Neutral Citation Number: [2013] EWCA Civ 93

Case No: A3/2012/0931 & 0933

**IN THE COURT OF APPEAL (CIVIL DIVISION)**
**ON APPEAL FROM THE HIGH COURT OF JUSTICE**
**CHANCERY DIVISION (PATENTS COURT)**
**The Hon Mr Justice Floyd**
**[2012] EWHC 657 (Pat)**

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 21/02/2013

**Before:**

**LORD JUSTICE LONGMORE**
**LORD JUSTICE MOSES**
and
**LORD JUSTICE KITCHIN**

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**Between:**

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| **(1) Regeneron Pharmaceuticals Inc (a company incorporated under the laws of New York, USA)** | **Appellant in Action 0931** |
| **(2) Bayer Pharma AG (a company incorporated under the laws of Germany)** | **Appellant in Action 0933** |
| **- and -** | |
| **Genentech Inc (a company incorporated under the laws of Delaware, USA)** | **Respondent** |

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Andrew Waugh QC and Thomas Mitcheson (instructed by Simmons & Simmons) appeared for Bayer
Mark Chacksfield (instructed by Bird & Bird LLP) appeared for Regeneron
Michael Tappin QC and Miss Isabel Jamal (instructed by Marks & Clerk Solicitors LLP) appeared for Genentech

Hearing dates: 17/18/19/20 December 2012

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# Judgment

## Lord Justice Kitchin:

## Introduction

1. These are appeals from the judgment of Floyd J given on 22 March 2012 and his consequential order dated 4 April 2012 in two actions concerning the infringement and validity of EP (UK) 1,238,986 (the patent) owned by the respondent (Genentech).

2. The patent discloses and claims the use of particular agents called human vascular endothelial growth factor (hVEGF) antagonists for the treatment of non-cancerous (non-neoplastic) diseases which are characterised by excessive blood vessel growth (neovascularisation or angiogenesis). It has a filing date of 28 October 1992.

3. The appellants (Regeneron in one action and Bayer in the other) sought revocation of the patent on the grounds of lack of novelty, obviousness and insufficiency. They also sought a declaration of non-infringement in respect of a product called VEGF-Trap which has been developed by Regeneron and which Bayer wishes to sell in the UK for the treatment of neovascular age-related macular degeneration (ARMD), a leading cause of premature blindness. The proceedings were designed to clear the way in advance of launch. Genentech counterclaimed for infringement.

4. The judge rejected all the attacks on the patent, holding the claims novel, inventive and sufficient. He also held that they encompass VEGF-Trap. On this appeal, the appellants submit that, in so concluding, the judge made a number of errors of principle which may be summarised as follows:

    i) *Construction*: The appellants say the judge misconstrued the claims of the patent as not requiring any therapeutic effect on the disease or disorder in question, and that he was inconsistent in his application of his claim construction in considering the various attacks on the patent. They also say the judge wrongly held that the claims encompass any variant of a naturally occurring receptor which retains the ability to bind VEGF and inhibit its activity.

    ii) *Infringement*: The appellants contend that, had the judge properly construed the claims, he would have found that VEGF-Trap does not fall within their scope.

    iii) *Novelty*: The appellants argue that the judge ought to have found that Kim 1992 discloses VEGF antagonists in the form of antibodies and their use for treating relevant diseases and disorders. The patent merely provides more information about that known use, and this cannot found novelty.

    iv) *Inventive step*: The appellants say the judge applied the wrong test in assessing whether it was obvious to take the step from the prior art to the invention. Further, he should have held the patent obvious because it was not plausible that all VEGF antagonists would be useful in the treatment of non-neoplastic neovascular diseases.

v) *Sufficiency*: The appellants argue that the judge's conclusions are based upon an inconsistent approach to the interpretation of the claims and that, on his own factual findings, he ought to have held the claims insufficient. Despite being framed as a medical use patent, the claims are entirely speculative and cover a huge range of non-neoplastic diseases and disorders without the experimental work needed to support them. More specifically, some non-neoplastic neovascular diseases cannot be treated with VEGF antagonists; some VEGF antagonists are not therapeutically active; and the patent imposes on the skilled person an undue burden to establish which antagonists are effective for which disease states. Moreover, VEGF-Trap does not fall within the claims on their proper interpretation; alternatively, if it does, the claims cover products which they do not enable and are insufficient for this reason too.

## The skilled team and the witnesses

5. The judge identified the skilled team to whom the patent is addressed as being 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.

6. The parties each called two witnesses to assist the judge as to the knowledge and understanding of such a team. Genentech called Professor David Shima and Dr Ewa Paleolog, both as expert witnesses. The appellants called Professor Adrian Harris and Professor Karlheinz Plate, the former as an expert witness and the latter as a witness of fact.

7. Professor Shima is the Professor of Translational Vision Research at University College London Institute of Opthalmology. In 1992 he was engaged in research for his PhD at Harvard University in the laboratories of Dr Judah Folkman and Dr Patricia D'Amore. Dr Folkman's laboratory was at that time, and had been for many years, a focal point for pioneering vascular biology and a leader in identifying novel angiogenic growth factors. The judge found Professor Shima to be a helpful and knowledgeable witness.

8. Dr Paleolog is Reader and Director of Post Graduate Studies at the Kennedy Institute of Rheumatology and in 1992 was a post-doctoral researcher at that Institute. The appellants criticised the evidence she gave about two of the relevant scientific papers but although the judge characterised this aspect of her evidence as unfortunate, he was satisfied it did not affect her evidence as a whole.

9. Professor Harris 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. The judge recognised Professor Harris as a man of outstanding intellect, with enormous breadth and depth of knowledge of his subject. However, he 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. The judge was sure that this was not deliberate, but that it was happening was apparent to him from a number of incidents which, collectively, gave him serious concern about accepting Professor Harris' evidence as a whole. Indeed, the judge came to the conclusion

that he must regard with considerable caution some of the more extreme statements made by Professor Harris in the witness box. These were serious findings and they affected the judge's approach to the key issues in the case, as I shall explain.

10. Finally, the judge heard evidence from Professor Plate who is a Professor and Director at the Edinger Institute at Goethe University, Frankfurt. In 1992 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. No criticism was made of Professor Plate as a witness of fact beyond the fact that he was plainly highly skilled and so not representative of the notional addressee of the patent.

## Technical background and common general knowledge

11. The judge summarised the technical background at [4]-[16]. I gratefully adopt the following aspects of that description which have a particular bearing on the issues arising on this appeal. I begin with the structure of blood vessels, angiogenesis and neoplastic and non-neoplastic diseases:

> "*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."

