Neutral Citation Number: [2012] EWHC 657 (Pat)

Case No: HC 11 C00127
HC11 C00131

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL
Date: 22/03/2012

Before :

THE HON MR JUSTICE FLOYD

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Between :

REGENERON PHARMACUETICALS INC	**Claimant in HC 11 C00127**
BAYER PHARMA AG	**Claimant in HC 11 C00131**
- and -	
GENENTECH INC	**Defendant**

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- -

Andrew Waugh QC and **Thomas Mitcheson** (instructed by **Simmons & Simmons LLP**) for the **Claimant in HC 11 C00131**
Richard Meade QC and **Mark Chacksfield** (instructed by **Bird & Bird LLP**) for the **Claimant in HC 11 C00127**
Michael Tappin QC and **Isabel Jamal** (instructed by **Marks & Clerk Solicitors**) for the **Defendant**

Hearing dates: 13th, 16th-19th, 24th and 25th January 2012

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Judgment

Mr Justice Floyd :

1. In two separate actions Regeneron Pharmaceuticals Inc and Bayer Pharma AG ("Regeneron" and "Bayer" respectively) have applied for revocation of European Patent (UK) No 1 238 986 ("the patent"), which belongs to Genentech Inc. Regeneron are planning to market a product called VEGF Trap Eye ("VTE") for the treatment of age-related macular degeneration of the eye. Bayer are licensees of Regeneron in respect of this product. Regeneron and Bayer also seek a declaration of non-infringement of the patent in respect of VTE. Genentech counterclaimed,

positively alleging that VTE is an infringement. Regeneron and Bayer were represented by separate teams of leading and junior counsel and solicitors, Mr Waugh QC appeared for Bayer, with Mr Thomas Mitcheson; Mr Meade QC appeared for Regeneron with Mr Chacksfield. Bayer and Regeneron presented the same case, through Mr Waugh, although Mr Meade cross-examined one of the experts. Mr Tappin QC and Ms Jamal presented the case for Genentech. Genentech, although nominally defendant, opened the case and called its evidence first.

2. The patent is concerned with therapeutic agents for the treatment of a range of diseases by preventing the growth of blood vessels ("angiogenesis") which is associated with them. In particular it is concerned with agents which inhibit the action of VEGF (vascular endothelial growth factor). The claims are limited to non-neoplastic, that is to say non-cancerous, diseases.

3. The validity of the patent is attacked on the grounds of lack of novelty and lack of inventive step over a single prior art citation, and insufficiency of description.

Technical background

Blood vessels and angiogenesis

4. Blood vessels comprise two main cellular components: the endothelium and the mural cells. The endothelium is a continuous, cylindrical layer of cells, called endothelial cells, which interface with blood in the vessel.

5. Vasculogenesis is the formation of blood vessels from scratch. Vasculogenesis primarily occurs during embryonic development of the circulatory system. Angiogenesis, or neo-vascularisation, on the other hand is the process of new blood vessel growth by endothelial cell proliferation and outgrowth from pre-existing vessels. In a number of normal physiological processes, such as wound healing and during the female reproductive cycle, new blood vessels are required to supply oxygen and nutrients to developing tissues. In these processes new blood vessels are produced by angiogenesis from the existing vasculature. Excessive angiogenesis, on the other hand, is a contributing factor to the pathology of a number of diseases, including cancer. In cancer, tumour cells cause new blood vessels to be produced by angiogenesis in order to supply nutrients and oxygen to the tumour, enabling it to survive and grow. These new blood vessels also enable tumour cells to escape into the bloodstream and spread to other areas of the body in a process known as metastasis. In diseases such as diabetic retinopathy and neovascular age-related macular degeneration, new blood vessels directly disrupt or interfere with the structure or normal function of other tissues.

Neoplastic and non-neoplastic diseases

6. A neoplasm, which is also known as a tumour, is an aberrant new growth of abnormal cells or tissues, in which cell growth is not under normal physiological control. Thus neoplastic diseases are those that involve tumour growth, whilst non-neoplastic diseases are all those which do not.

Antigens, antibodies, and receptors

7. Antibodies are molecules which are generated by the immune system to assist in neutralizing or destroying foreign material (such as bacteria and viruses). When foreign material enters the body, the proteins on its surface are recognized as foreign by the immune system, which then operates to destroy, remove or neutralize the foreign material, in part through the use of antibodies. Antibodies aid the immune response by blocking some adverse activity of the foreign molecule or by recruiting other components of the immune system to destroy or remove the material to which they are bound.

8. Each foreign molecule (known as an antigen) will usually have a number of sites on its surface that antibodies can bind to. Each binding site will have a unique structure and an antibody must have a complementary structure in order to bind to it. The immune system is capable of naturally engineering antibodies to have the necessary structure to bind foreign antigens.

9. Because of their ability to recognize specific antigen binding sites, antibodies are important in cell biology research, and in therapy. It is possible to block interactions using antibodies which recognize a binding site which is within, or adjacent to, the region of the antigen which is responsible for receptor binding. By binding in this region, the antibody obstructs normal or unwanted interactions between the antigen and its receptor.

10. A receptor is a site or structure which binds a signal molecule (a ligand). Cell-surface receptors are located in or on the plasma membrane with their ligand-binding site exposed on the outside of the cell. Intracellular receptors bind ligands that diffuse into the cell across the plasma membrane. Soluble receptors are receptors that are not cell-associated and that bind to a particular ligand without stimulating a cellular response. Soluble receptors can be used to antagonize a ligand's effect by reducing the amount of free ligand available to bind to efficacious receptors.

11. One common type of cell-surface receptor is the receptor tyrosine kinase family (RTK). RTKs generally comprise three basic elements: an extracellular domain (ECD) which is responsible for ligand binding, a transmembrane domain which anchors the receptor in the cell membrane, and an intracellular domain. The figure below shows a tyrosine kinase receptor spanning a cell wall.

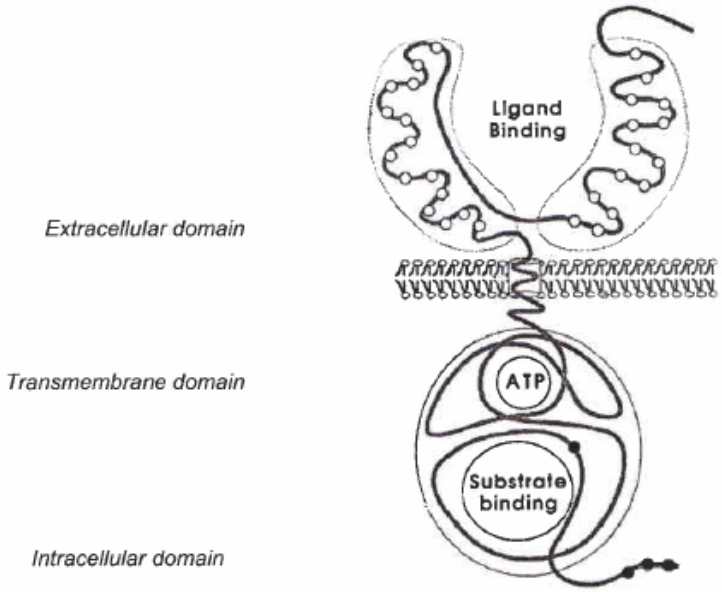


Figure 1. Diagram showing the general structure of a tyrosine kinase receptor. Adapted from "Growth factor receptor tyrosine kinases" (Yarden et al. *Ann Rev Biochem*, 1988, ref. 12

12. A number of growth factor receptors belong to the RTK family, including the receptors for the growth factors EGF, bFGF, PD-ECGF and VEGF (see below).

Angiogenesis and cancer assays

13. The chick chorioallantoic membrane assay (CAM) is a model for studying the angiogenic or anti-angiogenic properties of a compound. The membrane is found underneath the external shell of chick eggs. In a typical CAM assay, fertilized chick eggs are incubated at 37^{o}C for 3 to 4 days. The egg shell is then partially removed to produce a window in which the assay may be performed. To assess the angiogenic or anti-angiogenic activity of a particular substance, the compound is contacted locally with the CAM, usually by its incorporation into a slow release polymer pellet or absorption into a porous disc or sponge which is then implanted onto the CAM. The angiogenic or anti-angiogenic effects of the compound may be assessed by examination of the vasculature around the delivery vehicle following incubation for a further 3-4 days. The newly formed blood vessels appear in a radial pattern around the implant.

14. Miles' permeability assay is an assay for measuring the leakiness of blood vessels. Blue dye with a very high affinity for serum albumin, the most abundant protein in blood plasma, is injected into a test animal's veins. The dye leads to vivid and long-lasting staining of the blood serum. Following the injection, test substances are injected intradermally into shaved regions on the back or flank of the animal. Increased vascular permeability leads to an increase in extravasation of the dye, which can be visually observed as a blue patch around the injection site.

15. Neither the CAM assay nor Miles' permeability assay can be used to determine whether a factor is necessary for *pathological* angiogenesis. By contrast, the mouse

> xenograft test is a widely used in vivo model for determining the anti-cancer properties of test compounds. The assay involves implantation of tumour cells into mice with subsequent measurement of the resulting tumor. The anti-cancer effects of test compounds are determined by comparing the size of tumours, with or without treatment, at fixed time points following implantation. Use of "nude" mice allows human cancers to be examined in the mouse model. Nude mice have a genetic mutation which prevents the mouse from mounting an immune rejection response. Human tumour cells can therefore be grown in these mice without being recognized as foreign and thus without being attacked by the mouse's immune system.

Rheumatoid arthritis

16. Rheumatoid arthritis (RA) is a disease of the joints. RA involves the formation of pannus in the joint. Pannus is highly inflamed tissue which is infiltrated by cells from the bloodstream, and invading cartilage, bone and possibly tendon. It is also characterised by an abundance of blood vessels.

The patent

17. The patent is entitled “Use of vascular endothelial cell growth factor antagonists”. It has a filing date of 28th October 1992, and does not claim any earlier convention priority.

18. In the section headed “Background to the Invention”, the patent explains that endothelial cells are an important component for the development of new blood vessels and capillaries. These cells proliferate during angiogenesis or neovascularisation associated with tumour growth and metastasis and a variety of non-neoplastic diseases or disorders. A list is given which comprises RA, psoriasis, atherosclerosis, diabetic retinopathy, retrolental fibroplasia, neovascular glaucoma, hemangiomas, immune rejection of transplanted corneal tissue and other tissues, and chronic inflammation.

19. It is explained that a number of molecules have been reported to induce proliferation of endothelial cells, amongst which are fibroblast growth factors (FGF); platelet-derived endothelial cell growth factor (PD-ECGF); and vascular endothelial growth factor (VEGF). The patent then goes on to give more information about what was known of VEGF, including its identification in and isolation from human cells. The background section concludes:

> > “In view of the role of vascular endothelial cell growth and angiogenesis, and the role of those processes in many diseases and disorders, it is desirable to have a means of reducing or inhibiting one or more of the biological effects of VEGF. It is also desirable to have a means of assaying for the presence of VEGF in normal and pathological conditions, and especially cancer.”

20. The invention is summarised at [0010] in the following terms:

> > “The present invention as defined in the claims provides the use of antagonists of VEGF, including (a) antibodies and variants

> thereof which are capable of specifically binding to hVEGF or hVEGF receptor and (b) hVEGF receptor and variants thereof in the manufacture of a medicament for the treatment of non-neoplastic diseases or disorders characterized by undesirable excessive neovascularization, including by way of example rheumatoid arthritis, psoriasis, atherosclerosis, diabetic and other retinopathies, retrolental fibroplasia, neovascular glaucoma, hemangiomas, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, and chronic inflammation."

21. The specification describes the antagonists of human VEGF (hVEGF) with which it is concerned at [0016] in the following way:

> "The present invention provides antagonists of hVEGF which are capable of inhibiting one or more of the biological activities of hVEGF, for example, its mitogenic or angiogenic activity. Antagonists of hVEGF act by interfering with the binding of hVEGF to a cellular receptor. Included within the scope of the invention are antibodies, and preferably monoclonal antibodies, or fragments thereof, that bind to hVEGF or hVEGF receptor. Also included within the scope of the invention are hVEGF receptor and fragments and amino acid sequence variants thereof which are capable of binding hVEGF."

22. There follows a description of two known receptors named flt-1 and flk-1. At [0020] the specification explains that variants are included, that the receptor may include only the extra-cellular domain of the receptor, or may be a fusion protein or complex.

23. At [0035] to [0036] the specification gives more detail on the subject of antibodies:

> "The antibodies included within the scope of the invention include variant antibodies, such as chimeric (including "humanized") antibodies and hybrid antibodies comprising immunoglobulin chains capable of binding hVEGF or hVEGFr, and a non-hVEGF epitope.
>
> The antibodies herein include all species of origin, and immunoglobulin classes (e.g., IgA, IgD, IgE, IgG, and IgM) and subclasses, as well as antibody fragments (e.g., Fab, $F(ab')_2$ and Fv), so long as they are capable of binding hVEGF or hVEGFr. and are capable of antagonizing a biological activity of hVEGF."

24. In terms of therapeutic utility the important examples are Examples 4-6. Example 4 is described as being by way of background. This is because it relates to inhibition of tumour growth, which is outside the scope of the claims (which are to non-neoplastic indications only).

25. In Example 4, three different tumour cell lines were examined in a mouse xenograft test. These cells were injected into nude mice and after tumour nodules formed, the

anti-VEGF antibody or controls were administered. The anti-VEGF antibody caused a significant decrease in the rate of tumour growth in one of the cell lines and the size and weight of the tumours at the end of the 5 week experiment were substantially lower in mice treated with the antibody when compared to the negative controls. The results also show a dose-dependent response. Tumour weights from the other two cell lines were also significantly lower in the antibody treated mice compared to the negative controls, and also showed a dose-dependent response. The antibody is identified as A4.6.1. This antibody is described in the prior art relied on in this action, Kim 1992.

26. Example 5 shows that cells from two of the tumour cell lines in culture exposed to a range of VEGF antibody concentrations grew similarly to those exposed to negative controls. This experiment demonstrates that antibody A4.6.1 is not cytotoxic, i.e. that it does not kill cells.

27. Example 6 shows the effect of the VEGF antagonist antibody on endothelial cell chemotaxis induced by synovial fluid from RA patients. Cell chemotaxis is the process by which cells direct their movements according to chemicals in their environment. Synovial fluid of the RA patients contained an activity which caused endothelial cells to migrate - which is required as part of the angiogenic process. This chemotactic activity was significantly and reproducibly inhibited by the A4.6.1 antibody. By contrast, it had little effect on the (lesser) chemotaxis induced by synovial fluid from patients with osteoarthritis (in which angiogenesis does not occur).

The claims

28. Genentech rely on claims 1 and 14. It is sufficient if I set out claim 1 below:

> "Use of a hVEGF antagonist in the preparation of a medicament for the treatment of a non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation, wherein the hVEGF antagonist is:
>
> (a) an anti-VEGF antibody or antibody fragment;
>
> (b) an anti-VEGF receptor antibody or antibody fragment; or
>
> (c) an isolated hVEGF receptor."

The skilled addressee

29. The patent is addressed to a team concerned with the development of a therapeutic agent for use in the treatment of non-neoplastic neovascular conditions. The team would include a vascular biologist and a molecular biologist.

30. There was some rather half-hearted discussion of the extent of involvement of a clinician in the skilled team. Neither principal expert witness had suggested that there would inevitably be such a person on the skilled team. But there was no dispute that vascular and molecular biologists worked closely with clinicians and therefore had a

good knowledge of how blood vessels operate in a range of disease states characterised by excessive angiogenesis.

