problem he is addressing or require him to take it forward. Having considered it, he may conclude that it is simply not a worthwhile starting point and so put it to one side.

296. I believe this is such a case. The Fujiwara EST was not characterised or highlighted when placed on GenBank. As such, it was indistinguishable from hundreds of thousands of other uncharacterised ESTs on GenBank at the priority date. On the face of it, there was no reason to do anything with this EST rather than any other. I understood both experts to confirm this in the course of their evidence. Dr Apweiler said that prior to conducting a mass search there was no reason to focus on this sequence or, indeed, to select any other EST. Dr Martin was asked to assume that, as a member of the skilled team, he was given the Fujiwara EST and it was then suggested to him that he would seek to characterise it. He did not agree. He would not have done anything with it unless told a good reason for doing so. So the evidence is all one

way. It was not obvious to carry out Lilly's experiments with the Fujiwara EST in 1996.

297. The second approach, the mass screen or pipeline was not the subject of any experiment and I not satisfied it was either obvious or would have worked. I have found the use of such a technique to identify new putative members of a protein family was not common general knowledge and Dr Martin was clear it was not an obvious strategy to adopt. It involves searching an unknown (the hundreds of thousands of uncharacterised ESTs) against another unknown (the uncharacterised proteins on Swiss-Prot) and that made no sense to him. Rather, he would have searched a known (the members of the TNF family) against an unknown (the uncharacterised ESTs). As he said on Day 7 at 961-2:

> "A. Yes, so we have two possible scenarios. One is that we have a whole set of ESTs, perhaps we are interested in, I do not know, fetal brain diseases, for example, so you would take all this fetal cDNA library and you would screen all of it to see what you could find out was expressed in the fetal brain and therefore might be an interesting drug target. On the other hand, you have particular protein families that you are interested in, such as TNF, in which case the straightforward strategy, which I believe would be the strategy that would be adopted, would be to take the members of that family and to search with those against the EST data. I mean, why would you bother screening 390,000 ESTs when you know you are only interested in a small number and you know you are interested in the ones that related to TNF and maybe a dozen other families.
>
> Q. What I want to put to you, Dr. Martin, is that although you would say that that is not a strategy you would employ, a protein database strategy, it is a strategy which some in the bioinformatics field were very familiar with and although you may not do it, others might have done. Would you accept that?
>
> A. It is always possible that somebody might do anything, but it is not a strategy that appears to me a clear route for solving a particular problem. And I cannot see that it would be the clear route that anybody would try to take if they were interested in a particular family."

298. Further, the pipeline approach would have taken a very great deal of computer time, as he explained at 963-4:

> "A. Why would they screen 390,000 sequences by doing 390,000 separate searches rather than doing a single search? I mean, it is possible that somebody might do it but I cannot see a justification for doing it. If I were in a company and I were given this problem and said to my boss, "Well, I could do it this way, which I believe will work, because it is a case of take sequences that are a member of this family and searching them

> against the database, I can get the answer in a day. Or would you like me to take 390,000 ESTs, 389,999 of which are almost certainly of no relevance whatsoever, and search all of them over a period of 390 days of computer time?" I just do not see why one would ever try to do that."

299. Dr Martin's favoured strategy is by no means perfect. In particular, it suffers from the drawback that it requires further work to determine whether an interesting EST with a low e-value represents a new member of the family of interest or a member which has already been characterised. I also have well in mind Dr Apweiler's evidence that it would have been possible to conduct a pipeline search in the way he suggests. Nevertheless, I found Dr Martin's reasoning persuasive. I do not think pipelining was an obvious strategy to adopt.

300. On the other hand, had Dr Martin's strategy been adopted then such evidence as there is before me suggests it would not have worked. This takes the form of HGS's experiment 5. This was conducted using each of the protein sequences disclosed in Figure 2 of Gruss and Dower and the program TFASTA which compares each sequence against a six frame translation of each sequence in the database. The search did not pick up the Fujiwara EST or identify Neutrokine-α in any other way.

301. Moreover, I am not satisfied the Lilly strategy would have led to the identification of Neutrokine-α in any event. Dr Apweiler accepted on a number of occasions that had a pipeline strategy been adopted, all the results would have had to be considered. He could not say whether the results obtained in Lilly's experiments would have proved of interest unless he had compared them to the thousands of other analyses which, on this hypothesis, he would have conducted.