12. The judge then turned to explain the nature of antigens, antibodies and receptors. I need say little about antigens and antibodies save that, as the judge noted at [9], antibodies are important in cell biology research and in therapy because it is possible to use them to block interactions between ligands and receptors. The judge explained the structure and function of receptors in the field of the invention in these terms at [10]-[12]:

> "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.
>
> 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 …"

13. That brings me to the common general knowledge concerning angiogenesis. This important subject was addressed by the judge from [57]-[88]. First, as a result of work pioneered by Dr Folkman and his colleagues at the Children's Hospital, Boston, it was generally accepted that all neovascular diseases were linked by the common thread of angiogenesis. Further, a large number of angiogenic growth factors had been shown to have activity in one or more assays. These included FGF, VEGF, PD-ECGF, EGF, TGF-β, TNF-α, angiogenin and angiotropin.

14. As for VEGF, it was known that this 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. Further, receptors for VEGF known as flt-1 and flk-1 had been identified.

15. The known selectivity of VEGF for endothelial cells did not, however, mean its inhibition would necessarily produce a therapeutic effect. The reason was redundancy, as explained in a review paper by Klagsbrun and D'Amore published in 1991:

> "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."

16. The authors concluded under their heading "Summary and future directions":

> "Finally, although a variety of substances have been demonstrated to block angiogenesis using in vivo assays, none has been demonstrated to function physiologically."

17. In the words of the judge, these authors thought the playing field on which the various factors were arrayed was a more or less level one.

18. Other reviews painted a similar picture. Thus a review by Folkman and Ingber published in April 1992 suggested three feasible strategies for inhibiting angiogenesis: (i) blocking expression from tumour cells of angiogenic factors; (ii) blocking angiogenic factors after they had been released from tumour cells; (iii) preventing endothelial cells from responding to any angiogenic stimulus.

19. A further review published by Folkman and Shing in June 1992 stated:

> "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."

20. Professor Harris and Professor Plate suggested there was some confidence in the field that VEGF would prove to be a factor necessary for angiogenesis. But the judge thought that this was an area where Professor Harris was plainly allowing himself to exaggerate the position. Further, Professor Harris accepted that it was generally accepted that, having regard to the number of angiogenic factors released, devising an anti-angiogenic therapy for tumour growth would be difficult. As for Professor Plate, the judge considered his opinion was attributable, at least in part, to knowledge that Genentech was working on VEGF. The judge regarded this as not being a sound enough technical foundation upon which to base a finding of common general knowledge.

21. The judge expressed his overall conclusion in these terms at [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."

22. This, it seems to me, was a conclusion to which the judge was plainly entitled to come and it provided the foundation for his later findings.

## The patent

23. The specification begins at [0001] with a description of the field of the invention. It is said to relate to VEGF antagonists, to therapeutic compositions comprising the antagonists, and to methods of use of the antagonists for diagnostic and therapeutic purposes.

24. The background to the invention is then described from [0002]-[0009]. The specification explains that endothelial cells are an important component in the development of new blood vessels and proliferate during the angiogenesis associated with tumour growth and a variety of non-neoplastic diseases and disorders including rheumatoid arthritis (RA), psoriasis, atherosclerosis, diabetic retinopathy, retrolental fibroplasia, neovascular glaucoma, hemangiomas, immune rejection of transplanted corneal tissue and other tissues, and chronic inflammation.

25. It is also explained that various naturally occurring polypeptides have been reported to induce the proliferation of endothelial cells, and that such polypeptides include VEGF. The section concludes that, in view of the role of vascular endothelial cell growth and angiogenesis, and the role of these 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.

26. The invention is then summarised in these terms at [0010]:

> "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."

27. There follows a detailed description of the invention which includes the following passage which is of particular importance to the issue of infringement:

> "[0016] 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.
>
> [0017] The term "hVEGF receptor" or hVEGFr" as used herein refers to a cellular [receptor] for hVEGF, ordinarily a cell-surface receptor found on vascular endothelial cells, as well as variants thereof which retain the ability to bind hVEGF..."

28. Two known receptors, flt-1 and flk-1, are described and then, at [0020], the specification continues with this further passage which is also of great importance to the issue of infringement:

> "Variants of hVEGFr also are included within the scope hereof. Representative examples include truncated forms of a receptor in which the transmembrane and cytoplasmic domains are deleted from the receptor, and fusions proteins in which non-hVEGFr polymers or polypeptides are conjugated to the hVEGFr or, preferably, truncated forms thereof…"

29. This section of the specification concludes with a description of the therapeutic uses of the antagonists of the invention. The appellants particularly focus on [0071]-[0072] which identify a wide range of diseases and disorders:

> "[0071] The hVEGF antagonists are useful in the treatment of various non-neoplastic diseases and disorders.
>
> [0072] Non-neoplastic conditions that are amendable to treatment include rheumatoid arthritis, psoriasis, atherosclerosis, diabetic and other retinopathies, retrolental fibroplasias, neovascular glaucoma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, chronic inflammation, lung inflammation, nephrotic syndrome, pre-eclampsia, ascites, pericardial effusion (such as that associated with pericarditis), and pleural effusion."

30. The description concludes with a series of examples. Example 1 describes the preparation of anti-VEGF monoclonal antibodies and their production from A4.6.1

and B2.6.2 hybridoma clones. These antibodies are then characterised in Example 2.

31. Example 3 describes the preparation of a fusion protein comprising the extracellular domain of the flt-1 receptor and the heavy chain of a human immunoglobulin G1 antibody by routine molecular biology techniques.

32. Example 4 describes an important investigation into the effect of the A4.6.1 antibody on three different human tumour cell lines producing VEGF in the mouse xenograft test. In summary, nude mice were injected with tumour cells from one of three different human tumour cell lines. The mice were then injected with various doses of A4.6.1 antibody or a control antibody and the effect on tumour growth after different time intervals was measured. It was found that the A4.6.1 antibody caused a significant decrease in the rate of tumour growth, explained by the judge in non-contentious terms at [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."

33. Example 5 contains an analysis of the direct effect of the A4.6.1 antibody on tumour cells growing in culture. Finally, Example 6 describes an in-vitro test investigating the chemotaxis, that is to say migration, of endothelial cells towards samples of synovial fluid taken from patients with RA and osteoarthritis. Again, it was summarised by the judge in the following non-contentious terms at [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*

34. There were only two claims in issue, 1 and 14. Claim 1 is in conventional Swiss form as permitted under the EPC 1973. Claim 14 is a product for specific use claim as permitted under the EPC 2000. They are in substance the same and so I need only refer to claim 1:

> "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."

## Construction

35. The first issue of construction concerns the meaning of the words "a medicament for the treatment of a non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation".

36. The judge recorded the parties' submissions at [52]:

> "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 disease state. The claimants contend that the phrase under consideration means any disease in which excessive neo-vascularisation is known to be associated with the disease state, whether that neo-vascularisation is causative of the pathology, or caused by it, and whether it is VEGF mediated or not."