The witnesses

Professor Shima

31. Genentech called Professor David Shima. Professor Shima is the Professor of Translational Vision Research at University College London Institute of Opthalmology. At the filing date in 1992 he was engaged in research for his PhD at Harvard University in the laboratories of Judah Folkman and Patricia D'Amore. His research was on the identification of VEGF as an oxygen-regulated mediator of ocular angiogenesis. Thereafter he worked at the Imperial Cancer Research Fund, becoming head of their Endothelial Cell Biology Laboratory in 1999. He is a vascular biologist.

32. Mr Waugh took a number of points about the weight I should give to Professor Shima's evidence. He submitted that his own witness, Professor Harris, was in a better position to assess the outlook and attitude of the skilled team involved in angiogenesis research. He submitted that Professor Harris' views were more in accordance with the contemporaneous review articles than those of Professor Shima. That is a matter to which I shall have to return in its proper context. As will be seen, I have reservations about the evidence of Professor Harris. Moreover Professor Shima's position at the priority date in the laboratories of Judah Folkman, in which there was extensive discussion of all the research at seminars, means that he was well placed to assist the court on the prevailing thinking. That does not mean that I should invariably prefer Professor Shima's evidence. I will have to take into account the reasoning of both experts and their overall expertise.

33. Mr Waugh also made other points about Professor Shima's evidence, in particular his reluctance to agree that specificity of a growth factor was a desirable property in the search for a factor to target in a therapeutic context. For reasons which will become apparent, I do not think that this reluctance was based on anything other than his own genuinely held views.

34. For my part I found Professor Shima to be a helpful and knowledgeable witness. I accept that he had a tendency to answer questions about whether it was possible to make a reasonable scientific prediction by reference to whether the prediction was "plausible", rather than by reference to the terms in which the question was asked. This may, as Mr Waugh suggested, have come from over-exposure to lawyers. I will have to form my own view based on his answers and those of the other witnesses where questions of reasonable prediction are at issue.

Dr Paleolog

35. Following the first exchange of expert reports, Genentech served a report from Dr Ewa Paleolog, concerned mainly with the conclusions to be drawn from the data in the patent about the use of the disclosed agents for the treatment of RA. Dr Paleolog is Reader and Director of Post Graduate Studies at the Kennedy Institute of Rheumatology. At the filing date she was a post-doctoral researcher at that Institute. She specialises in the study of the vascular endothelial lining of blood vessels in the pathogenesis of RA.

36. Mr Waugh criticised her evidence about two scientific papers, Luttun and De Bandt. In her cross-examination she suggested that the conclusions drawn in these papers were seriously flawed. On the other hand, for some purposes she had relied on those papers. I think it was unfortunate that Dr Paleolog had not pointed out her reservations about Luttun and De Bandt earlier, not least because it took the claimants by surprise. However, I cannot accept that this omission, which I am sure was not deliberate, affected her evidence as a whole. I will of course have to consider the significance of the Luttun and De Bandt work in due course, in the context of the issue to which it relates.

Professor Harris

37. The claimants called Professor Adrian Harris, who is Professor of Medical Oncology at the University of Oxford. He is also leader of the Growth Factor Group at the Weatherall Institute for Molecular Medicine, which he set up in the late 1980s. At the filing date he was Professor of Clinical Oncology at Oxford. He came across as a man of outstanding intellect, with enormous breadth and depth of knowledge of his subject. His enthusiasm for the subject was plain for anyone to see.

38. Mr Tappin launched a courteous but sustained attack on the evidence of Professor Harris. He submitted that Professor Harris was allowing his view of the state of the art at the priority date to be infected with hindsight. His evidence, he submitted, was inconsistent with Professor Harris' writings at the time. He also submitted that Professor Harris was prone to inaccuracy and exaggeration in his evidence. This is important to Genentech's case because they invite me to reject large parts of Professor Harris' opinion evidence in relation to both obviousness and insufficiency. I therefore propose to deal with these criticisms at this stage, although the reader may find this section of my judgment easier to digest when the later parts of it have been read.

39. I formed the view when listening to Professor Harris that he was allowing his obvious enthusiasm for the subject to transfer to enthusiasm, in some cases misplaced, for the case which he was presenting. I am sure this was not deliberate, but that this was happening was clear to me from a number of incidents. Whilst some of these are quite unimportant on their own, collectively they give me serious concern about accepting his evidence as a whole. I explain this in more detail below by reference to some examples.

40. Crew *et al*. is an article published in 1997, of which Professor Harris was one of the authors. It contains the statement that "*Antineoplastic strategies directed against VEGF can reduce tumor growth and systemic spread in solid tumors*" citing Kim's 1992 paper, together with another paper as support. In cross-examination Professor Shima said that this was "definitely a miscitation" of Kim 1992. Mr Waugh remarked that Professor Harris would explain that it was not. Evidence in chief was not called from Professor Harris. Under cross-examination on this point, Professor Harris gave a very long explanation about citations which had little relevance. He then accepted that Kim 1992 did not establish the proposition in the text, but continued to justify the reference on the basis that Kim 1992 disclosed a potentially very useful therapeutic agent, namely the antibody. That is entirely different to the case put to Professor Shima, does not explain the relationship between the text and the citation, and was accordingly unconvincing.

41. At another point in his cross-examination Professor Harris was being asked about a time-line in a paper in Nature Reviews by Gschwind. The paper identifies each scientific "breakthrough" in a box in a timeline spanning pages 362-363 of the article. The time-line covers the period 1952 to 2004. Gschwind identified the Kim *1993* paper as one of the breakthrough discoveries in the field. The box reads "*Anti-VEGF antibodies are shown to reduce the growth of cancer cells in nude mice*". Professor Harris disagreed with the description of Kim 1993 as a breakthrough, saying that Kim 1992 had "placed all the ducks in the row". I asked Professor Harris what he would have put in the box for Kim 1992, had this been identified as the breakthrough. His answer was:

> "Anti-VEGF antibodies are effective systemically in mice because they were able to block VEGF [when] administered subcutaneously in high amounts. So anti-VEGF administered systemically are effective in mice"

42. When Professor Harris was subsequently shown the data and assays in Kim 1992 he had to accept that he was wrong about the antibodies being administered systemically. Systemic administration was something which Professor Harris regarded as important, as a previous answer of his had shown. I think this illustrates that Professor Harris was trying to read more into the prior art than was there, and that he was influenced by hindsight to regard Kim 1992 as more important than it actually was. Mr Waugh said that it was hard for the witness to be put on the spot in this way. I do not agree. Kim 1992 was the main, and by then the only, citation in the case.

43. In his second report Professor Harris sought to support his views by extracts from his 1992 review without explaining the context, namely in the case of one that it depended in part on his own unpublished work, and in the case of the other that it was concerned with low molecular weight peptide inhibitors.

44. In the same report Professor Harris also sought to confirm his views by reference to a Genentech memorandum, disclosed in the course of the action, which related to a meeting at which the researchers were deciding on the further course of their work. He deployed it, amongst other things, to show that the researchers regarded the next step from Kim 1992 as performing tests in animal models. He said it confirmed the views which he had expressed in his first report. However, as his cross-examination showed, Genentech already had the animal model results of Kim 1993 at the date of the meeting. To misinterpret the document is an entirely forgivable mistake, and is not the point. What I found worrying is that Professor Harris was not prepared to accept that he had made a mistake and continued to assert that the document supported his case. He tried to assert that he was deploying the document to show that researchers would carry on testing in other species. That was not seriously in issue; it was not a view which he had expressed in his first report which he could realistically be seeking to confirm in his second; and it was not the purpose for which he deployed the report originally. His evidence in cross-examination was a change of position once he had appreciated his error.

45. Professor Harris significantly increased the confidence with which he expressed his views between his expert report and his cross-examination, sometimes to the point where his views became so extreme as to be unsupportable. Thus, for example, in his expert report he said that, VEGF was the most promising candidate, but one could not

prove that it had a causal role in any angiogenic disease. By contrast, in his cross-examination he said that "We just knew that VEGF was going to be the target", and "from Kim '92 we already knew this would be an effective thing to use", and see the following:

> Q. You would not be able to deduce from the known properties of VEGF that it would have a significant role in pathological angiogenesis.
>
> A. Yes, you would be able to deduce from all these properties listed here that it would be the best candidate to look at. That is why I personally, and many others, switched to have a look at it.
>
> Q. I am not sure you are answering quite the same question. I am not asking whether you would have thought it was the best candidate to look at. I am asking you whether you would be able to deduce from the properties that it would have a significant role in pathological ----
>
> A. I am saying it would.

46. Professor Harris had not even attempted to make such a deduction in his expert report, nor do I know, even now, how such a deduction could be made. There is a world of difference between a good or even the best candidate to look at, and being able to prove or deduce its role in pathological angiogenesis.

47. I have therefore reluctantly come to the conclusion that I must regard with considerable caution some of the more extreme statements made by Professor Harris in the witness box.

Professor Plate

48. The claimants also called factual evidence from Professor Karlheinz Plate who is currently a Professor and Director at the Edinger Institute at Goethe University, Frankfurt. At the filing date he was conducting post-doctoral research on the molecular mechanisms of tumour angiogenesis mediated by VEGF, in the laboratory of Professor Werner Risau at the Max-Planck Institute in Munich. Professor Risau was one of the youngest ever heads of a Max-Planck Institute, which is in turn the most prestigious position in German science. Professor Risau's death from cancer at the very early age of 44 was regarded as having robbed the world of a great scientist. Mr Tappin made no criticism of Professor Plate as a witness of fact, beyond drawing attention to the very high and atypical level of skill which he possessed and which was possessed by those to whose work he was exposed.

Issues of construction

49. There was no dispute as to the proper approach to construction. In *Kirin Amgen v TKT* [2005] RPC 9 the House of Lords explained that the determination of the extent of protection only involves asking what a person skilled in the art would have understood the patentee to have used the language of the claim to mean. Guidelines

to assist the court in construing the patent are summarised by the Court of Appeal in *Virgin Atlantic v Premium Aircraft* [2010] FSR 10 at paragraph 5. I have had regard to those principles here.

"*Use … for the treatment of a non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation"*

50. Two specific points can be dealt with at the outset. First, the neo-vascularisation must be undesired. There was a point made about the patent's reference at [0010] and in claim 2 to "corneal and other tissue transplantation". Professor Harris accepted that in corneal transplantation one would not want new blood vessel growth, but explained that in other forms of transplantation new blood vessel growth was an important aspect of repair, which one would not want to block. Professor Shima explained that there were other (i.e. non-corneal) ocular tissues which could be transplanted but where new blood vessel growth would be undesirable. Thus there is no difficulty in understanding that the patent only extends to those transplant situations where new blood vessel growth is not desired.

51. Secondly, a point was made that there was uncertainty over whether pre-eclampsia was a disease covered by the claims. Pre-eclampsia is mentioned at [0072] as a non-neoplastic disease that was amenable to treatment. However it is not one of those diseases listed in [0010] as being characterised by excessive undesirable neo-vascularisation, and there is no evidence that it is such a disease. I do not think that the reference to pre-eclampsia gives rise to any difficulty about the meaning to be given to the claim. It is not a disease characterised by excessive undesired neo-vascularisation, and the skilled person would so understand.

52. As to the more general question as to the identification of diseases, Genentech contends that the claim would be understood by the skilled reader to refer to a disease or disorder in which new blood vessel growth contributes directly or indirectly to the pathology of the condition. Accordingly they submit that the claim is directed to reducing the undesired angiogenesis in that diseased state. The claimants contend that the phrase under consideration means any disease in which excessive neo-vascularisation is known to be associated with the diseased state, whether that neo-vascularisation is causative of the pathology, or caused by it, and whether it is VEGF mediated or not.

53. In my judgment the skilled person would understand that the diseases in question were those characterised by excessive undesired angiogenesis. That is the question which has to be answered for the purposes of infringement. I see no reason to recast the definition either as sought by Genentech or by the claimants. There was no evidence that anyone skilled in the art would have any difficulty in identifying a disease which is characterised by undesirable, excessive angiogenesis and one which is not. Further, the skilled person would not understand that the patentee was saying that the treatment would necessarily successfully deal with anything other than undesired angiogenesis in that disease. Thus, for example, the skilled person would not understand that the treatment would necessarily deal with other aspects of the disease state which were independent of angiogenesis.

"an isolated hVEGF receptor"

54. The interpretation of this phrase underlies the major issue on infringement. One starts by putting to one side a linguistic point based on the fact that paragraphs (a) and (b) of claim 1 specifically include "fragments" but that paragraph (c) does not. Construed in isolation this might provide the basis for an argument that the patentee was staking his claim to complete receptors and nothing less. Such a construction is however impossible to maintain in the light of paragraph [0020] referred to above, which plainly shows that something less than an entire receptor will do. Faced with this problem, the claimants contend that, if the claim is to be understood to include fragments of receptors, it should only include fragments which contain the whole of the ECD. Nothing less will do. They submit that this would be consistent with the exemplification of the invention. They submit that the skilled reader, who is deemed to know something about patent law, would think that such a limitation would represent the furthest that the patentee was prepared to go without rendering the patent invalid for insufficiency.

55. Genentech submit that the term includes fragments and variants of the naturally occurring receptors which retain the ability to bind hVEGF and inhibit its biological activity. This they submit is in accordance with the teaching of the specification, the purpose of the invention and the language of the claim.

56. I have no hesitation in preferring Genentech's submissions on this point. Once it is accepted that the claim is not excluding fragments as a matter of language, I see no technical reason why the claim should be read as limited to any particular size of fragment provided that the fragment retains the essential ability to bind hVEGF and inhibit its biological activity. I do not think that the skilled person would have a perception that anything less than the complete ECD would lead to insufficiency. On the contrary, he or she would be surprised if the patentee had intended to leave the field open to anyone who could eliminate unnecessary domains, whilst still making use of the invention. Whether in fact the claim so construed is insufficient is a matter which I will have to return to under that head.

The common general knowledge

The work of Dr Judah Folkman

57. The field of angiogenesis was pioneered in the early 1970s by Dr Judah Folkman, working at the Children's Hospital, Boston. Dr Folkman first developed the theory that tumours must necessarily elicit angiogenesis in order to provide oxygen and nutrients to their rapidly multiplying cells. The corollary was that antagonists to angiogenesis could be used as a form of therapy. Dr Folkman is commonly regarded as the "father of angiogenesis".

58. In his landmark paper in 1971, Dr Folkman demonstrated that a diffusible factor or factors, which he referred to generally as tumour angiogenic factor or TAF, could be isolated from tumours and was capable of eliciting growth of blood vessels (and accompanying endothelial cells) in rat skins. He suggested that blockade of this factor might arrest the growth of tumours at a very small size. He later coined the term "anti-angiogenesis" to describe the therapeutic approach which involved blocking the activity of angiogenic factors.

59. Dr Folkman's research through the 1970s also suggested a connection between angiogenesis associated with tumours and other neo-vascularisation, such as that which occurs in the cornea and iris, and in psoriasis. Accordingly he suggested that anti-angiogenesis could be a possible therapeutic approach. By the filing date it was generally accepted that all neovascular diseases were linked by the common thread of angiogenesis.

60. Folkman's work led many teams of researchers to seek to identify angiogenic and anti-angiogenic factors in the hope of discovering an agent capable of modulating neovascular disease.

Angiogenesis research

61. A large number of angiogenic growth factors had been shown to have activity in one or more assays by the filing date. These included: FGF, VEGF, PD-ECGF, EGF, TGF-β, TNF-α, angiogenin and angiotropin.

62. By the priority date it was generally known that VEGF was produced by a number of cancer cell lines; was associated with blood vessel growth; was a secreted growth factor; was selective for endothelial cells; and had vascular permeability enhancing activity. It was also known that a receptor for VEGF, known as flt-1, had been identified.