302. A number of other detailed points on Lilly's experiments were taken by HGS which I can deal with quite shortly. In my judgment there is nothing in any of them.

303. HGS said, correctly, that version 34 of Swiss-Prot was not available until after the priority date. This is important because Lilly has not performed an experiment to show that a search of the Fujiwara EST against version 33 would have thrown up Neutrokine-α. HGS, on the other hand, has performed searches against version 33 using FASTX and SSEARCH and did not get a positive result, as Lilly accepted.

304. The answer provided by Lilly is that Swiss-Prot was updated regularly between the issue of the various different versions and Dr Martin confirmed that it was standard practice for those using databases to obtain such updates. Moreover, although the way the evidence emerged was not entirely satisfactory, I have reached the conclusion that no relevant TNF sequences were added after 5 July 1996. It follows that the objection falls away.

305. Another point taken by HGS was that Lilly should have used FASTX rather than FASTA to carry out the search, the benefit of the former being that it performs the three frame translation automatically, so removing the need to carry out this step with another program. I reject this criticism. I am satisfied that FASTX was available from May 1996, but both were still very much in use at the priority date and I believe it was acceptable and obvious to use either.

306. A more substantive point arises in relation to the question of how the "cut off" is to be assessed. It is conveniently considered by reference to the Lilly experiments. These show that the top two hits in each case, that is to say the sequences in the Swiss-Prot database that appear to be most closely related to the Fujiwara EST using e-values, are proteins quite unrelated to TNF. One is an insect protein called chitin synthase and the other is a protein associated with tuberculosis. On the other hand, the "top 20" include 7 hits against TNF proteins, albeit some with very high e-values. As I have said, I do not believe it was common general knowledge to adopt a top hits approach. However, I have reached the conclusion in the light of all the evidence that the considerable number of hits against TNF sequences would have struck the skilled person as being of interest assuming, contrary to my findings, he carried out these experiments on their own in the first place.

307. Despite my rejection of these points of detail, it follows from my earlier conclusions that the attack of obviousness based on the Fujiwara EST must be rejected. I am confirmed in this view by the evidence of Dr Farrow as to the work done at GlaxoSmithKline. His team found a new TNF receptor called DR3 and then began to look for ligands with which it interacted. They tried traditional molecular biology techniques using both DR3 expression clones and probes derived from known TNF ligands to screen cDNA expression libraries, both without success. Before the priority date, they also tried various bioinformatics based approaches. In particular, they used TFASTA to screen particular search sequences comprising full length sequences of known TNF ligand superfamily members (and fragments of them) against GenBank and EMBL. They also used a consensus sequence derived from Wiley in the same way. Neither resulted in the identification of a novel TNF ligand. Eventually, some time after the priority date, they achieved success by developing a particular motif from a study of the sequences of the known TNF ligand superfamily members.

Image clone

Introduction

308. I have explained the nature of the Image clone in considering the issue of novelty in paragraphs [261]-[264]. The allegation of obviousness to which it gives rise differs in two important respects from that based on the Fujiwara EST. The first is that the clone had not been sequenced by the priority date. It is therefore not possible for Lilly to run a pipelining argument. There was no EST sequence on GenBank which could have formed part of a mass screen against Swiss-Prot or any other protein sequence database. Instead, the case must be that it was obvious to sequence the Image clone and then use the derived sequence to screen Swiss-Prot. The second is that Lilly's experiments show that *if* the sequence of the Image clone had been screened against version 33 of Swiss-Prot there can be no doubt the skilled person would have recognised it to encode a fragment of a TNF protein. On this point the experts were in complete agreement. The case is therefore much more straightforward.

Questions (i) and (ii)

309. These are the same as for the Fujiwara EST.

Question (iii)

310. Taking the Image clone as the starting point, it consists of at least 40% of the entire protein coding region of the Neutrokine-α polypeptide. Hence the difference between the clone and the nucleotide of proposed claim 1 is the again the length of the sequence. As Lilly points out, claim 1 covers a molecule whether or not that molecule has been sequenced.