37. He was not attracted by the interpretation contended for by either party, and concluded the words should be given their plain meaning:

> "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."

38. The appellants submit that the judge fell into error in holding that the claim does not require that the anti-VEGF treatment must be effective to treat the disease or any of its clinical symptoms, so long as there is some effect on angiogenesis. They continue that while the judge was right to conclude that the claim covers any and all diseases or disorders in which excessive undesired angiogenesis is observed, he was wrong to suggest that the claimed treatments do not have to provide any clinical or therapeutic effect. The claim is to the manufacture of a medicament for the treatment of angiogenic non-neoplastic diseases or disorders, and so a requirement of treatment is at the centre of the claim. It follows that an effect merely on angiogenesis, without a corresponding therapeutic effect, is not enough.

39. I have to say I have some difficulty in following these submissions and in identifying precisely where it is said that the judge has fallen into error. The following points are, I think, material. First, the claim is concerned with non-neoplastic diseases which have, as one of their characteristics, undesirable excessive neovascularisation, that is to say angiogenesis. The angiogenesis must therefore contribute to the pathology of the disease though it need not necessarily be the cause of it. Hence the specification explains in the section to which I have referred at [24] above, angiogenesis is an important component of a variety of diseases of which a number are then identified.

40. Second, the medicament must treat the disease. That is not to say that the medicament must cure the disease; plainly many diseases characterised by angiogenesis cannot be cured. But it must improve the patient's condition, and it must do so by treating the angiogenic component of the disease from which the patient is suffering.

41. Third, the medicament does not have to treat all, or indeed any other, aspects of the disease, of which, in the case of some diseases, such as RA, there may be many. It is only directed at the angiogenic aspect of the disease and its efficacy is derived from its activity as a VEGF antagonist.

42. Against this background, I do not believe the judge's analysis can be faulted. It was not suggested by any party at trial that the claim does not require any therapeutic effect. It clearly does, and the judge so held. But it does not require a medicament which will cure or even treat all aspects of a disease and, in particular, it does not require treatment of those aspects of a disease which are independent of angiogenesis.

*An isolated hVEGF receptor*

43. As the judge observed, the interpretation of this phrase underlies the major issue on infringement. At trial, Genentech argued that the phrase includes fragments and variants of the naturally occurring receptors which retain the ability to bind hVEGF and inhibit its biological activity. The appellants contended the phrase is limited to

complete receptors and nothing less, alternatively to fragments which contain the whole of the extracellular domain or ECD.

44. The judge preferred Genentech's submissions. He considered the interpretation contended for by the appellants was impossible to maintain in the light of paragraph [0020] of the specification which I have set forth at [28] above and, once it was accepted that the claim includes fragments, there was no technical reason to limit its scope to any particular size of fragment provided that it retains the essential ability to bind hVEGF and inhibit its biological activity.

45. On this appeal, the appellants contend that the judge fell into error in that he did not give adequate weight to the fact that there is no reference to a fragment of a receptor in part (c) of the claim, in contrast to the reference to a fragment in parts (a) and (b). The omission of fragments from (c) in contrast to (a) and (b) is, they say, striking. Further, the reader would have reason to think that the omission of fragments from (c) was deliberate. They continue that the use of antibody fragments as potential therapeutics was widely known in 1992; and it was also well known that antibodies could be treated with an enzyme and fragmented into discrete and useful sub-units by clipping at well established internal junction points. This is, they say, in stark contrast to the use of fragments of soluble receptors as potential therapeutics, which was not well known.

46. Moreover, the appellants continue, nothing is taught in the specification about the structure-function relationship of the VEGF receptors that would allow fragments other than the entire ECD to be developed. Apart from the junction between the membrane bound domain and the ECD as used in Example 3, there were no other established internal junction points within receptors which could facilitate or guide a fragmentation programme.

47. The appellants also say that the skilled person would appreciate that to construe the claim more broadly and in the manner contended for by Genentech would render it vulnerable to an attack of insufficiency, and that is a result that the patentee is unlikely to have intended.

48. Attractively though these submissions were presented, I find myself unable to accept them. It is well established that the question is what the person skilled in the art would have understood the patentee to be using the language of the claim to mean. The language of the claim is usually of critical importance but it must be interpreted purposively in the context of the whole specification.

49. In this case it seems to me that the specification makes it clear what the patentee intended the phrase "an isolated hVEGF receptor" to mean. In paragraph [0010] of the specification it is said that the invention as defined in the claims includes "hVEGF receptor and variants thereof". At [0016], it is said there are also included within the scope of the invention hVEGF receptors and fragments and amino acid sequence variants thereof which are capable of binding hVEGF. At [0017], the term "hVEGF receptor" (or "hVEGFr") is defined as referring to a cellular receptor for hVEGF as well as variants thereof which retain the ability to bind hVEGF. Then, at [0020], it is said that variants of hVEGFr are also included within the scope of the invention and that representative examples include truncated forms of a receptor in which the transmembrane and cytoplasmic domains are deleted from the receptor,