63. The development of the field of angiogenesis research up to the priority date can be traced through a number of review papers, recognising of course that such reviews are necessarily somewhat out of date by the time they were published. The skilled person would of course read such reviews, as part of keeping up to date in the field. No one suggested that such reviews were not part of the common general knowledge.

64. Klagsbrun & D'Amore 1991 was a comprehensive review of regulators of angiogenesis by researchers at the Boston Children's' Hospital. The Boston Children's Hospital was an acknowledged centre of expertise in the field. The first family of factors considered is fibroblast growth factors (bFGF and aFGF). The authors state that it is not clear how these factors mediate angiogenesis in vivo. VEGF/VPF is next considered. VPF stands for vascular permeability factor. The authors recognise the connection between VEGF and VPF, but add "*The relationship between stimulating endothelial cell proliferation, angiogenesis, and vascular permeabilty is not understood at present.*" PD-ECDF, EGF, angiogenin and angiotropin, TGF-β and TNF-α are also mentioned. Their properties are summarised in a table from which it is clear that, of the properties dealt with, VEGF/VPF is the only one with a positive mark against each property. The authors' summary does not, however, volunteer any preference:

> "In summary there appear to be many stimulators of angiogenesis. Their properties, in particular the ability to stimulate endothelial cell migration and proliferation, their specificity, and their ability to be secreted are summarized in Table 1. The effects of angiogenesis factors on endothelial cells in culture vary dramatically. FGF, VEGF/VPF, PD-ECGF and TGF-α, are examples of angiogenesis factors that directly stimulate endothelial cell migration and proliferation.

> Angiotropin stimulates migration, but not proliferation. Angiogenin seems to have no effect on endothelial cell migration and proliferation. TGF-ß and TNF-α are inhibitors of endothelial cell proliferation, but they can induce 3-dimensional tube formation and angiogenesis. Angiogenesis factors differ in target cell specificity. VEGF, PD-ECGF, and angiotropin are the only angiogenesis factors that appear to be specific for endothelial cells. Finally, with the exception of FGF and PD-ECGF, most of the angiogenesis factors are secreted, which suggests paracrine[1] functions. FGF and PD-ECGF may be released by cell lysis. Thus it is clear from the different properties of these various factors that angiogenesis can be induced by different mechanisms, most or which have yet to be elucidated. Some factors influence angiogenesis by stimulating migration and proliferation, while others appear to be more active in the differentiation pathway. Some angiogenesis factors probably work directly on endothelium, while others most likely work indirectly by activating a secondary cell to produce angiogenesis factors. The large number of angiogenesis factors suggests redundancy in the vascularization process. The process of angiogenesis is sufficiently important so that tissues do not rely on one angiogenesis factor alone. The redundancy of angiogenesis factors, however, might make anti-angiogenesis therapy difficult. It will be of interest to see if the various angiogenesis factors act synergistically and are differentially regulated."

65. Redundancy is a phenomenon that featured in the evidence. It arises from the fact that with any biological process there may be several factors at work, no single one of which is responsible on its own for the process. I accept Professor Harris' evidence about the reason for the authors' statement that angiogenesis therapy was likely to be difficult:

> Q. What they say in here, is it not, is that anti-angiogenic therapy is likely to be difficult?
>
> A. Correct.
>
> Q. The reason for that is that unless one can find a factor which is necessary for the pathological angiogenesis, inhibiting that factor is not going to produce a therapeutic effect.
>
> A. Correct.

66. The authors also have sections on inhibitors of angiogenesis and endothelial cell inhibitors. Under their heading "Summary and future directions" the authors say this:

> "The field of angiogenesis has seen dramatic progress over the last two decades since Folkman first pointed out the importance

[1] release into surrounding tissue

> of this process to tumor vascularization. Initially it seemed that there might be an angiogenic factor unique to tumors. This concept was displaced by the finding that at least one angiogenic factor (bFGF) had wide tissue distribution in both tumors and normal tissue. Furthermore, it is now obvious that there are a number of angiogenic factors. Since the distribution and action of these factors is not yet known, it is difficult to speculate on their relative contributions to angiogenesis. It is clear that our knowledge is fragmentary and that a number of important questions remain to be answered before a complete picture will be elucidated concerning the control of angiogenesis. For instance, two of the angiogenic factors described (the FGFs and PD-ECGF) lack signal sequence and the mechanism of their release is therefore unclear. Localization of FGF to cell surfaces and matrix associated heparin-like molecules has led to the speculation that these may act as easily accessible reservoirs of FGF. How does the FGF gain access to these sites? Since no significant functional differences have been demonstrated between acidic and basic FGF, what is the purpose of the two forms of FGF? Are there qualitative differences among the various kinds of angiogenesis (e.g. embryogenesis, wound healing, tumor vascularization, and so on)? How is the process of angiogenesis regulated? Is quiescence maintained by a balance between stimulators and inhibitors? If so, might one be able to induce or block neovascularization simply by interfering with this balance? Some insight into these questions will require the use of specific reagents that can specifically block or stimulate vessel growth. A good example is provided by studies in which neutralizing antibodies against bFGF were shown to block neovascularization induced by a sponge implant, which strongly implicates a role for bFGF in wound repair. Finally, although a variety of substances have been demonstrated to block angiogenesis using in vivo assays, none has been demonstrated to function physiologically."

67. Professor Harris accepted, rightly in my judgment, that this review presented a confusing picture as to how one might go about blocking angiogenesis and certainly did not suggest it was obvious how to reach the goal of anti-angiogenesis therapy. He pointed out that it was effectively reporting the position in 1990, and that the Table indicated that VEGF was the one factor which "ticked all the boxes".

68. It is important to recognise that the key factors said by the claimants to point towards the ultimate success of VEGF were already known to the authors and discussed in the paper. Thus the authors recognise that VEGF is specific to endothelial cells, is a secreted factor, and is related to vascular permeability. Yet the authors do not single out VEGF in their summary as to the future direction. Professor Harris' explanation for this was that more was known about VEGF by the filing date. He drew attention in particular to a paper by Dvorak published in 1991. Genentech does not accept that

that paper had become common general knowledge by the priority date, an issue to which I will return in due course.

69. I think that the Table in Klagsbrun and D'Amore 1991 needs to be seen in the context of the review as a whole. With the benefit of hindsight it is easy to focus on the Table and suggest that it would enable the skilled person to make predictions about the suitability of VEGF for therapy. I think that the fact that the authors themselves did not make any such predictions, and explained why they could not, is significant. Professor Harris' suggestion that the reason the authors did not single out VEGF was lack of space, or something that it was not necessary for the authors to cover, is unsupportable. The authors had a section on future directions, and to have singled out VEGF would have been inconsistent with the remainder of the text, which clearly suggests that there is no obvious target for therapy.

70. So far as the properties listed in the Table are concerned, they are of course properties of interest to the researcher. But Professor Shima's evidence was that such lists were not at the forefront of the researchers' minds. What was important to discover was which if any factor would turn out to be necessary for pathological angiogenesis. Until one knows that, the lists of properties were secondary. To put it another way, a factor which ticks all the boxes is of no direct use unless and until it is shown that it is necessary for pathological angiogenesis. Viewed in that light, which I accept to be the correct one, the playing field on which the various factors were arrayed was a more or less level one.

71. Professor Harris co-authored a further review in 1991: Bicknell & Harris 1991. The authors report the surge in the number of factors known to stimulate or inhibit angiogenesis in the previous two years, and that the picture is rather complex. The article points out that:

> "VEGF is of particular interest in that it appears to be a specific growth factor for endothelium in contrast to the FGF and EGF families which are mitogenic for a wide range of cells."

72. Professor Harris accepted that it was a generally accepted view, as recorded in this paper, that, having regard to the number of angiogenic factors released, devising an anti-angiogenic therapy for tumour growth would be difficult. This point is illustrated by reference to the experience with FGF and papers by Reilly, and Matsusaki. Reilly's experiments had artificially created a situation in which FGF was the only angiogenic factor and had shown that an antibody to it blocked angiogenesis. Matsusaki had looked to see whether anti-bFGF antibodies blocked tumour growth and vascularisation in mice, and had failed to show any blocking.

73. The authors conclude:

> "The number of factors known to affect endothelial growth has increased markedly. However, many of these are much less potent than FGF and it will be important to establish which are relevant *in vivo*. Analysis of human tumour biopsies to determine which particular angiogenic factors are produced by given tumour type and studies with human capillary endothelium may be particularly helpful in this regard.

> Capillary endothelium from different organs appears to respond to a different repertoire of growth factors, for example, lung capillary endothelium is stimulated by EGF but not that from adrenals. Nevertheless, it is likely that mechanisms of angiogenesis are common to many tumour types and the hope is that anti-angiogenic therapies may be widely applicable."

74. Folkman & Ingber published a further review in April 1992, still before the priority date. The review was concerned with strategies for inhibiting angiogenesis. The authors identify three feasible strategies: (i) blocking expression from tumour cells of angiogenic factors, (ii) blocking angiogenic factors after they have been released from tumour cells and (iii) preventing endothelial cells from responding to any angiogenic stimulus. The second of these approaches is that adopted by the patent. Most of the inhibitors thus far discovered were of the third class.

75. As an example of the second class of strategy, the authors cite the successful blocking of FGF, and the work of Hori. The majority of the paper focuses on the third class, and the group's recent work on fumagillin, a fungal derived angiogenesis inhibitor.

76. A further review, Folkman and Shing published in June 1992 also makes clear that there was no obvious route forward:

> "Angiogenic factors and inhibitors have been discovered only in the past decade, and while their properties can be listed (Table 1) the elucidation of their interactions with each other is only beginning to be uncovered.
>
> Now, completely sequenced angiogenic molecules can be tabulated, but we only have a dim conception about how they operate, how they mediate angiogenesis and how they are regulated. Also, most of these molecules have other effects, and the interrelations between the different factors and their effects are still largely unknown."

Reliance on Dvorak

77. Professor Harris' evidence about the common general knowledge, and the extent to which VEGF would be singled out for development, relied strongly, as I have already indicated, on the publication of a paper by Dvorak et al in the Journal of Experimental Medicine in 1991. Dvorak's experiments used staining techniques to look at sites of VPF synthesis and the accumulation in tumours and nearby blood vessels. Staining was evident within 5 hours after tumour transplantation. Professor Shima's view was that Dvorak 1991 was not common general knowledge. Professor Harris disagreed.

78. In my judgment Dvorak 1991 was not part of the common general knowledge at the priority date. Firstly, none of the reviews in the field of angiogenesis published before the priority date make any reference to the paper. Professor Harris' explanation, in relation to one of the reviews, was that they had already had over 100 references, and that you could not list every paper in angiogenesis research. I think that if the paper had achieved the status of common general knowledge it would have

made it into the reviews. At the very least it shows that those in the art were not according the Dvorak paper the significance which Professor Harris attaches to it.

79. Secondly, it is true that the paper was mentioned in a further review by Klagsbrun and Soker published in late 1993; however there are obvious difficulties with relying on post patent reviews for this purpose. My task is to establish the state of the common general knowledge at the priority date, and in particular the weight to be accorded to and width of knowledge of a publication at that date. By 1993, it is quite possible that the significance and width of knowledge that a paper enjoyed may have altered by reason of subsequent events. There is a real danger that, by focussing on VEGF with the benefit of hindsight, one will endeavour to pull together every single piece of knowledge about VEGF at the priority date. In so doing one runs a very real risk of attributing greater significance to a document than it enjoyed at the time, when the skilled person had a different and a wider perspective.

80. Thirdly, I think it is telling that the paper is not cited in Professor Harris' 1992 review. I did not find the Professor's explanation – that Dvorak had published more significant work thereafter – to be convincing.

Conclusion on common general knowledge on VEGF

81. VEGF undoubtedly had properties of interest for the researcher, but it was not established that any of these, either individually or in combination, were sufficient to allow the skilled person to deduce that VEGF was necessary for pathological angiogenesis and was therefore the factor to target to the exclusion of others. Thus, for example, Professor Shima accepted that endothelial cell specificity was an interesting property, but his view was that it was not generally accepted that this property was an indication that a growth factor was necessary for angiogenesis. Professor Harris accepted that there was no necessary connection between the two. Moreover factors other than VEGF also had endothelial cell specificity. Similar considerations apply to the fact that VEGF was also associated with vascular permeability.

82. A property which assumed some importance was that VEGF is a classically secreted protein. FGF lacks a signal sequence and must therefore be released from cells by some other mechanism, such as cell damage. The evidence did not establish that this ruled FGF out, however.

83. Professor Shima's view is well expressed in this passage from his cross-examination:

> Q. All those hypotheses made it a more interesting factor than the others in terms of prospects of success. Correct?
>
> A. I do not believe that those would have actually given you any confidence of success.
>
> Q. That was not an answer to my question. So far as prospects are concerned, VEGF had better prospects on the basis of those hypotheses, accepting that they are, than FGF or any of the others?

> A. I do not agree.
>
> Q. On what basis?
>
> A. As I have already explained to you, FGF has been shown to be an extremely potent angiogenesis factor, as was TGF beta, working in completely different ways but they were shown to be relevant angiogenesis candidates. What I am saying is I think that those properties of VEGF are interesting but we do not really know their relevance until we understand how it works in vivo, either during embryonic angiogenesis or in a relevant animal model of disease.
>
> Q. But you understand the relevance of secretion. You understand the relevance of selectivity.
>
> A. I do not understand the relevance of selectivity. As I already said to you, that is an interesting property. We did not know how relevant it was going to be. I do understand, that I have already explained, that the properties were interesting, but they were not absolutely required at the time. We did not know. The field was not sure how to place that in context.
>
> Q. Selectivity; you understood the proposition that if it was more selective it was a more desirable therapeutic target?
>
> A. No, in fact, the opposite has also been proposed. It was too selective and maybe it would not be involved in pathological situations but maybe more likely in embryonic situations.

84. I trust that it is now clear why I do not regard Professor Shima's reluctance to accept the relevance of selectivity as constituting a reason for rejecting or giving reduced weight to his evidence. Reliance on selectivity, in the state of knowledge before the invention, could have led the skilled person astray. It is only when one knows that VEGF is necessary for pathological angiogenesis that it is possible to say that its selectivity is definitely a valuable property. This neatly illustrates the dangers of hindsight.

85. Against this I have to set the evidence of Professor Harris and Professor Plate who suggested that there was much more confidence in VEGF proving to be a factor necessary for angiogenesis. This is an area where I thought that Professor Harris was plainly allowing himself to exaggerate the position. As I have said, in his cross-examination he said that the skilled person would be able to deduce from its properties that VEGF would have a significant role in angiogenesis. I am unable to accept that evidence for a number of reasons. Firstly, that degree of enthusiasm for VEGF from the common general knowledge is simply not reflected in any contemporaneous document. Secondly, in his 1992 review, which was written in the summer of 1992, Professor Harris says:

> "Thus, blocking of a single angiogenic factor may indeed, in some cases, prevent tumour vascularisation. However, with the

> existence of multiple angiogenic factors it is unlikely to be a panacea. There exists an urgent need for more information concerning the release of angiogenic factors by different tumour types. How prevalent are the different factors? Which should we target?
>
> We have found that some breast carcinoma cell lines produce mRNA for multiple angiogenic factors. For example, line MDA-23 I produces bFGF, VEGF (vascular endothelial growth factor), pleiotrophin and PDECGF (platelet-derived endothelial cell growth factor), and possibly many others. Thus, blocking the activity of a single angiogenic factor by whatever means is unlikely to give rise to a widely applicable therapy. Such a strategy has a chance of success only if it is found that certain types of tumours secrete a single common angiogenic factor that may be targeted. A notable candidate is VEGF which appears to be virtually universal to breast and brain tumours, in marked contrast to the FGF family of peptides which are quite rare in breast tumours."