Question (iv)

311. Lilly submits there can be no dispute that the well plate on which the Image clone was situated was made available to the public. The clone had an identification number 450662 and was made available by being sent to Washington University free of any obligation of confidence for the purpose of sequencing it as part of the Image project. Further, from the time of its receipt, none of the activities performed on it, from sequencing to characterisation, involved any inventive step. Thereafter it was routine to derive the whole sequence and so make a polynucleotide within the scope of claim 1 as proposed to be amended.

312. In responding to this case, HGS again did not advance any argument to the effect that nothing about the clone (or its sequence) revealed its nature and hence did not place any reliance upon the decision in *Merrell Dow.* It also accepts that if it was obvious to make a sequence in the claim then the claim is invalid. However, just as it did in relation to the Fujiwara EST, it does take the point that the Image clone did not form part of the art, at least not as a separate clone, and relies for that purpose upon the decision of the decision of the EPO Board of Appeal *Biogen/Recombinant DNA*. I have discussed that decision in considering the Fujiwara EST and that discussion is equally apposite here.

313. The Image clone was one of some 9,000 sent to Washington University. It was catalogued and identified by a number. It could be sequenced and reproduced without undue difficulty. There is no suggestion that the University was under any obligation of confidence in relation to it. In my judgment it (that is to say, the clone as such) formed part of the state of the art. It would have been an interesting question whether, absent the amendment, it would have anticipated the unamended claim. But that is not a matter I have to decide.

314. My task is a different one: to consider whether the clone renders the proposed amended claim obvious. In my judgment it can only do so if it was obvious to sequence it, identify it as a nucleotide encoding a TNF like protein and then obtain a longer sequence falling within the claim. Here, it seems to me, the attack faces the same fate as that based on the Fujiwara EST. The skilled team looking for another TNF ligand would not have started with this clone rather than any other (just as he would not have started with the Fujiwara EST rather than any other of the hundreds of thousands of uncharacterised ESTs) unless given a good reason to so. But in this case Lilly faces the additional difficulty that at the priority date the Image clone had not been sequenced and so could not be subject to a pipeline search or the search commended by Dr Martin.

315. For like reasons to those given in relation to the Fujiwara EST, the obviousness case based upon the Image clone therefore fails.

Obviousness – no contribution to the art

316. I can deal with this quite shortly. The approach I must adopt is discussed in paragraphs [271] and [274].

317. In my judgment, and for the reasons I have explored in detail in considering the allegation of lack of industrial applicability, the specification contains no more than speculation about how Neutrokine-α might be useful. It does not teach the person skilled in the art how to solve any technical problem and its teaching as to the range of applications of Neutrokine-α is implausible. In short, the reader is left with a research programme to put it to use. I conclude that this allegation of obviousness succeeds.

Amendment and added matter

318. A number of objections to the proposed amendments have fallen away, but five remain.

Extension of the scope of protection

319. Lilly argues that deletion of the words "having Neutrokine-α activity" from proposed claim 10 extends the scope of protection. The argument is very simple. Before amendment the claim was limited to a process which produced a protein having Neutrokine-α activity whereas the proposed amendment removes that limitation. As a result, the amended claim would cover processes for producing proteins which do not have that elusive quality.

320. HGS responds as follows. Proposed claim 10 is ultimately dependent upon proposed claim 1 which is limited to two particular sequences which encode Neutrokine-α. Claim 1 no longer includes other homologous sequences which encode other proteins which may or may not possess the characteristics of Neutrokine-α. Moreover, proposed claim 10 is now limited (via proposed claim 9) to proteins expressed in mammalian cells. Hence those proteins will possess the characteristics of Neutrokine-α, whatever they may be.

321. I have no doubt that the expression of the polynucleotides of proposed claim 1 in mammalian cells will generally produce active proteins. Indeed I understood Professor Saklatvala to accept as much. However, the claim extends to all Neutrokine-α polypeptides, including those which may have been the subject of further processing or purification steps and, as Professor Saklatvala explained, these may be conducted under conditions such that the purified polypeptides may not retain their native structure and hence become denatured and lose their activity. Such denatured polypeptides will fall within the scope of the proposed amended claim whereas previously they would have been excluded. In my judgment the objection is therefore a good one. The proposed amendment would extend the scope of protection and is not permissible.