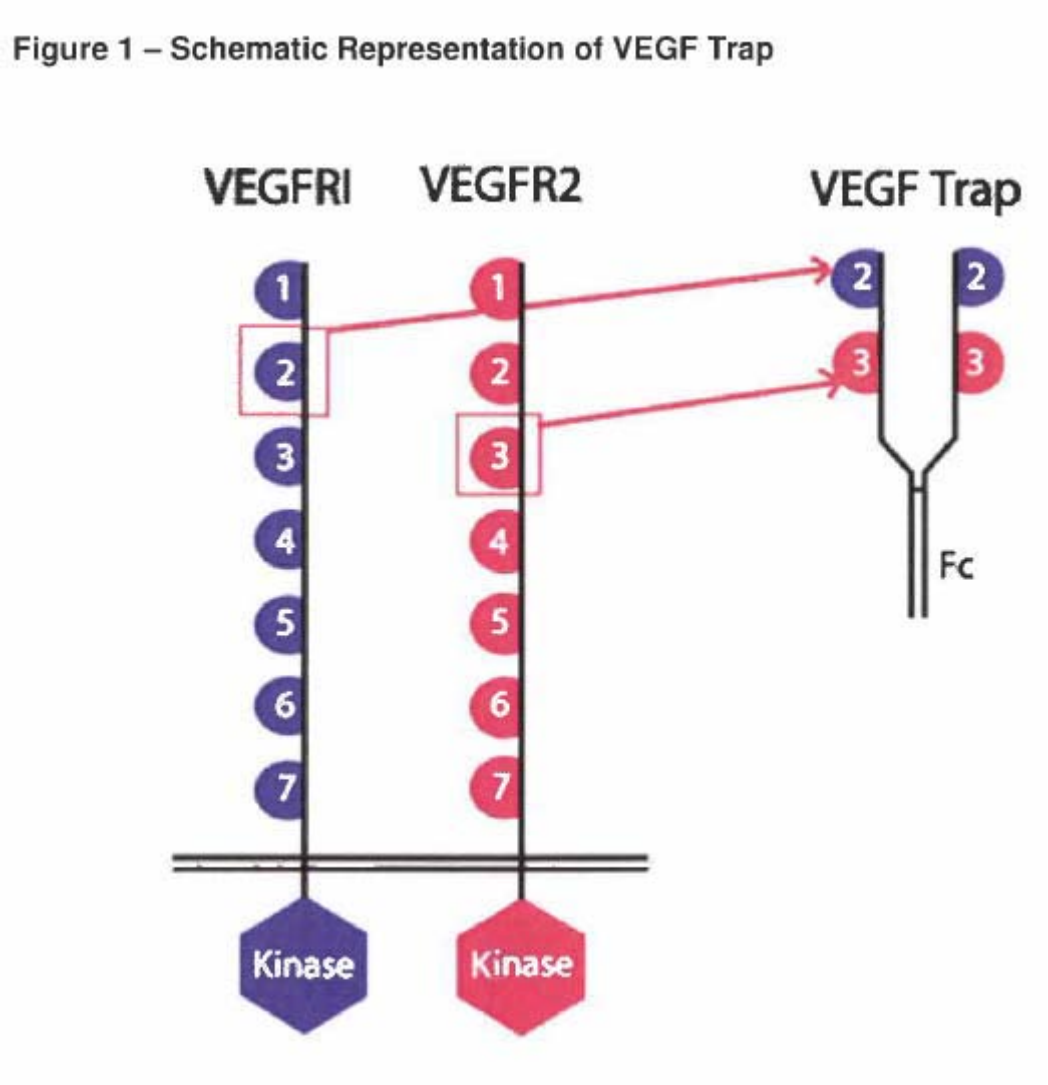
and fusion proteins in which non-hVEGFr polymers or polypeptides are conjugated to the hVEGFr or truncated forms of it.

50. In my judgment all these passages show the patentee intended variants to be included within the scope of the monopoly. Indeed, as Moses LJ said in the course of argument, the linguistic points taken by the appellants on the wording of the claim ignore this dictionary in the body of the specification. Further, as for the submission that the only variants contemplated by the claim are those which contain the whole ECD, paragraph [0020] makes it clear that these are simply representative examples. Moreover, as Professor Harris accepted in cross-examination, the skilled team would understand that what matters for the patentee's purpose is whether the "hVEGF receptor" binds to VEGF and inhibits its biological activity.

**Infringement**

51. VEGF-Trap is a chimeric molecule which contains two monomers, each comprising the amino acid sequence of two individual domains from the flt-1 (VEGF R1) and flk-1 (VEGF R2) receptors linked to the constant region (Fc) of human immunoglobulin G1. It looks like this:

Figure 1 – Schematic Representation of VEGF Trap



52. The appellants accept that VEGF-Trap as a whole is able to bind VEGF and inhibit its biological activity. Nevertheless, they contend it does not fall within the scope of the claims of the patent for two reasons. First, the claims do not include fragments or variants of hVEGF receptors. Second, as a chimera, it is not a fragment or variant within the contemplation of the claims in any event.

53. I am unable to accept these submissions. In my judgment, they both turn on the proper interpretation of the phrase "hVEGF receptor" and, for the reasons I have given, I am satisfied that it does include variants of naturally occurring receptors which retain the ability to bind VEGF. VEGF-Trap as a whole is plainly a variant of both flt-1 and flk-1 and, as the appellants accept, it does retain the ability to bind VEGF and inhibit its biological activity. It therefore falls within the scope of the claims and the judge was right to so hold.

## Novelty

54. The appellants contend that the patent lacks novelty in the light of Kim 1992, an article by Dr K Jin Kim, Dr Napoleone Ferrara and co-workers at Genentech which was published in the journal *Growth Factors* in the summer of 1992. Dr Kim and Dr Ferrara are the two named inventors in the patent.

55. The correct approach to the assessment of novelty was described by Lord Hoffmann in *Synthon BV v SmithKline Beecham plc* [2005] UKHL 59, [2006] RPC 10 at [22]. In summary, 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. Alternatively, if subject matter described in the prior art is capable of being performed and is such that, if performed, it must result in the patent being infringed, the disclosure condition is again satisfied.

56. It must also be borne in mind that, as the Technical Board of Appeal of the EPO explained in decision T609/02 *The Salk Institute for Biological Studies* at [9], where a therapeutic application is claimed in the form allowed by the Enlarged Board of Appeal in decision G5/83 *EISAI*, attaining the claimed therapeutic effect is a functional technical feature of the claim.

57. In the present case, the claims are directed to the use of a VEGF antagonist in the treatment of a non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation. The question to be determined, therefore, is whether Kim 1992 discloses the use of a VEGF antagonist for the treatment of such a non-neoplastic disease or whether it gives clear and unmistakeable directions to use a VEGF antagonist for that purpose.

58. I come then to the disclosure of Kim 1992. This was considered by the judge from [102]-[106]. In summary, Kim 1992 discloses a number of murine monoclonal antibodies, including A4.6.1, with high affinity for VEGF and their use in three functional assays. A4.6.1 was shown effectively to block the VEGF induced proliferation of adrenal cortex capillary endothelial (ACE) cells; completely to block a VEGF induced increase in fluid permeability from blood vessels in the Miles Permeability assay; and completely to block VEGF induced angiogenesis in the chick chorioallantoic membrane (CAM) assay. The latter two assays are *in vivo*

assays. It was, however, common ground between the experts that they did not show that VEGF antagonists would have a therapeutic effect on pathological angiogenesis in neovascular diseases. In that regard, Professor Shima explained that Kim 1992 does not teach the skilled team that VEGF is necessary for pathological angiogenesis or that inhibiting VEGF could be used to treat angiogenic diseases. Similarly, Professor Harris accepted that Kim 1992 was not saying that the anti-VEGF monoclonals had a therapeutic effect in diseases involving excess endothelial cell proliferation or on pathological angiogenesis.

59. Nevertheless, the authors say:

> "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."

60. This echoes a statement in the abstract of the paper:

> "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."

61. The authors conclude:

> "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."

62. It follows from the foregoing that Kim 1992 does not describe the use of monoclonal antibody A4.6.1 (or any of the other antibodies it discloses) in therapy; does not disclose that the inhibition of VEGF using monoclonal antibodies can be used to treat angiogenic diseases; and does not give clear and unmistakeable directions to use monoclonal antibodies for this purpose. To the contrary, the authors explain that they expect their monoclonal antibodies to serve as powerful tools for elucidating the role of VEGF in its various forms and for exploring the structural and functional relationship of VEGF with its receptors. They offer no more than a prediction that these antibodies could have therapeutic potential.