86. The implication of the first part of that passage was, as Professor Harris accepted, that it was unclear, even at that late stage, which factor should be targeted. The second part of the extract refers to VEGF as "a notable candidate" in contrast to FGF which is not so widely expressed in breast cancers. However this conclusion was based on Professor Harris' own unpublished work. In his expert report he had made a more guarded comment about VEGF being suspected to be the most widely expressed of the growth factors. He said that this comment was based on other work, which no doubt led to the more guarded nature of the comment.

87. So far as Professor Plate is concerned, it is clear that he was an enthusiast for VEGF, and said that he was not alone in being one. It was also clear from his answers that part of his enthusiasm for VEGF was due to his knowledge that the group at Genentech, which included "major players" such as Napoleone Ferrara, were working on it. Professor Harris also appears to have been influenced by this knowledge as well. I am not persuaded that confidence that one is on the right track, based on placing one's faith in particular groups or individuals, is indicative of common general knowledge in the field. The common general knowledge must be based on a more sound technical foundation than that.

88. In my judgment, at the filing date, there was nothing approaching a concluded view as to which if any of the many growth factors which had been identified would be the right or best one to target for therapeutic purposes. Each of the growth factors had its enthusiasts, but there was no way of predicting which of the growth factors would be necessary for pathological angiogenesis. There was plainly a justifiable concern that a process as important as angiogenesis would have built in redundancy, so that no single factor could be targeted alone to achieve an effect. Workers in the field were continuing research on factors other than VEGF. The obviousness and insufficiency cases will have to be approached with this state of the art in mind.

Infringement

VEGF Trap-Eye

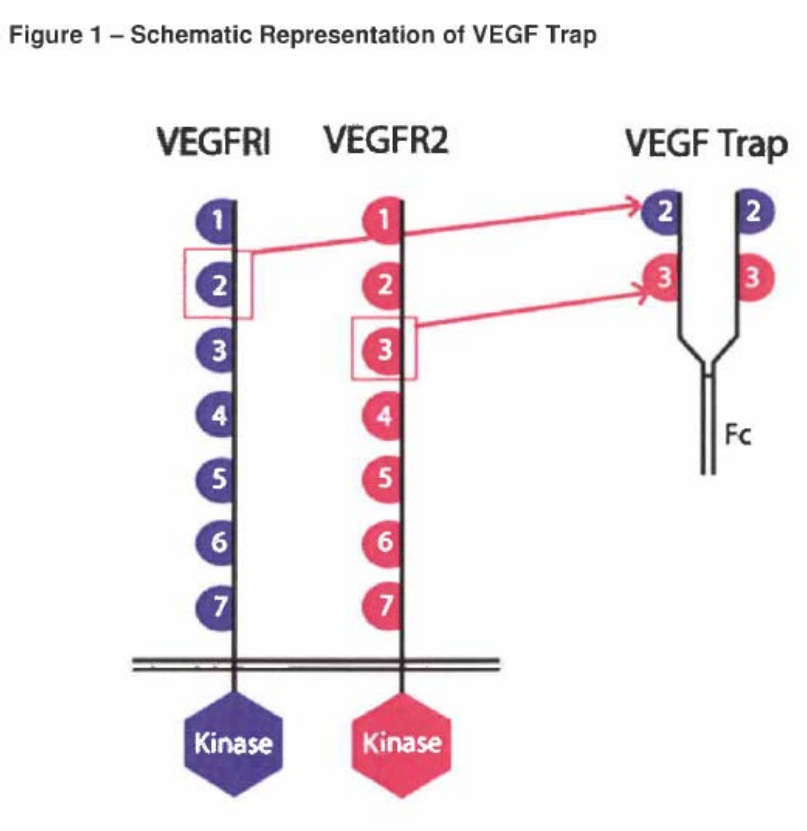
89. VTE is an ophthalmic solution which will be used to treat patients suffering from neovascular ("wet") age related macular degeneration ("ARMD").

90. More specifically, the active component is a recombinant chimeric homodimer, each monomer comprising:

- the immunoglobulin-like domain 2 of the VEGF-R1 receptor; and
- the immunoglobulin-like domain 3 of the VEGF-R2 receptor; fused to
- the constant region (Fc) of human immunoglobulin G1.

91. Figure 1 from the agreed product description below shows a schematic representation of VTE:

Figure 1 – Schematic Representation of VEGF Trap



Is VTE an isolated VEGF receptor?

92. This is the sole issue on infringement. It turns on the issue of construction which I have dealt with above. There is of course no description of VTE in the patent. But the patent speaks in general terms of variants and truncated forms of the full length receptors. The evidence establishes that VTE involved a major research project. Professor Harris was of the view that the overall approach of using domains from different receptors for a therapeutic purpose was an innovative one. Accordingly, the claimants submit that the skilled reader would not understand such a product to be within the contemplation of the claims.

93. I do not think that the claimants' submissions reflect the correct approach to the issue of infringement. Once the claims of the patent have been construed as to their proper meaning, the task for the court is to determine whether the alleged infringement falls within claims as so construed. It is no part of that exercise to embark on a consideration of whether the specific construct alleged to infringe was contemplated by the patentee, or on an analysis of the route or amount of effort involved in arriving at the construct.

94. As its nomenclature suggests, VTE is an effective antagonist of VEGF. It binds VEGF to a sufficient degree to achieve a therapeutic effect. In my judgment it falls plainly within the language of the claim as it would be understood by a skilled reader.

Lack of novelty

95. The claimants contend that the claims lack novelty over Kim 1992.

Lack of novelty –Law

96. Section 2(1) of the Patents Act 1977 provides:

> "2.-(1) An invention shall be taken to be new if it does not form part of the state of the art.
>
> (2) The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way."

97. This part of the law of patents was reviewed by the House of Lords in *Synthon v SKBt* [2006] RPC 10. There are two requirements for a claim to be anticipated by a prior document: disclosure and enablement. As to disclosure, Lord Hoffmann, who gave the leading judgment, began by citing passages from what he described as two judgments of "unquestionable authority": the speech of Lord Westbury LC in *Hills v Evans* (1862) 31 LJ Ch (NS) 457 at 463 and the judgment of the Court of Appeal in *General Tire and Rubber Co v Firestone Tyre and Rubber Co Ltd* [1972] RPC 457 at 485-486. In the latter case the Court of Appeal said:

> "If the prior inventor's publication contains a clear description of, or clear instructions to do or make, something that would infringe the patentee's claim if carried out after the grant of the patentee's patent, the patentee's claim will be shown to lack the necessary novelty. The prior inventor, however, and the patentee may have approached the same device from different starting points and may for this reason, or it may be for other reasons, have so described their devices that it cannot be immediately discerned from a reading of the language which they have respectively used that they have discovered in truth the same device; but if carrying out the directions contained in

> the prior inventor's publication will inevitably result in something being made or done which, if the patentee's claim were valid, would constitute an infringement of the patentee's claim, this circumstance demonstrates that the patentee's claim has in fact been anticipated.
>
> If, on the other hand, the prior publication contains a direction which is capable of being carried out in a manner which would infringe the patentee's claim, but would be at least as likely to be carried out in a way which would not do so, the patentee's claim will not have been anticipated, although it may fail on the ground of obviousness. To anticipate the patentee's claim the prior publication must contain clear and unmistakeable directions to do what the patentee claims to have invented…A signpost, however clear, upon the road to the patentee's invention will not suffice. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee."

98. At paragraph 22 Lord Hoffmann says this:

> "If I may summarise the effect of these two well-known statements, the matter relied upon as prior art must disclose subject-matter which, if performed, would necessarily result in an infringement of the patent. That may be because the prior art discloses the same invention. In that case there will be no question that performance of the earlier invention would infringe and usually it will be apparent to someone who is aware of both the prior art and the patent that it will do so. But patent infringement does not require that one should be aware that one is infringing: "whether or not a person is working [an] ... invention is an objective fact independent of what he knows or thinks about what he is doing": *Merrell Dow Pharmaceuticals Inc v H N Norton & Co Ltd* [1996] R.P.C. 76, 90. It follows that, whether or not it would be apparent to anyone at the time, whenever subject-matter described in the prior disclosure is capable of being performed and is such that, if performed, it must result in the patent being infringed, the disclosure condition is satisfied. The flag has been planted, even though the author or maker of the prior art was not aware that he was doing so."

99. The claims in the present case specify a medical use for a product either in the so called Swiss form ("use of compound X in the manufacture of a medicament to treat disease Y") or in the form permitted by the European Patent Convention 2000 ("compound X for use in treating disease Y"). In the European Patent Office the view is taken that, with claims in either form, the actual achievement of the therapeutic effect is a functional technical feature of the claim, as opposed to a mere statement of purpose or intention. That this is so can be seen from decision T 0609/02 *The Salk Institute for Biological Studies*, at paragraph 9 of the Reasons and the cases cited there, which include, in the non-medical field, the well known *Mobil* decision

G2/88. The claimants did not have any convincing reason why that should not apply here.

100. Mr Waugh reminded me that novelty is not created merely by describing something old in different language, or merely by providing new information about what is old. He had in mind, no doubt, cases such as *Bristol Myers Squibb v Baker Norton Pharmaceuticals* [2001] RPC 1. That submission is correct.

Kim 1992 – disclosure

101. The sole citation ultimately relied on by the claimants is a paper by the inventors of the patent and co-workers entitled "The vascular endothelial growth factor proteins: identification of biologically relevant regions by neutralizing monoclonal antibodies" published in *Growth Factors*, 1992; 7(1): 53-64 ("Kim 1992").

102. Kim 1992 starts by explaining that angiogenesis plays an important role in embryonic development, wound healing, reproductive processes as well as in a variety of pathological conditions such as atherosclerosis, tumour growth and RA. Thus, the authors explain, the elucidation of the factors which regulate angiogenesis is of considerable relevance to both physiological and pathological processes. They further explain that, in recent years, several putative angiogenic factors have been identified, but that with the exception of FGF and PD-ECGF and possibly also EGF, they have not shown direct mitogenic action for epithelial cells. It also points out that even though FGF and PD-ECGF were proposed to be major mediators of angiogenesis, neither is a secreted protein and would be therefore unlikely to function as direct stimulators of angiogenesis, except following cell injury. By contrast VEGF was a secreted protein and may therefore affect endothelial cell maintenance and proliferation as well as pathological conditions.

103. Kim 1992 describes the development of monoclonal antibodies to recombinant human VEGF. The authors predict the following:

> "These mAbs are expected to serve as powerful tools for elucidating the physiological role of VEGF, exploring the significance of the multiple forms of VEGF and the structural and functional relationship of VEGF with its receptor(s). Furthermore, in light of the importance of angiogenesis in chronic inflammation, atherosclerosis, diabetic retinopathy, rheumatoid arthritis and cancer … mAbs capable of neutralizing the biological activities of VEGF could be of therapeutic potential"

104. The statement of therapeutic potential is one made in the abstract of the paper in the following terms:

> "These well-defined mAbs should be very powerful tools to understand the structure-function relationship of various domains of VEGF and may have therapeutic potential."

105. The article includes experiments to show that the monoclonal antibodies are effective to bind to endothelial cells, block the growth of such cells *in vitro*, and neutralise the

angiogenic and vascular permeability activities of VEGF *in vivo*. Thus Kim 1992 includes a CAM assay and Miles' permeability assay showing that the antibody neutralises the angiogenic and vascular permeability activities of VEGF *in vivo*.

106. The authors conclude, amongst other things:

> "The potent neutralizing mAb A4.6.1, which binds three forms of VEGF, may be valuable in determining the importance of the production of VEGF in regulating the growth and metastasis of tumor cells and in inflammation. These well defined mAbs could be potential tools to determine the level of VEGF in many pathological conditions and to understand the structural and functional relationship of VEGF with its receptor(s). Further, VEGF neutralizing mAbs could be potential therapeutic agents in diseases involving excess endothelial cell proliferation."

Novelty over Kim 1992?

107. Mr Tappin submitted that the disclosure of Kim 1992 did not deprive the claims in issue of novelty. There was no disclosure in Kim 1992 of the use of VEGF antibodies in the treatment of disease. He accepts that Kim 1992 discloses the relevant antibodies to VEGF, mentions a number of non-neoplastic disorders and conjectures that the antibodies may have therapeutic potential. That, he says is not enough in the absence of material from which it can be directly and unambiguously deduced that the antibodies can be used for therapy. Put another way, he submits that the claim requires the achievement of a therapeutic effect as a functional technical feature of the claim. Kim 1992 neither discloses this effect nor gives clear and unmistakeable directions to achieve it. It is at most a signpost. Kim 1992 has not planted the flag at the precise destination specified by the patentee's claim.

108. Mr Waugh submitted that Kim 1992 taught the use of the identical antibodies to those claimed in the treatment of patients suffering from non-neoplastic diseases characterised by excessive neovascularisation. It followed that use of those antibodies in treatment would produce the therapeutic effect claimed in the patent. The fact that the patent contains additional data (the mouse xenograft tests and the data about RA) is irrelevant to the issue of novelty, as the differences between the claim and the disclosure of Kim 1992 were merely linguistic.

109. This has given rise to a dispute about what is required to deprive such a claim of novelty. Is it enough if the prior disclosure states that the medicament might have the stated therapeutic effect? Or must the prior disclosure go further and establish that it will have the therapeutic effect? I asked Mr Tappin if he went as far as to say that the prior disclosure must demonstrate actual use in human therapy, for example by means of a clinical trial. He accepted that this was not required. He said that the prior disclosure must contain material from which you can directly and unambiguously deduce the claimed therapeutic effect.

110. I think Mr Tappin is right about this. If one approaches the matter in the way suggested by *Synthon* and *General Tire* one asks first about what is disclosed. A disclosure that a compound might have a therapeutic effect is not a disclosure of the

fact that it does have that effect. If one then asks whether there are clear and unmistakeable directions to do what the patentee has invented, namely use it in therapy, the answer is that there are not. The prior inventor is not giving clear and unmistakeable directions to use the compound in therapy. The directions in the prior document are equivocal, which is the opposite of clarity and lack of ambiguity. The reason that the directions are equivocal is that the prior inventor has not arrived at the same invention as the patentee. What he has said might be a signpost, but he has not planted a flag at the precise destination defined by the claim.

111. In my judgment, Kim 1992 falls short of being an anticipation of the claims of the patent. It is true that Kim 1992 discloses an antibody which in fact has the properties claimed. But it cannot sensibly be argued that the disclosure of the antibody alone - ignoring for a moment the passages of the text which suggest potential use in therapy - discloses the fact that the antibody in use achieves the claimed therapeutic effect. Equally it seems to me, the passages in the text which discuss the potential use in therapy do not disclose that the therapeutic effect is in fact achieved. The data in Kim 1992 does not amount to a disclosure from which it can be directly and unambiguously deduced that the antibody will have a therapeutic effect. Those conclusions are fatal to a finding of anticipation based on the disclosure limb of the test in *General Tire*.

112. That is not the end of the enquiry, however. The author of the prior document may have given clear directions to do something falling within the claims, even though he was unable to state that the technical effect would be realised by doing so. Here, again, I think the disclosure of Kim is inadequate. In my judgment there are no clear or unambiguous directions in Kim to do something falling within the claims. A suggestion that an antibody may have therapeutic potential is not the same as a direction to use it in therapy. No real attempt was made by the claimants to elicit evidence to that effect. Professor Harris said that the passages in Kim 1992 strongly suggested use in treatment. I do not think the cautious statements in Kim 1992 can be so described.