Deletion to select a narrower sub-class shorn of its functional language

322. Lilly says the amendment to proposed claims 1 and 10 have the effect of removing from the claims any reference to activity. They delete all the functional language and so introduce ambiguity and change the nature of the invention. I disagree. To my mind they remove the ambiguity that existed before. Claim 1(a) and (b) are and were

directed to specific Neutrokine-α sequences and contained no functional limitation. All the other claims are now dependent upon only these sequences. As a result, they are perfectly clear. Of course this does not address the fundamental deficiencies in the specification which I have addressed. But this separate objection to the amendment is misconceived.

Exacerbation of the existing objections

323. Lilly argues that if any definition of Neutrokine-α is removed from the claims it makes the objections of lack of industrial applicability worse. This is a debating point. It adds nothing by way of separate objection to the proposed amendments.

Amendments to the specification and added matter

324. Lilly points out that very few amendments are proposed by HGS to the specification despite the wholesale narrowing of the claims. Thus, for example, all the text which corresponded to the wider parts of claim 1 is to remain. It submits this is highly problematic since the amended specification as a whole would leave the reader with the impression that this wider matter has some relevance to the invention. Moreover the expression "we describe" is inserted in various places in order to attempt to address the fact that various parts are no longer claimed. That insertion leads to absurdities whereby the specification claims to describe things it simply does not.

325. I reject this objection. It adds nothing to the substantive objections to the Patent. It is entirely conventional to use the expression "we describe" to identify aspects of the description which do not (or, in this case, are no longer said) to form part of the invention and this would be well understood by the skilled person.

The proposed further amendment to claim 15

326. This is a matter I have considered in addressing the proper interpretation of the Patent in paragraphs [138]-[140] and I need say no more about it.

Conclusion

327. The Patent is invalid for lack of industrial applicability, insufficiency and obviousness. Whatever the merit of the discovery of Neutrokine-α, the specification contains no more than speculation about how it might be useful. It does not teach the person skilled in the art how to solve any technical problem and its teaching as to the range of applications of Neutrokine-α is implausible. Moreover, the claims to therapeutic and diagnostic products are insufficient in any event.

328. This was a field in which many researchers were active. The application was filed at a time when rapid advances were being made in terms of the public availability of gene sequences and how they might be searched. Not surprisingly, other teams found Neutrokine-α soon after the priority date. Perhaps anticipating this, HGS filed its application very promptly. But in doing so it failed to disclose how the protein might be used and it required a research programme to make good this deficiency. HGS secured broad protection over an unexplored technical field without providing an adequate compensating benefit to the public.

Annex A - The Patent Claims (as proposed to be amended)

1. An isolated nucleic acid molecule comprising a polynucleotide sequence encoding a Neutrokine-α polypeptide wherein said polynucleotide sequence is selected from the group consisting of:

   (a) a polynucleotide sequence encoding the full length Neutrokine-α polypeptide having the amino acid sequence of residues 1 to 285 of SEQ ID NO:2; and

   (b) a polynucleotide sequence encoding the extracellular domain of the Neutrokine-α polypeptide having the amino acid sequence of residues 73 to 285 of SEQ ID NO:2;

2. A nucleic acid molecule of claim 1, wherein the amino acid sequence of said full-length Neutrokine-α polypeptide is the one encoded by the cDNA clone contained in ATCC Deposit No. 97768.

3. A nucleic acid molecule of claim 1, wherein the amino acid sequence of said extracellular domain of the Neutrokine-α polypeptide is the one encoded by the cDNA clone contained in ATCC Deposit No. 97768.

4. The nucleic acid molecule of any one of claims 1 to 3 which is DNA or RNA.

5. A method of making a recombinant vector comprising inserting the nucleic acid molecule of any one of claims 1 to 4 into a vector.

6. A recombinant vector containing the nucleic acid molecule of any one of claims 1 to 4

7. The vector of claim 6 in which the nucleic acid molecule is operatively linked to an expression control sequence allowing expression of said polynucleotide in prokaryotic or eukaryotic host cells wherein the expression control sequence is a promoter.