63. The judge summarised his conclusions at [110]-[111] in these terms:

> "110. … 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 …"

64. The appellants contend that, in so concluding, the judge fell into error in a number of respects. First, it is said that he erred in his approach to novelty because Kim 1992 provides the same teaching as the patent in that it discloses the use of monoclonal antibodies to VEGF and the use of such antibodies in the treatment of patients suffering from a non-neoplastic disease characterised by undesirable excessive neovascularisation. At most, they say, the disclosure of the patent provides more information about that use, and cannot confer novelty.

65. I am unable to accept this submission. For the reasons I have given, I do not believe that Kim 1992 provides the same teaching as the patent. The patent discloses and claims the use of a hVEGF antagonist to achieve a particular therapeutic effect. This is, I have said, a technical feature of the claimed invention. This is not a case where the disclosure of the patent merely provides more information about a use which is described in the prior art because Kim 1992 does not teach that the antibodies in question have the therapeutic effect claimed in the patent. Nor does Kim 1992 give clear and unmistakeable directions to perform the claimed invention.

66. Second, the appellants say that the judge adopted an approach that was inconsistent with his own interpretation of the claim. They continue that the judge held the claims do not require therapeutic utility but none the less imposed such a requirement in addressing the issue of novelty.

67. Again, I do not accept this submission. It is clear that the judge construed the claims entirely correctly as requiring the achievement of a therapeutic effect, and he duly applied this construction when considering novelty.

## Obviousness

68. The judge began by considering the law. At [117] he cited the statement I made in *Generics (UK) Ltd v H Lundbeck A/S* [2007] RPC 32 at [72] which was approved by the House of Lords in *Conor v Angiotech* [2008] UKHL 49; [2008] RPC 28 at [42]:

> "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."

69. Then, at [121], the judge cited the following passage from the judgment of Jacob LJ in the Court of Appeal in *Conor* [2007] EWCA Civ 5; [2007] RPC 20 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."

70. The judge also cited, at [122], Lord Hoffmann's apparent approval of that summary in *Conor* at [42]:

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

71. Having reminded himself of these general principles, the judge then turned to address the question of obviousness in this case by using the structured approach explained by this court in *Pozzoli v BDMO* [2007] EWCA Civ 588; [2007] FSR 37:

> "(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?"

72. The judge had earlier identified the person skilled in the art and the common general knowledge and so he turned to step (2). Here he correctly reminded himself that it is the invention which must be found to be obvious and the invention is to be found in the claim in issue. In the case of a claim to the use of a product for a particular purpose, the correct question is whether it is obvious to use the product for that purpose. Hence, at [134], the judge identified the inventive concept in this case as the use of one of the specified hVEGF antagonists in the treatment of a non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation. It followed, as the judge found at [135], the difference between the disclosure of Kim 1992 and the inventive concept is that Kim 1992, while mentioning therapeutic potential, does not disclose the use of antibodies in the treatment of a non-neoplastic disease.

73. That brought the judge to the crucial question embodied in step (4), namely whether it was obvious to take the step to the invention in the light of Kim 1992 and the common general knowledge.

74. The appellants' case was summarised by the judge at [136] as follows. The next logical step for the skilled team upon reading Kim 1992 would be to test the hypothesis that the antibody has therapeutic potential by carrying out the mouse xenograft test. Secondly, having performed that test and shown the 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.

75. Genentech's answer to that case was set out by the judge at [139]. It argued that the attack on the patent was a classic stepwise obviousness attack which the law does not permit. First, the evidence did 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, it argued that the mouse xenograft test would not be embarked upon with the necessary fair expectation of success.

76. In assessing these rival submissions, the judge made the following important findings of fact. First, at [137], he observed that there was no real dispute that the skilled team, on reading Kim 1992, would have had a motive to take the first step and perform the mouse xenograft test. He continued:

> "Professor Shima said 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."

77. Then, at [138], the judge found that the results of the mouse xenograft test would provide a basis for making a reasonable prediction that the anti-VEGF antibodies would work to reduce angiogenesis for at least some non-neoplastic diseases.

78. The judge's next important finding, at [143], was that Kim 1992 did not 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 in the form of an antibody for inhibiting its effect. Further, there was a danger of attributing too much significance to the *in vivo* assays in Kim 1992 with the benefit of hindsight. The reason was explained by Professor Shima as being that lots of 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 necessary for neovascular pathology. So also, inhibitors to certain growth factors had also been tested in CAM 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 factor alone was responsible for neovascular pathology.

79. Then, at [141], the judge evidently accepted Professor Shima's evidence that one could not embark upon the mouse xenograft test with optimism about the outcome if one did not know, as the skilled person would not know, that VEGF was a valid target for anti-angiogenic therapy.

80. Finally, the judge considered that the statements in Kim 1992 about therapeutic potential for the antibodies described had to be viewed against the background that the vast majority of research in the area on all relevant factors would have had therapy as an end objective and each research group would have been able to say that the agent on which they were working had therapeutic potential.

81. That brought the judge to his conclusion at [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."

82. The judge also referred to the reaction to the invention of those in the field, although he recognised that, as secondary evidence of non-obviousness, it needed to be kept in its place. In particular he referred to the honouring of Dr Ferrara with the Lasker-DeBakey Medical Award in 2010 for, amongst other things, the discovery of VEGF as a major mediator of angiogenesis. As the judge explained, this award is recognised to be amongst the highest achievements in science, falling just short of a Nobel Prize.

83. The appellants argue that in reaching this conclusion the judge erred in five respects. First, they say that the judge was wrong to approach the case on the basis that an assessment of the prospects of success is mandatory in every case. They continue that the question is always just the statutory one: does the claimed invention involve an inventive step?

84. I do not believe the judge fell into any such error. He reminded himself that it is the invention which must be found to be obvious; that the question of obviousness must be considered on the facts of each case; that one of the factors which it may be appropriate to take into account is whether something was obvious to try; that in such a case it may be relevant to consider whether there was a fair expectation of success; and that how much of an expectation of success is necessary will depend upon the particular facts of the case. There is no suggestion here that the judge considered that whether something was obvious to try must necessarily play a part in the assessment of obviousness in every case. In the present case, however, such an assessment was plainly relevant in the light of the way the appellants presented their case. It was their contention that the next logical step for the skilled team to take upon reading Kim 1992 would be to carry out the mouse xenograft test. Then, having performed that test and shown the anti-angiogenic activity of the tested antibody in a neoplastic disease model, it would be possible to make a prediction that the antibody would be effective in the treatment of a non-neoplastic disease characterised by undesirable angiogenesis. It was entirely reasonable for the judge to consider that the notional skilled but uninventive team would not carry out the mouse xenograft test unless they considered they had a fair expectation that it would provide a positive result. The judge took this factor into account along with other relevant factors at [145] of his judgment. He weighed this and those other factors in arriving at his overall conclusion as to whether or not the invention was obvious. This is something which he was plainly entitled to do and it cannot be said that in adopting this course he made an error of principle.