113. Mr Tappin ran a further point based on the language of the Swiss form of claim "use in … the preparation of a medicament". The point only goes to claim 1. It is not necessary for me to decide this point, and it does not really help one way or the other. If I had thought that Kim 1992 contained a clear disclosure of, or clear and unambiguous directions to use VEGF antibodies in the treatment of disease, I would have been inclined to hold that the preparation of a medicament was inherent in the teaching. But as, in my judgment, it does not contain such a disclosure or directions, the preparation of a medicament is not inherent or taught.

114. For those reasons I consider that the claimed invention does not merely describe the same thing as Kim 1992 in other language, or provide more information about that which is described in Kim 1992. In the result I do not consider that Kim 1992 deprived the claim, properly understood, of novelty.

Obviousness

115. Obviousness is alleged based, again, on the disclosure of Kim 1992. No case of obviousness based on the common general knowledge alone was advanced.

Obviousness - law

116. Section 3 of the Patents Act 1977 provides:

> "An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which formed part of the state of the art…"

117. In *Conor v Angiotech* [2008] UKHL 49; [2008] RPC 28 at [42] Lord Hoffmann approved the following statement by Kitchin J in *Generics (UK) Ltd v H Lundbeck A/S* [2007] RPC 32 at [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."

118. It is, of course, the invention which must be found to be obvious, see for example *Conor* at [17] to [19]. If the invention lies in the claim that a product has a particular use, the correct question is whether it was obvious to use the product for that purpose, see *Conor* at [17] and [40]. The question is not whether the product might work for that purpose, see *Conor* at [18], [28].

119. Lord Hoffman went on, at [29] to [36], to point out that inventive step cannot be acknowledged unless the specification makes the claimed effect plausible, in the sense of it being a reasonable prediction from the available information, citing T 939/92 *AgrEvo Triazoles* and T 1329/04 *Johns Hopkins Growth Differentiation factor*.

120. In *St Gobain v Fusion Provida* [2005] EWCA Civ 177 Jacob LJ had explained the role of "obvious to try" in the assessment of inventive step in this way:

> "Mere possible inclusion of something within a research programme on the basis you will find out more and something might turn up is not enough. If it were otherwise there would be few inventions which were patentable. The only research which would be worthwhile (because of the prospect of protection) would be in areas totally devoid of prospect. The "obvious to try" test really only works where it is more-or-less self evident that what is being tested ought to work."

121. Subsequently, in *Conor v Angiotech* [2007] EWCA Civ 5, Jacob LJ in the Court of Appeal again dealt with the authorities in relation to "obvious to try", including his own earlier judgment in *St Gobain v Fusion Provida*. He summarised the position at [45]:

> "In the end the question is simply "was the invention obvious?" This involves taking into account a number of factors, for

> instance the attributes and cgk of the skilled man, the difference between what is claimed and the prior art, whether there is a motive provided or hinted by the prior art and so on. Some factors are more important than others. Sometimes commercial success can demonstrate that an idea was a good one. In others "obvious to try" may come into the assessment. But such a formula cannot itself necessarily provide the answer. Of particular importance is of course the nature of the invention itself."

122. However, Jacob LJ went on to say at [48] that *Conor* was not an "obvious to try" case, nevertheless finding that the invention was obvious. The House of Lords came to a different conclusion from the trial judge and the Court of Appeal on the issue of obviousness. Lord Hoffman said this about "obvious to try" at [42], apparently approving Jacob LJ's summary:

> "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."

123. Lord Justice Jacob's *St Gobain* phrase "more-or-less self-evident that what is being tested ought to work" is thus explained by Lord Hoffmann as a "fair expectation of success", with the degree of expectation depending on the facts of the case.

124. Mr Tappin submits, and I accept, that the "success" which is discussed in these cases is success in the claimed use.

125. Mr Waugh submitted that the above analysis relegates the role of the "obvious to try" line of authority, starting with *Johns Manville Corporation's Patent* [1967] RPC 479, to history. I do not agree. Both Jacob LJ and Lord Hoffmann in *Conor* recognise that "obvious to try" plays a part in the assessment in certain cases. However it is the invention which must be obvious to try: obvious to try does not mean obvious to embark on a research program which might lead to the invention: see Jacob LJ in *Saint Gobain*. Moreover, in a use case like the present, the expectation of success must be sufficient to induce the skilled person to use the invention. In *Conor* this meant having a sufficient expectation of success to use taxol in a drug eluting stent: see Lord Hoffmann at [40] to [41]. Here it means having a sufficient expectation of success in using anti-VEGF agents in the treatment of diseases characterised by undesired angiogenesis.

126. Mr Waugh sought to obtain assistance from two EPO cases which recognise a role for "obvious to try". These were T 1045/98 *Schering Corporation/anatagonist to interleukin-5* and T 230/01 *Sepracor/Descarboethoxyloratidine*.

127. *Schering* was concerned with an antagonist to interleukin-5 for preventing or reducing eosinophilia, a disorder of the blood. The patentees had claimed the use of such an antagonist for reducing eosinophilia in a patient. The background to the Board's finding of obviousness is seen in the following extract:

> "16. In the board's judgement, the skilled person, although knowing that IL-5, as an endogenous humoral factor, was involved in a number of complex biological processes of activation and regulation, and although aware that any interference which (*semble* with) such phenomena could result in adverse responses by the organism, would not have been deterred from testing in an in vivo animal model the activity of an antagonist which had been shown by document (7) to have a dose-dependent effect in an in vitro model. In bio-medical sciences, studies in vitro wherein a given product is shown to have a biological effect, are normally, and logically, followed by experiments in vivo in an animal model where the effect can be tested in the more complex context of a living organism. One of the purposes of such animal models, from the simplest to the more complex, is indeed to serve as an intermediary step before clinical testing in patients, thus as a sort of barrier between potentially harmful products and human exposure. Thus, as already stated, far from being deterred, the skilled person would have considered the in vivo testing in mice as being the next logical step. The question here is rather whether this test would have been approached by the skilled person with scepticism, with a neutral attitude or with some expectation of success.
>
> 17. Although - as stated eg in document (35) - the control of eosinophilia was not completely understood at the date of the invention and an univocal link between eosinophilia and IL-5 was not yet demonstrated, the skilled person had good indications from the prior art (cf points 10 and 12 above) that IL-5, being involved in the final stages of eosinophilopoiesis, was the factor likely to be responsible for the increase in eosinophil numbers in response to infection. Although knowing that in vitro experiments cannot mimic the in vivo settings and that in vitro results are not always confirmed upon in vivo testing, the skilled person would have perceived the experiment reported in document (7) which showed in vitro dose-dependent neutralisation of the eosinophilopoietic effect of IL-5 by anti-IL-5 antibody as being encouraging, also in view of the raised IL-5 levels observed in vivo in mice infected with a parasite (cf document (35)). Thus, in spite of the understandable uncertainties which always characterise biological experiments, the skilled person had no reasons to adopt a sceptical attitude. He or she would have had either some expectations of success or, at worst, no particular expectations of any sort, but only a "try and see" attitude, which

> - as pointed out eg in decisions T 333/97 of 5 October 2000 and T 377/95 of 24 April 2001 - does not equate with an absence of a reasonable expectation of success."

128. I resist the temptation to draw factual analogies with decided cases on obviousness: see per Nicholls LJ in *Molnlycke v Procter & Gamble* [1994] RPC 49 at 113-4. I certainly do not read the closing words as setting a standard inconsistent with the requirement for a fair expectation of success, with the degree of expectation depending on the facts of the case.

129. *Sepracor* was concerned with the use of DCL for treating allergic rhinitis in humans. It was well known that DCL was the metabolite of loratidine, a successful anti-histamine used for that condition. The prior art disclosed the the antihistaminic properties of DCL and proposed its use in treatment of allergic conditions in general. The claims which were sought included a dosage requirement. The Board held the invention to be obvious:

> "8.2 In the board's view, the cited state of the art pointed the notional skilled person in the direction of the claimed invention, and it only remained to confirm experimentally by a small number of routine tests that the thoroughly obvious result, namely the efficacy of DCL in the treatment of allergic rhinitis using the claimed dosage regimen, was in fact obtained. However, the necessity of experimentally confirming a reasonably expected result cannot contribute to an inventive step. Thus, in the absence of any evidence showing that the selection of allergic rhinitis was unexpectedly associated with a beneficial effect, or a significant advantage or a worthwhile improvement in the broadest sense, the conclusion must be drawn that the claimed use of the DCL shows only predictable effects and is therefore obvious. "

130. I think this passage reinforces the view which I have taken of the law. The Board asked itself whether the result was "reasonably expected". The Board's view was that this test was satisfied in that case - in fact they thought the result "thoroughly obvious" and "predictable". Accordingly there was no invention in mere experimental confirmation that it was so.

131. It is convenient to address the question of obviousness by using the structured approach explained by the Court of Appeal in *Pozzoli v BDMO* [2007] EWCA Civ 588; [2007] FSR 37. This involves the following steps:

> "(1) (a) Identify the notional 'person skilled in the art'.
>
> (b) Identify the relevant common general knowledge of that person.
>
> (2) Identify the inventive concept of the claim in question or, if that cannot readily be done, construe it.

> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed.
>
> (4) Ask whether, when viewed without any knowledge of the alleged invention as claimed: do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?"

132. The importance of avoiding hindsight is emphasised in step 4 – "without any knowledge of the alleged invention". The contemporaneous writings of those in the field without knowledge of the invention can be of assistance in avoiding hindsight, as can the reaction of those in the field when told of, or when reviewing, the invention. Events, as in other spheres, are also important. See, on both points, *Schlumberger Holdings v Electromagnetic Geoservices* [2010] RPC 33 at [81] to [82] and [112].

133. Though decided many years ago, it is also worth bearing in mind Fletcher Moulton LJ's warning in *British Westinghouse Electric and Manufacturing Company v Braulik* [1910] RPC 209 at 230 about the dangers of an *ex post facto*, step by step analysis of inventions. He noted how, with an invention "when it has once been established, it is easy to show how it might be arrived at by starting from something known and taking a series of apparently easy steps".

Obviousness - facts

134. I have dealt above with the person skilled in the art and the common general knowledge. The inventive concept is the use of one of the specified VEGF antagonists in the treatment of a non-neoplastic disease characterised by undesired excessive neovascularisation.

Difference over Kim 1992

135. The difference between the disclosure of Kim 1992 and the inventive concept is that Kim 1992, whilst mentioning therapeutic potential, does not disclose the use of the antibodies in the treatment of a non-neoplastic disease.

Claimants' first obviousness case – obvious course of research

136. The claimants' main case of obviousness over Kim 1992, as it was put to Professor Shima, was that the next logical step for the skilled team on reading Kim 1992, would be to test the hypothesis that the antibody has therapeutic potential. In those circumstances the obvious next step to take would be the mouse xenograft test. Secondly, having performed that test and shown anti-angiogenic activity of the antibody in a disease model, it would be possible to make a sound prediction that the antibody would work in therapy, not merely for tumours but for other diseases as well.

137. There is no real dispute that the skilled team, on reading Kim 1992, would have a motive to take this first step and perform the mouse xenograft test. Professor Shima said that there were compelling reasons to do so. He accepted, in terms of a research objective, it was the next logical step. I accept that the skilled person would want to

discover whether anti-VEGF antibodies were effective in an animal model of disease to prevent angiogenesis. They would of course only be effective if VEGF was necessary for pathological angiogenesis, something which was not known at the time, and which the experiment might establish.

138. As to the second step, predicting therapeutic efficacy once the results of the mouse xenograft test are known, there is not much scope for dispute either. Indeed it is part of Genentech's answer to the case of insufficiency that the disclosure of the results of the mouse xenograft test provide a basis for making a reasonable prediction that the anti-VEGF antibodies will work for the full range of non-neoplastic diseases. The claimants do not themselves wholeheartedly embrace that proposition, but accept that the skilled person would be able to make a reasonable prediction from those results that the antibodies would work for at least some of the non-neoplastic diseases. I will have to return to that issue when I come to insufficiency, but for present purposes neither party is contending that it would not be possible to make a reasonable prediction from successful results in a mouse xenograft test that anti-VEGF therapy would work to reduce angiogenesis for some non-neoplastic diseases.

139. Genentech's answer to the claimants' case is that, even taken at face value, it does not establish obviousness of the invention. They say it is a classic stepwise obviousness attack which the law does not permit. First of all, they say that the evidence does not establish that Kim 1992 made it obvious to use anti-VEGF therapy. Secondly, in answer to the case that it was nevertheless obvious to try the mouse xenograft test, they say that the mouse xenograft test would not be embarked upon with the necessary fair expectation of success.

140. Part of Professor Shima's cross-examination went like this:

> Q. Indeed, it would be plausible that VEGF antagonist would work in the nude mouse xenograft model having got the positive results that Ferrara describes in this paper.
>
> A. I do not think that the results in this paper contribute in any way to the excitement you might have had or the plausibility about VEGF as a target. They are just characterising an antibody in this particular paper.
>
> Q. That was not my question, professor?
>
> A. Could you restate your question, please?
>
> Q. If you got a positive result with a potent antibody showing potent blocking activities in vivo in the Miles permeability assay and in the CAM assay, it would be plausible at the very least that it would be effective in the nude mouse xenograft model.
>
> A. It would be plausible, yes.

> Q. Indeed we put the case, Professor Harris puts it, going back to his report, that you would be optimistic that it would work. That is his evidence. Correct?
>
> A. I believe that is his evidence, yes.
>
> Q. And it is one of those things you beg to differ.
>
> A. I would not have been optimistic. I do not think that the skilled addressee would have been optimistic at that stage. Essentially what the Kim '92 paper does is describe the creation of an interesting tool.
>
> Q. It goes further than that, does it not, professor? Go back to the Kim paper. It does not just describe an interesting tool. It specifically flags up "could therefore be of therapeutic potential".
>
> A. It could be. It could potentially be if you knew that VEGF was a valid target, yes.
>
> Q. All you have to do to assess that is to put it in the mice, correct?
>
> A. That would be one way you could do it, yes.
>
> Q. And that is a standard test?
>
> A. It is a convincing test, yes.

141. Professor Shima's evidence was that one cannot embark on the test with optimism about the outcome if one does not know, as the skilled team would not know, that VEGF was a valid target for anti-angiogenic therapy.

142. It is here, therefore that it is essential to form a view as to how optimistic the skilled team would have been that VEGF was a valid target in the sense that it was a necessary factor for angiogenesis. I have explained in some detail above that the common general knowledge did not justify the degree of optimism that VEGF would turn out to be necessary for angiogenesis which Professor Harris and Professor Plate sought to ascribe to it.

143. Kim 1992 did not, in my judgment, materially increase the likelihood that VEGF would turn out to be necessary for pathological angiogenesis *in vivo*. Its contribution was the provision of a tool for research on VEGF - an antibody for inhibiting its effect. Both Professor Harris and Professor Shima so described the disclosure. There is also a danger of attributing too much significance to the *in vivo* assays in Kim with the benefit of hindsight. As Professor Shima explained:

> "… lots of any molecules had been put into CAM assays over the years to see if they could elicit a response. Many did, but that did not mean they were each necessary for the neovascular pathology. Similarly, inhibitors to certain growth factors (e.g.

> bFGF) had also been tested in CAM assays (or similar assays) and had been shown to block the angiogenic activity of the target growth factor. But again, that did not mean that the targeted growth factor alone was responsible for the neovascular pathology, for the reasons explained above."

144. It is true that Kim makes statements about therapeutic potential for the antibodies. These statements have to be viewed against the background that the vast majority of research in this area on all relevant factors would have had therapy as an end objective. Each group would have been able to say that the agent on which they were working had therapeutic potential. That is not the same as a claim to utility in the treatment of disease.