8. A method of making a recombinant host cell comprising introducing the vector of claim 6 or 7 into a host cell.

9. A mammalian host cell genetically engineered with the nucleic acid molecule of any one of claims 1 to 4

10. A process for producing a Neutrokine-α polypeptide comprising: culturing the host cell of claim 9 and recovering the Neutrokine-α polypeptide encoded by said nucleic acid molecule.

Deleted: (c) a polynucleotide sequence encoding the amino acid sequence of residues n to 285 of SEQ ID N02, where n is an integer in the range of 2-190, 1 to m of SEO ID N02, where m is an integer in the range of 274-284, or n to m of SEQ [D N02, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284, wherein the polynucleotide sequence encodes a polypeptide having Neutrokine-α activity;¶
¶

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Deleted: (d) a polynucleotide sequence that is at least 90% identical to a polynucleotide sequence defined in (a) or (b) and which encodes a polypeptide having Neutrokine-α activity;¶
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Deleted: (e) a polynucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 90% identical to the amino acid sequence defined in (a), (b) or (c), wherein said polypeptide has Neutrokin ... [1]

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11. A isolated Neutrokine-α polypeptide having the amino acid sequence encoded by a nucleic acid molecule of any one of claims 1 to 4 or obtainable by the process of claim 10.

12. The Neutrokine-α polypeptide of claim 11 which is proteolytically cleaved from the host cell of claim 9.

13. The polypeptide of claim 11 or 12 which is labeled.

14. The polypeptide of claim 13 which is radiolabeled.

15. An isolated antibody or portion thereof that binds specifically to the Neutrokine-α portion of a Neutrokine-α polypeptide having the amino acid sequence encoded by the nucleic acid molecule of any one of claim 1 or the Neutrokine-α portion of a Neutrokine-α polypeptide of claim 11 or 12.

16. The antibody or portion thereof of claim 15 which is selected from the group consisting of:

(a) a monoclonal antibody;
(b) a polyclonal antibody;
(c) a chimeric antibody;
(d) a Fab fragment; and
(e) an $F(ab')_2$ fragment.

17. The antibody or portion thereof of any one of claims 15 to 16 which is labeled.

18. The antibody or portion thereof of claim 17 which is labeled with a label selected from the group consisting of:

(a) an enzyme label;
(b) a radioisotope;
(c) a fluorescent label; and
(d) biotin.

19. The antibody or portion thereof of claim 18 wherein the label is a radioisotope selected from the group consisting of:

(a) ^{125}1;
(b) ^{121}1;
(c) ^{131}1;
(d) ^{112}1n; and
(e) ^{99M}Tc.

20. A pharmaceutical composition comprising the nucleic acid molecule of any one of claims 1 to 4, the polypeptide of any one of claims 11 to 14, or the antibody or portion thereof of any one of claims 15 to 19 and optionally, a pharmaceutically acceptable carrier.

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¶
(a) ^{131}1; ¶
(b) ^{125}1; ¶
(c) ^{121}1; ¶
(d) ^{112}1n; and ¶
(e) ^{99M}Tc.¶
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21. A diagnostic composition comprising the nucleic acid molecule of any one of claims 1 to 4, the polypeptide of any one of claims 11 to 14, or the antibody or portion thereof of any one of claims 20 to 25.

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(e) a polynucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 90% identical to the amino acid sequence defined in (a), (b) or (c), wherein said polypeptide has Neutrokine-α activity; and

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(f) a polynucleotide sequence that is the complement of the full length sequence of a polynucleotide sequence defined in (a) through (e).

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4. The nucleic acid molecule of claim 1, wherein the Neutrokine-α activity is modulation of iymphocyte proliferation, differentiation, or survival.

5. The nucleic acid molecule of claim 1 comprising a polynucleotide sequence encoding a polypeptide that is at least 95% identical to a polypeptide comprising amino acid residues 134 to 285 of SEQ ID N02.

6. The nucleic acid molecule of claim 5 comprising a polynucleotide sequence encoding amino acid residues 134 to 285 of SEQ ID N02.

7. The nucleic acid molecule of claim 5 which consists of a polynucleotide sequence encoding amino acid residues 134 to 285 of SEO]D N02.