85. Second, the appellants say that if and in so far as the prospects of success are relevant in this case, the judge applied the wrong test. In this regard they point to Diplock LJ's formulation in *Johns-Manville Corporation's Patent* [1967] RPC 479 at 332 that it is enough that the skilled person would assess the likelihood of success as sufficient to warrant actual trial. They also rely upon Lord Reid's statement in *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] RPC 346 at 355-356 that what the skilled person must be supposed to have done is to try everything which would appear to him as giving any prospect of valuable results. In the present case, the appellants say the judge appears to have added a further and inappropriate consideration, namely whether the skilled person would have been optimistic that the antagonists had therapeutic utility. In this regard they point, in particular, to [142] where the judge observed it was 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.

86. In my judgment the answer to this submission is that, as Lord Hoffmann himself explained in *Conor*, the notion of something being obvious to try is useful only in a case in which there is a fair expectation of success. How much of an expectation is needed depends upon the particular facts of the case. Indeed, as Diplock LJ himself said in *Johns-Manville*, it is to be doubted whether there is any verbal formula which is appropriate to all classes of claims. I put the matter this way in *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2012] EWCA Civ 1234 at [90]-[91]:

> "90. One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of technology such as pharmaceuticals and biotechnology which are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them worthwhile. But denial of patent protection in all such cases would act as a significant deterrent to research.
>
> 91. For these reasons, the judgments of the courts in England and Wales and of the Boards of Appeal of the EPO often reveal an enquiry by the tribunal into whether it was obvious to pursue a particular approach with a reasonable or fair expectation of success as opposed to a hope to succeed. Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way …"

87. It was therefore appropriate for the judge to consider 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. This formed part of his assessment as to whether the skilled team would have taken any step from Kim 1992 with a reasonable or fair expectation of success.

88. The appellants then say that, on the facts found by the judge, it is clear that the prospects of success were sufficient to warrant an actual trial, and the judge should

therefore have concluded that the invention was obvious. In this regard they point to the judge's finding at [137] that the skilled team, on reading Kim 1992, would have had a motive to take the first step and perform the mouse xenograft test. Professor Shima said there were compelling reasons to do so and he accepted, in terms of a research objective, it was the next logical step.

89. In my judgment, these findings must be seen in context. The judge was plainly conscious that the skilled team would have had a motive to take the first step. Indeed, at [145], he said in terms that he had in mind there was the strongest of motivations to discover a therapy that would target a molecule responsible for angiogenesis. But, as he continued, this motivation was being channelled down far more avenues than anti-VEGF therapy. Further, although Professor Shima said there were compelling reasons to perform the test and accepted that it was the next logical step, this was in the context of it being a research objective. So also, Professor Shima and Professor Harris considered Kim 1992's contribution to be the provision of a research tool in the form of an antibody for inhibiting VEGF. But that did not mean that one could embark upon the xenograft test with optimism about the outcome. Moreover, VEGF was only one of many factors and other agents which could be investigated and the commonly accepted view was that no single factor was responsible for angiogenesis. All of these matters were considered by the judge, together with the motivation to discover a therapy, in arriving at his conclusion at [145]. In so doing the judge weighed all the various factors in an entirely proper manner.

90. The appellants' fourth complaint is that if the judge was right in construing the claims as he did, then he failed to apply that construction when considering the issue of obviousness. That construction, they continue, did not require the claimed VEGF antagonists to possess any therapeutic efficacy, yet his approach to inventive step was based upon expectations of success about the therapeutic efficacy of the antibodies described in Kim 1992.

91. I am satisfied there is nothing in this point. For the reasons I have given, I have no doubt that the judge correctly interpreted the claims as requiring therapeutic efficacy and that he approached the issue of obviousness on that basis.

92. Finally, the appellants contend that the judge should have held that the claims cover ineffective antagonists and conditions for which VEGF-antagonist therapy is not effective and, as is well established, it is not inventive simply to claim a range of products which have no technical significance and solve no technical problem. The judge summarised this aspect of the case at [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."

93. The judge considered this argument covers the same ground as that raised by the insufficiency allegation and he dealt with it under that heading. I agree and shall do the same.

## Insufficiency

94. The appellants argued at trial and on appeal that the monopoly claimed in the patent is far too broad and encompasses the use of a vast number of antagonists in the treatment of a wide range of conditions which it falls far short of enabling. Their attacks fall into the following groups:

i) It was not possible at the filing date to make a reasonable prediction based upon the teaching in the patent and the common general knowledge that VEGF antagonists would be useful in the treatment of all non-neoplastic diseases characterised by undesirable neovascularisation. The assertion in the patent that VEGF antagonists are therapeutically active against all non-neoplastic diseases is implausible and the range of diseases covered by the claims is arbitrary and unsupported.

ii) In fact VEGF antagonists are not therapeutically active against some non-neoplastic neovascular diseases. Moreover, certain classes of VEGF antagonists are not therapeutically active against certain non-neoplastic neovascular diseases. The patent does not enable the skilled person to identify without undue effort which diseases can be treated, nor which VEGF antagonists are therapeutically active against which diseases.

iii) It involves undue effort to identify which VEGF antagonists are effective against which diseases.

iv) If the claims are broad enough to cover VEGF-Trap, they cover products they do not enable.

*Legal principles*

95. I will address these attacks in turn but must begin with the relevant legal principles. First, a patent may be revoked if the specification does not disclose the invention in a manner which is clear enough and complete enough for it to be performed by a person skilled in the art.

96. Second, it is now well established that the scope of the monopoly, as defined in the claims, must correspond to the technical contribution the patentee has made to the art. An aspect of this requirement is that the specification must enable the invention to be performed to the full extent of the monopoly claimed.

97. Third, the question whether the specification adequately discloses the invention is one of degree. I put it this way in *Novartis v Johnson & Johnson* [2009] EWHC 1671 in a passage cited by the judge in this case:

> "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."