145. I bear in mind that there was the strongest of motivations to discover a therapy that would target a molecule within the body responsible for angiogenesis. That motivation was, however, being channelled down far more avenues than anti-VEGF therapy. I also bear in mind that there is no suggestion that there would be any unusual difficulty in carrying out the mouse xenograft test. Against that I have to place the fact that VEGF was only one of many factors and other agents which could be investigated, the commonly accepted view that there was no single factor responsible, the confusing picture presented by the common general knowledge and the view that achieving anti-angiogenesis therapy would be difficult. I cannot accept that the publication of Kim 1992 altered the landscape to the extent that it was now obvious that VEGF could be used in therapy, or that it was now obvious to try that use.

Reaction to the invention

146. I think this is a case where the reaction to the invention plays a role in the assessment of obviousness, even though, as secondary evidence of non-obviousness, it needs to be kept in its place. Dr Ferrara, one of the inventors of the patent in suit, received the Lasker-DeBakey Medical Award in 2010 for, amongst other things, "*the discovery of VEGF as a major mediator of angiogenesis*". The Lasker awards are recognised to be amongst the highest achievements in science, falling just short of a Nobel Prize. The award said that the work, referring to Kim 1993, had "*opened the door to clinical use of anti-VEGF compounds*". Dr Yancopoulos of Regeneron said, on the occasion of the award, that the work of the inventors had established the primacy of VEGF in tumor angiogenesis. Not only had it provided the first convincing evidence that blocking angiogenesis could indeed prevent tumor growth, it simultaneously established VEGF as the critical target in the process. There can be no doubt that in these latter remarks he was referring to the work embodied in the patent in suit, and not merely to the provision of the antibody in Kim 1992.

147. There are other accolades in the literature. I have mentioned the Gschwind paper and its description of Kim 1993 as a breakthrough, but there were others.

148. Professor Harris sought to attribute all the plaudits to Kim 1992 rather than Kim 1993, suggesting that it was already known that VEGF was the target. I did not find his suggestions to be at all realistic. Kim 1992 can only be seen with hindsight to have anything approaching the importance Professor Harris sought to attribute to it. It did of course provide an important tool – the antibody to VEGF. But it did not provide

evidence that anti-VEGF therapy would be likely to work. That advance was attributed by the literature, and the Lasker Foundation, to the disclosure of Kim 1993, that is to say to the discovery that underlies the invention of the patent in suit.

149. Whilst an advance in scientific knowledge, even a breakthrough advance, is in no sense to be equated with an inventive step, I do think that the reaction of the scientific community to the work reported in the patent is of some significance here. That work provided a sound basis for what was previously only speculation. Dr Yancopoulos' assessment of that work accords with my own: it established VEGF as the critical target, and opened the door to a range of therapies. It is appropriate to describe that contribution as an inventive step.

Claimants' second obviousness case – Agrevo

150. The claimants also advance an obviousness case along the lines permitted by the decision of the Technical Board of Appeal in the *Agrevo* case: T 939/92. In substance they say that the claim that VEGF antagonists would be useful for preventing angiogenesis in the treatment of all non-neoplastic diseases was not plausible. Accordingly, in respect of those diseases for which it is implausible, the patent does not solve any technical problem. Indeed, they say that in fact the claim extends to diseases such as atherosclerosis for which the treatment would not work.

151. It seems to me that in the present case this argument traverses the identical ground to that raised by insufficiency. I propose to deal with it under that heading.

Insufficiency

152. The claimants allege that the patent is invalid for insufficiency on a large number of grounds. The particulars of insufficiency in the claimants' re-amended grounds of invalidity start with four very general allegations which do little more than restate the requirements for sufficiency in the context of the present case. The pleading then goes on to make a whole range of more specific allegations:

> "(1) The Claimant contends that the recombinant chimeric homodimer (VEGF Trap) identified in the Claimant's confidential product description served on 16 February 2011 is not a VEGF antagonist falling within any of sub-paragraphs (a), (b) and/or (c) of claims 1 and/or 14 of the Patent
>
> (i) If and insofar as it may contended otherwise then the specification is ambiguous and/or uncertain and is not sufficiently enabling to allow the skilled person to identify which polypeptides and/or proteins are hVEGF antagonists and/or within the scope of sub-paragraphs (a), (b) and/or (c) of claims 1 and/or 14 of the 986 Patent. Further or alternatively the 986 Patent does not allow them to do so without undue burden. Accordingly the claimed invention is not defined sufficiently for the skilled person to determine whether or not the claims are infringed.

(ii) If and insofar as it may be contended that any of the claims of the 986 Patent covers, or covers the use of an hVEGF antagonist which is an "isolated VEGF receptor" other than the full length hVEGF Receptor or the hVEGF Receptor - IgG Fusion Protein of Example 3 (column 21 lines 20 - 56) the 986 Patent contains no or no sufficient teaching as to how to identify and/or-manufacture such hVEGF antagonists. Further or alternatively the 986 Patent contains no, or no sufficient, teaching as to how to identify and/or manufacture such hVEGF antagonists across the scope the claims or any of them: *a fortiori* if and insofar as the claims of the 986 Patent (or any of them) are alleged to cover VEGF Trap.

(2) Not all hVEGF antagonists falling within the descriptions in sub-paragraphs (a) (b) and/or (c) of claims 1 and/or 14 are therapeutically active against all non-neoplastic diseases or disorders characterised by undesirable excessive neovascularisation (including those identified as such in the specification of the 986 Patent) or are therapeutically active against only some such diseases or disorders. The 986 Patent does not enable the skilled person to identify those that are therapeutically active against all non-neoplastic diseases or disorders characterised by undesirable excessive neovascularisation, further or alternatively those that are therapeutically active against specific diseases or disorders without undue burden.

(3) Further or alternatively there is no, or no sufficient, evidence in the 986 Patent to make it plausible that a solution was found to the problem purportedly solved still less so that such solution applies across the full width of the claims either as regards the scope of all hVEGF antagonists falling within the descriptions in sub-paragraphs (a) (b) and/or (c) of claims 1 and/or 14 and/or for all non-neoplastic diseases or disorders characterised by undesirable excessive neovascularisation.

Further or alternatively, claims 1 and 14 of the 986 Patent are ambiguous and/or their meaning is uncertain in that the specification does not teach the skilled person the meaning of the words "non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation". Accordingly the claimed invention is not defined sufficiently for the skilled person to determine whether or not the claims are infringed. Further or alternatively, if and in so far as claim 1 of the 986 Patent covers non-neoplastic diseases or disorders characterised by undesirable excessive neovascularisation other than those listed in claim 2, and/or if and in so far as claim 14 of the 986 Patent covers diseases or disorders characterised by undesirable excessive neovascularisation other than those listed in claim 15, then the 986 Patent contains no, or no sufficient, teaching as to

> how to identify such diseases or disorders without undue burden.

Insufficiency – law

153. Section 72(1)(c) of the Patents Act 1977 provides that a patent will be invalid if the specification does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art. As I said in *Zipher v Markem* [2008] EWHC 1379 (Pat); [2009] FSR 1, at [362] insufficiency is a single objection to the validity of a patent which may arise in different ways. In every case, however, the purpose behind the objection is to prevent the patentee laying claim to products or processes which the teaching of the specification has not enabled in the relevant sense. In that case, at [363] to [374], I summarised the three common types of insufficiency with which the courts have commonly to deal: classical insufficiency, *Biogen* insufficiency or insufficiency by excessive claim breadth, and insufficiency by ambiguity. A much more comprehensive collocation of the relevant authorities is now to be found in the judgment of Arnold J in *Sandvik v Kennametal* [2011] EWHC 3311 (Pat) at [106] to [124]. It is not necessary to attempt the exercise again, or possible to improve on it. One or two points do, however, need to be drawn out in the context of the present case.

154. The first point is concerned with insufficiency by excessive claim breadth. In *Medimmune v Novartis* [2011] EWHC 1699 (Pat) at [458] to [469], Arnold J analysed the judgment of the House of Lords in *Biogen*. I agree with his summary of the key points to emerge from that judgment, at [469]:

> "i) A claim will be invalid for insufficiency if the breadth of the claim exceeds the technical contribution to the art made by the invention. As Lord Hoffmann confirmed elsewhere in his opinion, it follows that it is not necessarily enough to disclose one way of performing the invention in the specification.
>
> ii) The breadth of the claim will exceed the technical contribution if the claim covers ways of achieving the desired result which owe nothing to the patent or any principle it discloses. Two classes of this are where the patent claims results which it does not enable, such as making a wider class of products when it enables only one and discloses no principle to enable the others to be made, and where the patent claims every way of achieving a result when it enables only one way and it is possible to envisage other ways of achieving that result which make no use of the invention. "
>
> iii) The patent in *Biogen v Medeva* was invalid because it was an example of the second class of objectionable claim."

155. That summary is of course, as Arnold J later recognises, subject to the explanations in the subsequent House of Lords cases of *Kirin Amgen v Hoechst Marion Roussel* [2004] UKHL 46; [2005] RPC 9 and *Generics v Lundbeck* [2009] UKHL 12; [2009] RPC 13. In *Kirin Amgen*, Lord Hoffmann explained further the notion of a principle of general application:

> "112. In my opinion there is nothing difficult or mysterious about [the notion of a principle of general application]. It simply means an element of the claim which is stated in general terms. Such a claim is sufficiently enabled if one can reasonably expect the invention to work with anything which falls within the general term. For example, in *Genentech I/Polypeptide expression* (T 292/85) [1989] O.J. EPO 275, the patentee claimed in general terms a plasmid suitable for transforming a bacterial host which included an expression control sequence to enable the expression of exogenous DNA as a recoverable polypeptide. The patentee had obviously not tried the invention on every plasmid, every bacterial host or every sequence of exogenous DNA. But the Technical Board of Appeal found that the invention was fully enabled because it could reasonably be expected to work with any of them.
>
> 113. This is an example of an invention of striking breadth and originality. But the notion of a 'principle of general application' applies to any element of the claim, however humble, which is stated in general terms. A reference to a requirement of 'connecting means' is enabled if the invention can reasonably be expected to work with any means of connection. The patentee does not have to have experimented with all of them."

156. *Generics v Lundbeck* was concerned with the specific case of a claim to a single product. That case has no application here.

157. The second point concerns claims with a functional limitation. No doubt conscious that not everything falling within the scope of a claim will achieve the object of the invention, patentees will often seek to limit claims by result. There is nothing wrong with this. Provided the patent specification, with or without the help of the common general knowledge, provides the skilled person with the means of achieving the functional result throughout the breadth of the claim without invention or undue effort, the functionally limited claim will be sufficient.

158. On the other hand, where the patent sets the reader an unduly burdensome task to determine whether an individual product or process has the claimed functional feature, the patent will not be saved from insufficiency by the functional feature. In other words a claim cannot in these circumstances be rendered "insufficiency proof" by claiming only the good ones. Kitchin J, as he then was, said as much in *Novartis v Johnson & Johnson* [2009] EWHC 1671 at [234] after a careful analysis of the judgment of the Court of Appeal in *American Home Products v Novartis* [2001] RPC 8:

> "It follows, in my judgment, that a claim to a class of products said to possess a useful activity must be based upon the identification of a common principle which permits a reasonable prediction to be made that substantially all the claimed products do indeed share that activity. Further, it is not permissible to by-pass that requirement simply by adding a functional limitation which restricts the scope of the claim to all

> the products which do have the relevant activity, that is to say all those which "work". In the case of a claim limited by function, it must still be possible to perform the invention across the scope of the scope of the claim without undue effort. That will involve a question of degree and depend upon all the circumstances including the nature of the invention and the art in which it is made. Such circumstances may include a consideration of whether the claims embrace products other than those specifically described for achieving the claimed purpose and, if they do, what those other products may be and how easily they may be found or made; whether it is possible to make a reasonable prediction as to whether any particular product satisfies the requirements of the claims; and the nature and extent of any testing which must be carried out to confirm any such prediction. "

159. The third point to emphasise is that sufficiency is highly fact specific. In *Kirin Amgen v TKT* [2004] UKHL 46; [2005] RPC 9 Lord Hoffmann put it this way:

> "Whether the specification is sufficient or not is highly sensitive to the nature of the invention. The first step is to identify the invention and decide what it claims to enable the skilled man to do. Then one can ask whether the specification enables him to do it. For example, in *American Home Products Corporation v Novartis Pharmaceuticals UK Ltd* [2001] RPC 159 the patentee claimed that the known drug rapamycin and any of its derivatives could be put to a new use. But the claim for such use of all derivatives was not enabled because only some derivatives could be so used and the specification did not enable the skilled man to identify which they were. The answer may well have been different if the claim was to a new process for making rapamycin and its derivatives or if rapamycin and its derivatives had been new products."

160. Fourthly, it is important to note that sufficiency involves a question of degree. Nowhere is this better expressed than by Kitchin J in *Novartis v Johnson v Johnson* at [236]:

> "Whether the specification discloses an invention clearly and completely enough for it to be performed by a person skilled in the art involves a question of degree. It is impossible to lay down any precise rule because the degree of clarity and completeness required will vary depending on the nature of the invention and of the art in which it is made. On the one hand, the specification need not set out every detail necessary for performance. The skilled person must be prepared to display a reasonable degree of skill and use the common general knowledge of the art in making routine trials and to correct obvious errors in the specification, if a means of correcting them can readily be found. Further, he may need to carry out 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. On the other hand, he should not be required to carry out any prolonged research, enquiry or experiment: *Mentor Corporation v Hollister Inc.* [1993] RPC 7."

161. Fifthly, where a patent lays claim to efficacy of a therapeutic treatment in a disease, the Boards of Appeal have adopted the approach that it is not necessary for the patent, in order to be sufficient, to demonstrate efficacy in clinical trials. In *T 609/02 Salk Institute* at [9] of the Reasons, the Board said this:

> "Where a therapeutic application is claimed in the form allowed by the Enlarged Board of Appeal in its decision G 5/83 (OJ EPO 1985, 64), ie in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, attaining the claimed therapeutic effect is a functional technical feature of the claim (see G 2/88 and G 6/88, OJ EPO 1993, 93 and 114, Headnote III. and point 9 of the reasons, for non-medical applications, see also T 158/96 of 28 October 1998, point 3.1 of the reasons). As a consequence, under Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application. It is a well-known fact that proving the suitability of a given compound as an active ingredient in a pharmaceutical composition might require years and very high developmental costs which will only be borne by the industry if it has some form of protective rights. Nonetheless, variously formulated claims to pharmaceutical products have been granted under the EPC, all through the years. The patent system takes account of the intrinsic difficulties for a compound to be officially certified as a drug by not requiring an absolute proof that the compound is approved as a drug before it may be claimed as such. The boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical. It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (T 241/95, OJ EPO 2001, 103, point 4.1.2 of the reasons, see also T 158/96 of 28 October

> 1998, point 3.5.2 of the reasons) or, as decision T 158/96 also put it, if there is a "clear and accepted established relationship" between the shown physiological activities and the disease (loc. cit.). Once this evidence is available from the patent application, then post-published (so-called) expert evidence (if any) may be taken into account, but only to back-up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on their own."

162. Mr Waugh relied on two EPO decisions to set this statement in context. The first was T 241/95 *Serotonin Receptor Eli Lilly*. The invention was based on the discovery that an isomer of fluoxetine showed high specificity for the serotonin 5-H_{IC} receptor. The claimed therapeutic indication was the treatment of any condition susceptible of being improved or prevented by selective occupation of that receptor. Not surprisingly, the Board pointed out that selective blocking of a receptor could not itself be regarded as a therapeutic application. At 3.1.2 of the Reasons they said:

> "The discovery on which the invention is based, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a **defined real** treatment of any pathological condition in order to make a technical contribution to the art and be considered an invention eligible for patent protection." (original emphasis)

163. The description listed a number of conditions intended to be treated by the selective blocking. The case turned on whether the skilled person would have means available of assessing whether conditions in addition to those mentioned were within the scope of the claim. The Board concluded on the facts that the skilled person would not.