98. Fourth, it is permissible to define an invention using general terms provided the patent discloses a principle of general application in the sense that it can reasonably be expected the invention will work with anything falling within the scope of these terms. As Lord Hoffmann said in *Biogen v Medeva* [1977] RPC 1 at 48-49:

> If the invention discloses a principle capable of general application, the claims may be in correspondingly general terms. The patentee need not show that he has proved its application in every individual instance. On the other hand, if the claims include a number of discrete methods or products, the patentee must enable the invention to be performed in respect of each of them.
>
> Thus if the patent has hit upon a new product which has a beneficial effect but cannot demonstrate that there is a common principle by which that effect will be shared by other products of the same class, he will be entitled to a patent for that product but not for the class, even though some may subsequently turn out to have the same beneficial effect: see *May & Baker Ltd v. Boots Pure Drug Co. Ltd.* (1950) 67 RPC 23, 50. On the other hand, if he has disclosed a beneficial property which is common to the class, he will be entitled to a patent for all products of that class (assuming them to be new) even though he has not himself made more than one or two of them.

99. In *Kirin Amgen v Hoechst Marion Roussel* [2004] UKHL 46; [2005] RPC 9 Lord Hoffmann further explained the concept of a principle of general application in this way:

> "112. In my opinion there is nothing difficult or mysterious about [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."

100. It must therefore be possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim or, put another way, the assertion that the invention will work across the scope of the claim must be plausible or credible. The products and methods within the claim are then tied together by a unifying characteristic or a common principle. If it is possible to make such a prediction then it cannot be said the claim is insufficient simply because the patentee has not demonstrated the invention works in every case.

101. On the other hand, if it is not possible to make such a prediction or if it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within the scope of the claim then the scope of the monopoly will exceed the technical contribution the patentee has made to the art and the claim will be insufficient. It may also be invalid for obviousness, there being no invention in simply providing a class of products or methods which have no technically useful properties or purpose.

102. Fifth, patentees not infrequently seek to avoid the possibility that a claim covers products or methods which do not work by inserting a functional limitation. Such a claim may be allowed by the EPO if the invention can only be defined in such terms or cannot otherwise be defined more precisely without unduly restricting its scope. But, it must still be possible to perform the invention across the scope of the claim without undue effort. As I said in *Novartis v Johnson & Johnson* at [244]:

> "… 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."

103. Finally, the Boards of Appeal of the EPO have recognised that in the case of a claim to the use of a product to make a medicine for a particular therapeutic purpose it would impose too great a burden on the patentee to require him to provide absolute proof that the compound has approval as a medicine. Further, it is not always necessary to report the results of clinical trials or even animal testing. Nevertheless, he must show, for example by appropriate experiments, that the product has an effect on a disease process so as to make the claimed therapeutic effect plausible. It was put this way in T609/02 *Salk* at [9]:

> "… 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."

*All non-neoplastic diseases characterised by undesirable excessive neovascularisation*

104. The judge began by identifying what he understood the arguments of the parties to be:

> "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."

105. The judge then proceeded to summarise the evidence of the experts, beginning with Professor Shima. In his first report he explained that the general view in the art was that all 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. The data in the patent provided the first proof that a VEGF antagonist could be used to reduce neoplastic angiogenesis and this would have provided the skilled team with significant confidence that such an antagonist could also be used to treat non-neoplastic neovascular diseases.

106. Professor Shima's evidence in his second report went rather further, explaining that VEGF was known to be widely expressed and was found at the right time and place to be driving angiogenic growth and disease. VEGF binding sites had been shown to be located on vasculature throughout the body. Coupled with the proof-of-concept data in the patent, the skilled team would have thought it likely that VEGF was a wide-acting factor that would present a viable target for anti-angiogenesis therapy in any context. 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.

107. Professor Shima was cross-examined and did not disagree with the proposition, put to him as part of the appellants' case of obviousness, that the skilled team would expect VEGF antagonism would work in at least some non-neoplastic diseases characterised by excessive neovascularisation. Further, and importantly, he did not accept that it was fanciful to suppose that one agent would be suitable to treat all non-neoplastic neovascular diseases. It was his view that, if neovascularisation was 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.

108. Dr Paleolog's expert report dealt primarily with Example 6 of the patent which, as I have explained, investigated the effect of the anti-VEGF antibody on endothelial cell chemotaxis induced by synovial fluid from RA patients. She also explained that Examples 4 and 5 of the patent would have encouraged the skilled team to test whether VEGF blockade would inhibit angiogenesis in RA and caused them to expect success in those models. The judge summarised her evidence in these terms at [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."

109. Professor Harris said in his first report that it was logical to assume that a blocker of angiogenesis would have potential therapeutic application in more than one disease. Further, in his second report, he expressly agreed with Professor Shima that angiogenesis was seen as the common thread in a range of neovascular diseases. But when it came to his cross-examination, Professor Harris said that neovascularisation was very different from disease to disease; that it was not necessarily going to be the same anti-angiogenic molecule which blocked angiogenesis in each disease; and it would have not have been possible to predict from the data in the patent that anti-VEGF therapy would work in any disease other than cancer. The judge considered that this rather trenchantly expressed evidence was not easy to reconcile with the evidence that Professor Harris had given in relation to obviousness, and that this was an area where he had to treat Professor Harris' evidence with particular caution.

110. The judge then set out his conclusions at [189]-[191]:

> "189. I consider that the patent discloses a principle of general application within the meaning of the authorities in so far 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."

111. Upon this appeal, the appellants make a number of criticisms of these findings. First they say that the judge approached the whole issue of insufficiency on the basis that the claims do not require a therapeutic effect and that, in so doing, he fell into error.

112. I am satisfied there is nothing in this point. It is clear from [189] that the judge considered the allegation of insufficiency on the basis that the patent claims VEGF antagonism as a treatment for all non-neoplastic diseases. Subject to the qualification that he plainly meant non-neoplastic neovascular diseases, this expression of the necessary therapeutic effect is, in my view, unimpeachable.

113. Nevertheless, we were taken to two separate paragraphs in the judgment in which, so it was said, the judge lost sight of this key requirement. First, at [200], in addressing the suggestion that getting the invention to work in the form of an approved treatment for any particular disease involved too much by way of research and experimentation, the judge said the appellants would need to show that the skilled person would not be able to establish without undue burden whether a given anti-VEGF therapy had an effect on angiogenesis in that disease.

114. The judge was, in my view, entirely right in making this observation. Genentech has only ever contended that the therapeutic effect is derived from the treatment of angiogenesis. Accordingly if, in any case, there is no effect on angiogenesis, there can be no relevant therapeutic effect. The judge was not here construing the claim. He was using a shorthand for the requirement he had earlier expressed, namely that

the invention requires the antagonist to have a therapeutic effect on the disease by acting on its angiogenic component.

115. Second, we were taken to [216] of the judgment where, in addressing the specific allegation that the inhibition of the flk-1 receptor did not affect RA, the judge said:

> "… I do not consider that it is established that claim 1 is insufficient in so far as it extends to anti-flk-1 as a treatment for RA by blocking angiogenesis. The evidence does not show that the treatment is ineffective to treat angiogenesis."