164. Mr Waugh submitted that this case stood for the general proposition that demonstrating that an antagonist binds a particular site is a pharmacological effect, and is not a sufficient basis for a claim to a therapeutic application. That may be so, but it is not a fair reflection of the position in the present case. The patent in the present case shows that blocking VEGF has an effect on tumor growth *in vivo*. This goes beyond mere knowledge of selective blocking.

165. The second case on which Mr Waugh relied was T 0699/06 *(Morphogenesis/Stryker).* In that case what was at stake was the patentee's general claim to "morphogens". The opposition was based on the suggestion that it was not possible to generalise the results in the patent to all morphogens. The Board was invited to come to the conclusion that later acquired expert evidence did establish that other morphogens within the scope of the claims possessed the asserted technical effect. The Board rejected this suggestion at [26] in the following terms, and held the patent to be insufficient:

> "However, when taking a closer look at the actual disclosure in the various references discussed in document (65), the Board is convinced that not only does this document not contain a disclosure that "the morphogens recited in the claims do demonstrate the technical effects asserted", but, on the contrary,

> that it is not possible to draw any conclusion from one specific morphogen and the biological effects obtained by it to any other morphogen. According to document (65) the generalization of the specific results obtained by the patent with regard to recombinant, mature human OP1 to other morphogens, as intended by the claims, is not scientifically tenable."

166. I do not consider that this decision cuts across the law as stated in *Biogen*. The Board is saying that it was not possible to make a reasonable prediction about the class of morphogens claimed.

Insufficiency -facts

167. I have set out the claimants' broad-ranging pleas of insufficiency above. As it emerged at trial, the case of insufficiency attacked the scope of the claim in two major ways. The first was directed at the fact that the claims extend to all non-neoplastic diseases, the second to the fact that they extend to all VEGF antagonists. Under each of these heads, the claimants contend that the claim is insufficient on the grounds of claim breadth, and then make a number of subsidiary but important points based on classical insufficiency. They further contend that there is insufficiency by ambiguity in respect of the definition of diseases.

All non-neoplastic diseases – breadth of claim

168. The claimants say that it was not possible to make a reasonable prediction from the data in the patent that anti-VEGF therapy would be effective in the whole range of diseases claimed. Accordingly they say that the patent is insufficient for undue breadth of claim. Genentech say that the patent discloses a principle of general application as regards the relevant claim integer, and accordingly justifies a claim of this breadth.

169. Given that there were several rounds of expert evidence in this case, it is fair to remark that the evidence on this issue was extracted in an unorthodox and unsatisfactory fashion. Mr Tappin complained in his final speech that the claimants' case on this point was not put to his principal expert, Professor Shima. He also submits that, given that this is another issue on which Professor Harris' oral evidence differed from that in his expert reports, the effect of the omission to put the case to Professor Shima meant that Professor Shima had no opportunity at all to deal with the case being advanced. Instead the claimants put their case on this point to Dr Paleolog, the arthritis expert, who was plainly somewhat out of her comfort zone in dealing with this broader subject matter. Moreover it was Professor Shima and not Dr Paleolog who had covered this topic in the written evidence. Nevertheless, no application was made to recall Professor Shima after Professor Harris had given evidence. I therefore have to deal with the issues on the evidence which has been adduced, giving appropriate weight to the unchallenged evidence of Professor Shima, the newly introduced evidence of Professor Harris, and the evidence of Dr Paleolog.

<u>Professor Shima's evidence</u>

170. Professor Shima's evidence in his first report was that, as early as the mid 1980s, the general view in the art was that both tumour and non-tumour neovascular diseases were linked by a common thread, namely angiogenesis, and that if you could suppress tumour growth you would expect to be able to use the same anti-angiogenic strategy to treat non-neoplastic diseases. He went on to say that the data in the patent provided the first proof-of-concept that a VEGF antagonist can be used to reduce tumour angiogenesis and the rate of tumour growth, and would have provided the skilled team with significant confidence that such an antagonist can also be used in non-tumor neovascular settings.

171. In Professor Shima's second report he went slightly further:

> "VEGF was known to be widely expressed by many different cell types and the papers I refer to at paragraph 57 of my First Report suggested that it was found in the right time and place to be driving angiogenic growth and disease. Moreover, VEGF binding sites had been shown (in animal models) to be located on vasculature all throughout the body. Coupled with the proof-of-concept data in the Patent which demonstrated that VEGF was necessary for angiogenesis in tumors, the skílled team would therefore have thought it likely that VEGF was a wide-acting factor that would present a viable target for anti-angiogenesis therapy in any context. Further evidence from specífic animal models would be required before a therapeutic product could progress into clinical trials for any particular disease state, but the data in the Patent would have provided the skilled team with a great deal of confidence that the strategy would work for any neovascular disease."

172. In cross-examination, as a part of the claimants' case of obviousness, it was put to Professor Shima that positive results in a mouse xenograft test would give one every reason to think that the VEGF antagonism would work in at least some diseases characterised by excessive neovascularisation. He did not disagree. Thus, far from it being put to Professor Shima that he had been wrong to generalise from the cancer results to non-neoplastic diseases, it was put to him that, at least for some such diseases, he was right.

173. More generally, it was suggested to Professor Shima that it was fanciful to suppose that one agent would be suitable to treat all non-neoplastic conditions. He did not accept that suggestion. In his view, if neovascularisation was a part of a disease, and you had something which you knew was effective in inhibiting angiogenesis, it was plausible to think you could treat that disease.

Dr Paleolog's evidence

174. Dr Paleolog's expert report dealt principally with example 6 of the patent. She also expressed the view that, Examples 4 and 5 of the patent (even without the benefit of example 6) would have encouraged the skilled team to test whether VEGF blockade would inhibit angiogenesis in RA and cause them to expect success in those models, thereby pointing to the usefulness of VEGF blockade in therapy. Her evidence was that Kim 1993 had led her group to test VEGF inhibition in models of arthritis.

175. At the outset of her cross-examination Dr Paleolog was asked to compare the main features of rheumatoid arthritis in comparison to cancer. She agreed that there was a lesser role for inflammation in cancer than in RA. She also agreed that, despite common features, the skilled person would not think that the vasculature in RA and tumours were "the same". Dr Paleolog also accepted in very general terms that the factors at work in cancer and RA were not "the same".

176. Dr Paleolog did accept that successful treatments for cancer and RA were not interchangeable:

> "Moving on from the date of the patent, it is known TNF-alpha is extremely important in rheumatoid arthritis.
>
> A. That is correct.
>
> Q. And agents against TNF, which work well in rheumatoid arthritis, have been found to be ineffective in cancer.
>
> A. That is my understanding, yes.
>
> Q. That is an observation that one can make now quite a few years on from the date of the patent. But it illustrates something that would have been realised at the date of the patent without knowledge of specific factors. Factors which would be effective to treat rheumatoid arthritis by antagonising them would not necessarily work for tumours and vice versa.
>
> A. That is true, yes."

177. These answers did not seem to me to take matters much further. Rheumatoid arthritis has a very considerable inflammatory component as well as an angiogenic one. One would not expect an anti-inflammatory drug to work for cancer. However, later she was asked about the extent one could extrapolate from data on tumours to RA:

> "Q. Can I suggest to you, doctor, that it is unsafe and unscientific to extrapolate from something you know about a tumour to rheumatoid arthritis, because of the differences between the tumour state and rheumatoid arthritis that I discussed with you right at the beginning of this discussion, i.e. the different constituents of the pannus in the tumour and the differences in the vasculature and the difference in the originating cause. You may hypothesise that what holds for a tumour holds for rheumatoid arthritis, but it is not really scientific to use it in sort of inductive reasoning.
>
> A. I do not think I would agree with that, that it is not scientific. I think it is a valid scientific hypothesis which underlies many scientific studies to try and extrapolate from one diseased condition to another."

178. The contrast in the question is between inductive reasoning on the one hand, and a mere hypothesis on the other. A reasonable prediction lies somewhere between these extremes.

179. Mr Waugh relies in particular on the following passage of Dr Paleolog's cross-examination where she was being asked about her criteria for embarking on clinical trials. These were (1) that the molecule is present in the given disease, (2) that suppressing the activity of the molecule leads to a reduction in a functionally relevant laboratory response, and (3) that suppressing the activity in an *in vivo* model leads to a reduction in a functionally relevant response. She answered as follows:

> "Q. For conditions [such as atherosclerosis and psoriasis] where VEGF had not been demonstrated to be present as at the date of the patent, if we look at your three criteria in paragraph 32, none of them would be satisfied, evidently.
>
> A. The criteria that I outline in paragraph 32 are used as a basis for a clinical trial of a particular approach. Whilst I cannot comment on whether VEGF expression was or was not known to be a feature of any of these diseases, I am, I guess, extrapolating that if angiogenesis was part of the process of these diseases, VEGF expression may have been demonstrated. As I said, I do not know specifically for the questions that you are asking.
>
> Q. So you would be building in the additional assumption that all angiogenesis in pathology involves VEGF?
>
> A. I do not think that is an assumption I should be building in, no.
>
> Q. For a condition where VEGF had simply not been demonstrated to be present in the tissue inflicted by the disease, it would be completely unscientific to conjecture that VEGF blockade would be [in]effective for treatment?
>
> A. If VEGF expression has not been demonstrated, then I do not think VEGF inhibition would be proposed as a therapeutic approach.
>
> Q. No, it would be completely unscientific to make any sort of prediction that it would be effective.
>
> A. That is true."

180. I think that viewed with her other evidence, Dr Paleolog's position overall was that the patent would not enable one to deduce that VEGF therapy would definitely be effective in treatment of non-neoplastic diseases. One would need first to confirm whether VEGF was expressed in the disease. But I do not think that she qualified her more general evidence that the skilled team would still be encouraged by data in the patent to expect success in animal testing, and thereby success in therapy.

Professor Harris' evidence

181. In Professor Harris' first report he made clear that he accepted that it was logical to assume that a blocker of angiogenesis would have potential therapeutic application in more than one disease:

> "A number of diseases were thought to be angiogenesis dependent and it was thought that the same angiogenic and antiangiogenic molecules would have a central role in both 'normal' angiogenesis and in disease (hence the relevance of work on pathological angiogenesis (e.g. cancer, angiogenic eye diseases and rheumatoid arthritis) to embryonic angiogenesis and vice versa). It was therefore logical to assume that a blocker of angiogenesis would have potential therapeutic application in the treatment of more than one disease."

182. Thus far Professor Harris' evidence seemed broadly in line with that of Professor Shima, with a possible question mark over the number of diseases for which it would be possible to make the generalisation. In his second report Professor Harris expressly agreed with Professor Shima that angiogenesis was seen as the common thread in a range of neovascular diseases. He pointed out that there was a quantitative difference in intensity between angiogenesis induced by tumours compared to other types of neovascularisation, leading to a belief that blocking angiogenesis in tumours might have a proportionately greater effect in tumours then in other diseases. His position in his third report was expressed in this way:

> "I do not believe that one can extrapolate from the cancer data of the Patent to conclude that VEGF antagonism would be effective in the treatment of all other angiogenic diseases. The tumour data of the Patent (repeated in Kim 1993, ref. 38) are important in demonstrating that blocking VEGF-driven angiogenesis inhibits growth of these tumours. These data show that in these cancers, blocking a single factor, VEGF, has a beneficial effect and so give additional encouragement to investigate whether the same is true in other angiogenic diseases e.g. to investigate the role of VEGF in RA. However, for the reasons I set out in my first report, I believe that by 1992 the skilled person would already have considered VEGF as a leading candidate for playing a central role in pathological angiogenesis. I do not believe that Examples 4 and 5 add materially to the expectation that VEGF antagonism would be therapeutically effective in other angiogenic diseases. This would need to be investigated individually for each disease irrespective of the data in Examples 4 and 5."

183. The distinction which Professor Harris is drawing here is a fine one. The examples in his opinion, do give additional encouragement to investigate the role of VEGF in non-neoplastic diseases, but do not add materially to the expectation that VEGF would be therapeutically effective in them. He seemed to accept that that the patent does make it plausible that VEGF antagonism would work in non-neoplastic diseases. That view is consistent with his first report, in which he had said that it was logical to assume

that a blocker of angiogenesis would have potential application in more than one disease.

184. When Professor Harris came to give evidence on oath, he interrupted his cross-examination to explain that neovascularisation was very different from disease to disease. He went as far as to put forward the view that one needed to be clear before using the term neovascularisation whether one was talking about neovascularisation in cancer or in some other disease because they were very different in terms of mechanism and appearance under the microscope. He said "*the actual mechanism of new blood vessels might be incredibly different between those until you actually look at it and find out what the mechanism is*."

185. Professor Harris nevertheless accepted that people in the art believed that there would be a commonality between cancer and non-cancer diseases. His reservation was that, until the work was done, it was not proven. As his cross-examination progressed, he developed the idea that it was not necessarily going to be the same anti-angiogenic molecule which blocked the angiogenesis, and not to the same extent, from disease to disease. In diseases other than cancer, where VEGF expression is less extensive and less persistent, he suggested that you would not be able to predict that anti-VEGF therapy would work on the basis that it worked for cancer. The reason was that the lower levels of expression made it less likely that VEGF was a major driver of the disease.

186. Commenting on a part of Dr Paleolog's evidence, Professor Harris said this:

> "It is completely not logical that you would show that VEGF is important in cancer. You have another disease, and it says -- there are questions about the molecules involved in arthritis. The ones that were known to be involved in angiogenesis were not VEGF in fact. They were much smaller in molecular weight. So the very evidence she cites shows conclusively that the molecule that was first isolated in 1980 was not VEGF. So why would you then think a VEGF antibody would work when you saw it worked in cancer? I just did not follow the logic of that part of the evidence….You have looked at it in cancer. It is high in cancer. You can see clearly some of these factors are not VEGF in the joints. Why is that? That does not follow in logical arguing at all, that comment there, to me. She actually says that VEGF had not been shown to be expressed in RA. I keep coming to the point that in cancer we knew a lot about it. Every other disease we knew nothing about - atherosclerosis, 1997; psoriasis, 1994. Dr. Paleolog says we did not know about it. What we did know was that it was not VEGF. What I do not understand why you could say because it worked in cancer, it would then work in this disease for which there was no evidence."

187. This rather trenchantly expressed evidence is not that easy to reconcile with other passages of Professor Harris' evidence. For example, in the context of obviousness he said this:

> "Although the concept of using Kim's monoclonal antibodies to investigate and treat a non-neoplastic disorder characterised by undesirable neovascularisation was obvious and this would have been an interesting avenue to pursue, there was less data that such diseases were dependent on angiogenesis and VEGF in the same way as cancer. Accordingly, before investigating the effect of blocking VEGF antibodies in a disease model for a disease other than cancer, one would ideally have wanted to demonstrate first the association between the disease in question and upregulation of VEGF activity (i.e. by demonstrating VEGF overexpression). This would have been relatively straightforward to investigate and, assuming that one had patient samples available for analysis, could have been accomplished within a few months. A positive finding would have heightened one's confidence that a VEGF antagonist could be used to treat the disease in question."

188. Given that Professor Harris' evidence was that one could deduce from Kim 1992 that anti-VEGF antibodies would prevent angiogenesis in tumours, it represented to him a teaching equivalent to the patent in suit. It is not entirely clear, therefore why he thought in the case of Kim 1992, but not in the case of the patent, that that the skilled person would have any confidence at all, absent proof of VEGF upregulation, that a VEGF therapy could be used to treat non-neoplastic disease. If his evidence given in cross-examination is to be accepted, such a conclusion would be completely illogical. This is an area where I have had to treat Professor Harris' evidence with particular caution.

Principle of general application?

189. I consider that the patent discloses a principle of general application within the meaning of the authorities insofar as it claims anti-VEGF antagonism as a treatment for all non-neoplastic diseases. The tumour data in the patent establish that VEGF blockade is likely to be a successful strategy for treatment in cancer. The skilled reader would appreciate that the reason it is likely to be successful is because blocking VEGF is a sufficient intervention to prevent angiogenesis, at least in models of cancer. It is common ground that it is possible to extrapolate that reasoning to at least some non-neoplastic diseases. Thus Professor Harris explained why he thought that VEGF antagonists would be likely candidates for treating diabetic retinopathy in these terms:

> "Other than cancer, I believe that diabetic retinopathy (and other eye diseases associated with neovascularisation) would have been the most promising indication for development of a VEGF antagonist. By 1992 the association between diabetic retinopathy and angiogenesis was well established. It was known that the proliferation and permeability of blood vessels was a hallmark of diabetic retinopathy and a number of other

> eye diseases causing blindness. Further, it was known that laser surgery to reduce the vascular proliferation in the eye could be used to treat these diseases."

190. It is implicit in this evidence that Professor Harris regarded it as possible to make a fair prediction that VEGF blockade would work for diabetic retinopathy. His reasoning is dependent on it being an angiogenic disease. As to whether it would be necessary, before making such a prediction, to have evidence that VEGF was upregulated in the disease, he said that this was something which one would have "ideally" wanted and which would have "heightened his confidence" that a VEGF antagonist could treat the disease in question. It was clearly not an obstacle to making a fair prediction.

191. It would of course not be possible to make a fair prediction if the evidence showed that angiogenesis was significantly different in character from disease to disease, so that entirely different molecules might be the target for VEGF antagonism in different diseases. In my judgment the evidence did not show this at all. Professor Harris' more extreme evidence on this topic was not supported by any references from the literature or put to any Genentech witness, and I am unable to accept it. Once the inventors had shown that blockade of VEGF was sufficient to prevent pathological angiogenesis in tumours, it was reasonable to predict that it would be sufficient in other diseases. Of course the patent had not proved that this was the case – but it does not have to. If the patent is to be held insufficient, therefore, it cannot be simply on the basis that it claims a therapeutic effect in all non-neoplastic diseases.

Specific diseases and disorders

192. Professor Harris also gave evidence about some specific non-neoplastic diseases or disorders. These were RA, tissue transplantation, pre-eclampsia and atherosclerosis. These points raise classical insufficiency objections.

Rheumatoid arthritis

193. Professor Harris pointed out that the role of angiogenesis in RA "may not be as pivotal as in cancer or diabetic retinopathy". He said that Example 6 of the patent does not show that VEGF was causative in RA or show that blocking VEGF "would be in any way beneficial in rheumatoid arthritis". He said he would require more evidence (than was contained in the patent) before accepting that VEGF antagonism had a role to play in treating RA. That of course does not establish insufficiency in the circumstances of the present case. I will consider separately the points made by the claimants as to whether specific categories of antagonist are ineffective against RA.

Other tissue transplantation

194. Professor Harris said that tissue transplantation (other than corneal transplantation) requires new blood vessel growth in order to avoid rejection of the transplanted tissue. I have touched on this issue when dealing with construction above. In the cases contemplated by Professor Harris the disorder is not one characterised by excessive *undesired* neovascularisation and so is not within the claims.

Pre-eclampsia

195. As to pre-eclampsia, Professor Harris' point was that it is now known that a soluble form of the Flt-1 receptor is found in elevated amounts in the placenta. Accordingly, administering a VEGF antagonist such as a soluble Flt-1 receptor would make matters worse, as it would increase the abnormal levels of Flt-1. He also pointed out that hypertension and proteinurea are now known to be side effects of pre-eclampsia. As hypertension and proteinurea are symptoms of pre-eclampsia, treatment with VEGF therapy would make matters worse. However, I have already pointed out that there was no evidence that pre-eclampsia was a disease characterised by excessive undesired neovascularisation. The point is therefore only illustrative of the fact that treatment with VEGF antagonist may have unwanted effects.

Atherosclerosis

196. It is common ground that atherosclerosis is a disease characterised by undesirable excessive neovascularisation. Professor Harris' point about atherosclerosis was that there would be too high a risk of serious side effects. Atherosclerosis is a disease of the arteries in which the arteries become blocked by atheroma. New blood vessels can grow into the atheroma and cause the vessels to burst. In principle it would make sense to target the growth of these vessels. However, one way in which the body responds to blockage of the arteries is by the outgrowth of capillary blood vessels. This is an important process in patients recovering from a stroke. Accordingly, there is a countervailing consideration which it is necessary to take into account.

197. Professor Harris was adamant that it would be absurd to treat atherosclerosis with VEGF therapy. He points out that the Summary of Product Characteristics for Avastin, which is Genentech's VEGF therapy for colorectal cancer, provides special warnings for patients who develop arterial thromboembolitic events.

198. Professor Shima gave a more moderate account of the position. He explained that there were two schools of thought. One school adheres to the view that you need VEGF to heal, the other saying that when the plaque develops it has to have neovasculature associated with it. Dr Paleolog confirmed that there were two schools of thought as well.

199. I do not consider that the evidence establishes that anti-VEGF treatment generally is ineffective for treatment of atherosclerosis. It is true that regulatory approval of such a treatment would be, on the evidence, unlikely due to the risk of unacceptable side effects. But the evidence does not establish that the VEGF antagonism would not deal effectively with angiogenesis in the context of atherosclerosis. I will deal separately below with the allegation that a particular antagonist, anti-Flk1, is ineffective against atherosclerosis.

Undue research and experimentation

200. Hovering around the case was a suggestion that the process of getting the invention to work in the form of an approved treatment for diseases such as RA involved too much by way of research and experimentation. The claimants pointed to the absence of any such approved treatment. I do not think that this is an adequate evidential approach to an allegation of classical insufficiency in a case such as this, as it imposes too high a standard. What the claimants need to show is that the skilled person would not be able to establish without undue burden whether a given anti VEGF therapy has an

effect on angiogenesis in a given disease. The evidence was not really directed to this issue at all. I reject this allegation as well.

All antagonists

201. This is the second major prong of the claimants' insufficiency attack. As I have trailed earlier in this judgment when dealing with infringement, the claimants say that if the claims cover anything less than the full extra-cellular domain of the VEGF receptor, then they are insufficient. As I have held that the claims do so extend, I need to go on to consider the substance of this insufficiency attack.

Truncated forms of the hVEGF receptor

202. The claimants accept that it would be within the capability of the skilled person armed with the patent to make an isolated hVEGF receptor for use in accordance with the invention. It is after all described in Example 3 by reference to the extra-cellular domain of Flt1. They contend, however, that it would involve an undue burden of research to discover more limited sections of the isolated VEGF receptor which would work as VEGF antagonists as well. These attacks are essentially aimed at the claim integer "isolated VEGF receptor".

203. Professor Harris told me that the work involved in making the isolated hVEGF receptor from the ECD of Flt1 would take about 18 months. Beyond the length of time involved, however, he did not point to any particular difficulties in so doing. His evidence about refining the receptor further was in the following terms:

> "To go beyond looking at the whole ECD would have required the production of fragments of the ECD, and the testing of such fragments to ascertain their ability to bind VEGF. The skilled addressee would have needed to perform a series of experiments, refining that series as each set of results was obtained, so as to focus on the part(s) of the ECD that are necessary for the protein to retain its affinity for VEGF. This would have required the cloning of deletion mutants of the ECD of the receptor, the expression of these proteins in a suitable host, and the subsequent purification and testing of the protein obtained.
>
> The skilled person would have appreciated that arriving at such a smaller fragment presented a number of challenges and there was no guarantee that a smaller fragment could be identified that would fold correctly and show good VEGF binding. In 1992 I would have expected that a project aimed at investigating the structure-function relationship of the receptor and identifying a fragment which could work as a VEGF antagonist would require several years work"

204. Professor Harris illustrated his evidence by reference to the efforts of groups of workers at Genentech and elsewhere who investigated the function and binding ability of parts of the ECDs of isolated VEGF receptors between 1996 and 1998. He explained graphically that one group, Davis-Smyth et al, had arrived at conclusions as

to where the relevant domain boundaries lay which were different to those later identified by Cunningham et al. Davis-Smyth's group concluded that the combination of domains 1 and 2 was incapable of binding, but that the combination of domains 1, 2 and 3 bound with the same affinity as full length Flt1. By contrast Cunningham concluded that domains 1 and 2 were sufficient to achieve VEGF binding (albeit at a lower binding affinity than the full ECD), but the addition of domain 3 restored high binding affinity. Cunningham et al address this discrepancy in their paper:

> "While this manuscript was in preparation, Davis-Smyth et al. reported that soluble secreted domains 1+2 of Flt-1 were unable to bind VEGF or PlGF. However, binding was achieved with the addition of domain 3 to their fusion protein. The reasons for the discrepancy between our results and theirs probably lies with the delineation of domain 2. Our domain 1+2 construct possesses 10 additional amino acids on the C-terminus which may add to the structural integrity of domains 1+2 or alternatively directly participate in ligand interactions. Davis-Smyth et al., predict that these amino acids would constitute the extreme N-terminus of domain 3."

205. Professor Harris says this highlights the pitfalls of the kind of work involved, and the serious impact of discrepancies in deciding where to draw the domain boundaries.

206. Whilst there is theoretical force in Professor Harris' point, I do not think it leads to a finding of insufficiency. Firstly, one has to bear in mind that the industry in question is one where careful experimentation with a degree of trial and error, sometimes extending over months and years, is entirely normal. Secondly, it is not necessary, in order to work the invention to identify the minimum binding domain of the receptor. The fact that one can continue to refine one's receptor beyond the point at which one has a viable construct does not, as it seems to me, matter. A patent is not insufficient because it may take much work to develop the most elegant or refined embodiment of its inventive concept. If one were to carry on with the refinement, one would still be making use of the principle disclosed in the patent, working towards an improved embodiment of it. The position was summarised in the cross examination of Professor Harris in this way:

> "Q. And the point you are making is that Cunningham found that a construct consisting of what they called domains 1 and 2 bound VEGF.
>
> A. Yes.
>
> Q. And the difference between them and Davis-Smyth lay in where they had cut between domains 2 and 3.
>
> A. Yes.
>
> Q. I think you go on and you make similar points relating to the work done on the Flk receptor as well.
>
> A. Yes.

> Q. All of these groups were able to prepare fragments of the receptor extracellular domain which bound VEGF using standard techniques.
>
> A. Yes.
>
> Q. They could have continued using the same standard techniques to further refine their fragment had they wished to do so.
>
> A. Yes.
>
> Q. I think your point is that you say there would not have been any motivation to do that because the Flt domain 1 to 3 construct produced by Davis-Smyth and also by Cunningham would have been regarded as suitable for taking into development.
>
> A. Yes.

207. Accordingly, I reject this ground of insufficiency as well.

The work done on VTE

208. The claimants also rely by way of illustration on the work done to produce their own construct, which I have described when dealing with infringement. Plainly the specification does not provide directions as to how to make the alleged infringement. Professor Harris explained that he regarded aspects of the product as very clever. He said that the combination of high affinity which it achieves and its improved pharmacokinetics could not have been predicted. Moreover he says that it was the result of a major research effort. I accept all that evidence.

209. The fact that a claim may extend to further inventions which make use of the principle disclosed in a patent does not necessarily render the patent insufficient. I do not consider that the fact that the claim extends to VTE makes the present patent insufficient, even in the light of the evidence which I have accepted. Lord Hoffmann put it pithily in *Kirin-Amgen* at [117]:

> "The choice of a particular form of an integer falling within the terms of the claims may improve the way the invention works and be in itself an inventive step. The specification is not insufficient merely because it does not enable the person skilled in the art to make such an invention. The use of the improvement is still a way of working the original invention."

210. All that applies here. The patent is not insufficient because it extends to VTE.

Anti-Flk1 treatment in RA

211. In his third report Professor Harris drew attention to a statement in a paper by Luttun et al that inhibition of the VEGF receptor Flk1 did not affect arthritis, indicating that

inhibition of Flk1-driven angiogenesis alone was not sufficient to halt disease progression. Similar observations were relied on in a paper by De Bandt et al.

212. Luttun's study was in a mouse CIA (collagen induced arthritis) model of RA. It showed that treatment with anti-Flt1 reduced the incidence of joint disease by 60%, but that treatment with anti-Flk1 was ineffective.

213. Genentech have two answers to this evidence of the ineffectiveness of anti-Flk1 therapy. The first is that advanced through the evidence of Dr Paleolog, that the experiments reported did not treat *established* RA. The treatment was administered before the artificially induced RA had had a chance to establish itself. According to Dr Paleolog, the best model for determining the efficacy of the treatment would be to allow the RA to become established, and then administer the treatment.

214. I was not persuaded by the evidence of Dr Paleolog that the evidence contained in the Luttun and De Bandt articles can be discounted on this first basis. Although the treatment was administered in part when the disease was developing, it continued after it had developed. The treatment was therefore given every opportunity to work.

215. The second basis on which it is sought to undermine the evidence in the Luttun and De Bandt articles is that they do not measure angiogenesis, merely the swelling and redness in the joints. The suggestion is that the treatment may be tackling the angiogenic component of the disease but not the inflammatory one. Dr Paleolog pointed out in re-examination that it was the case that the articles measured swelling and redness not angiogenesis. Professor Harris accepted that this was so as well.

216. Given where the burden on this issue lies, I do not consider that it is established that claim 1 is insufficient insofar as it extends to anti-flk1 as a treatment for RA by blocking angiogenesis. The evidence does not show that the treatment is ineffective to treat angiogenesis.

Anti-VEGF antibodies in RA

217. The claimants also contend that the evidence shows that anti-VEGF antibodies are ineffective in RA. De Bandt (above) shows that treatment with anti-VEGF antibodies merely produced a transient effect in delaying the onset of clinical symptoms, reverting to mirror the control after a few days. Lu et al showed that while the antibodies were effective during the early stages, mice treated for established disease failed to show improvement. In Sone et al some efficacy was shown for anti-VEGF antibodies.

218. I was not persuaded that this material, considered as a whole, established insufficiency in respect of anti-VEGF antibodies for RA.

Anti-Flk1 in atherosclerosis.

219. Luttun et al also reports results on anti-flt1 and flk1 in a mouse model of atherosclerosis. The authors report that, whilst the former appeared to work (although independently of angiogenesis), the latter was ineffective. In cross-examination Dr Paleolog was shown these conclusions, but not asked to express her agreement with them, far less to accept that they demonstrated that anti-Flk1 treatment was ineffective

in atherosclerosis. I do not consider that this point takes the claimants' case of insufficiency any further.

Ambiguity as to disease

220. The claimants said that there was difficulty in determining what was a disease or disorder characterised by undesirable excessive neo-vascularisation. In the end the evidence did not support this. Mr Waugh relied on a passage of cross-examination in which Professor Shima accepted that a clinical trial would be necessary to know whether one has a successful treatment. But that is an entirely separate question. There was no evidence that the skilled addressee would have any difficulty in determining whether a given disease would fall within the terms of the claim as I have construed them.

Conclusion on insufficiency

221. All the insufficiency attacks fail. It is not necessary for me to consider an amendment proffered in the course of trial to exclude the category (b) antagonists from the claims.

Overall conclusion

222. The patent is not invalid on any ground alleged. The patent is infringed by VEGF Trap Eye.