Once again, it is clear to me that, in context, the judge was considering the treatment of the disease by addressing its angiogenic component.

116. The appellants then say that the judge erred in law in his approach to a principle of general application. They continue that, ultimately, sufficiency requires enablement, not just plausibility or, in other words, what is claimed must actually work. The judge should therefore have held that the patent was not enabled and insufficient.

117. In my view this is not a fair criticism. In this section of his judgment, the judge was addressing the allegation that the claims are unsupported because the patent discloses no principle of general application and it was simply not credible or plausible that VEGF antagonism would be useful for the treatment of all non-neoplastic neovascular diseases. The judge went on to consider the more specific allegations of insufficiency, namely that VEGF antagonism is not useful in the treatment of particular diseases, and this is a matter to which I must return.

118. Third, the appellants say that the judge's approach to the issue of insufficiency was inconsistent with his approach to obviousness in the following respect. They say that, in considering insufficiency, he held it was reasonable to predict that blockade of VEGF was sufficient to inhibit pathological angiogenesis in all non-neoplastic neovascular disorders, despite there being no evidence in the patent to support this proposition. But, in considering obviousness, he came to the opposite conclusion. Had he applied the same standard to both issues, he would have come to the conclusion the patent was invalid for obviousness.

119. I think that this submission is founded upon a misunderstanding of the judgment. The judge found the patent to be inventive because it was not obvious in the light of Kim 1992 and the common general knowledge that VEGF antagonists could be used to treat any non-neoplastic neovascular disease. But the data in the patent showed that VEGF is necessary for pathological angiogenesis and that pathological angiogenesis can be inhibited by VEGF antagonism. It then became possible to make a reasonable prediction that VEGF antagonism could be used to treat all non-neoplastic neovascular diseases. There is thus no inconsistency in the judge's reasoning. But of course it depends fundamentally upon the evidence he heard and the findings he made. It is to the appellants' criticisms of those findings that I now turn.

120. The appellants submit that the judge erred in principle in his approach to the evidence in two respects; first, he considered that the evidence of Professor Shima

was unchallenged when, in fact, his evidence overlapped with that of Dr Paleolog and she was fully cross-examined; second, he reached a perverse conclusion on aspects of the evidence, and erred in not accepting evidence that was, in truth, common ground.

121. The appellants developed their first criticism of the judge's approach to the evidence in the following way. They argued that in the first round of experts' reports, Genentech adduced evidence from Professor Shima about the disclosure of Example 6 of the patent. Corresponding evidence was given on behalf of the appellants by Professor Harris. Then, in reply, Genentech adduced a report from Professor Shima and a report from Dr Paleolog. But in this reply evidence it was, they say, Dr Paleolog who took up the baton of what the skilled person would understand from the disclosure of the examples of the patent. She expressed agreement with Professor Shima's evidence about the disclosure of Example 6 of the patent and expanded upon it. She also referred to and criticised aspects of Professor Harris' report on this issue. In the light of all these matters, the appellants adopted what they describe as the usual approach of only cross-examining one of the experts on this issue and they chose Dr Paleolog because she had been brought in to address it. The judge was therefore wrong to treat the evidence given by Professor Shima as unchallenged.

122. In my judgment these submissions are misconceived. First, we were shown the transcript of submissions made by counsel for the appellants at the end of the trial from which it is clear that he accepted it was not appropriate for the judge to ignore Professor Shima's evidence; indeed, he submitted that the judge should look at the evidence as a whole.

123. Second, Professor Shima addressed in both of his reports the issue whether, having regard to the common general knowledge and the disclosure of the patent, the skilled team would expect VEGF antagonists to be effective across the range of neovascular diseases characterised by excessive neovascularisation. His conclusion was founded upon the general view in the art that all such neovascular diseases are linked by the common thread of angiogenesis and his opinion that if you could suppress tumour growth you would expect to be able to use the same anti-angiogenic strategy to treat non-neoplastic neovascular diseases. Further, as the judge recorded at [173], he maintained under cross-examination that, if neovascularisation was 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. I have no doubt that this was all evidence upon which the judge was entitled to rely.

124. Turning to Dr Paleolog, she made clear at [14]-[15] of her report that she had been asked to comment upon Professor Harris' views in so far as they related to RA and Example 6 of the patent. She was also asked to comment on other key aspects of the patent that were relevant to RA and explained that she thought that Examples 4 and 5 would be extremely informative to a person with an interest in that disease. She was not asked to comment upon any other aspect of Professor Harris' evidence. I agree with Genentech that there was, therefore, no suggestion that her evidence was intended to address any neovascular disease other than RA. As the judge himself observed at [169], it was Professor Shima and not Dr Paleolog who had covered the broader issue in his written evidence.

125. I would add that, as a general matter, it is highly undesirable for a party to adduce evidence from two different experts on the same issue. It is likely to lead to an increase in the cost and complexity of the case and to provide no corresponding benefit to the court in dealing with the case justly and in accordance with the overriding objective. Moreover, it is likely to create practical difficulties for the party faced with the evidence of precisely the kind which the appellants say arise in this case. But that party should raise the issue with the judge, preferably before or, at the latest, during the trial, and seek appropriate directions as to whether the party seeking to rely upon the evidence should be permitted to do so and, if he is, the appropriate course to be adopted in relation to it. It is wholly unsatisfactory for the point to be taken on appeal.

126. The appellants then say that the judge adopted a remarkable approach to the evidence of Dr Paleolog in any event. They say that an important part of their case on this point was the following simple proposition. If, at the filing date, the presence of VEGF had not been demonstrated in a particular disease, then the skilled team would not have been able to predict that anti-VEGF therapy would have any effect on that disease. This, they say, was a proposition with which Dr Paleolog agreed in a passage of her cross-examination cited by the judge at [179]. They continue that, inexplicably, the judge sought to water this evidence down in arriving at his summary of Dr Paleolog's position overall which I have cited at [108] above.

127. The difficulty facing the appellants in relation to this point is that the judge was required to assess Dr Paleolog's evidence as a whole. In the course of the hearing, we were taken to other passages in her cross-examination which do provide support for the judge's conclusion. In particular we were referred to the following passage on day 4 at 475-476:

> "Q. Take any condition in which the presence of VEGF had not yet been established in the tissue in question, okay?
>
> A. Okay.
>
> Q. A two-part question to you. I think the first one you have answered already. First of all, you just could not make a prediction about whether VEGF blockade worked or not at that stage?
>
> A. I can answer the question with confidence in the context of RA. VEGF had not been shown to be expressed in RA. However, VEGF was known to be a key angiogenic factor. Inhibition of VEGF in a disease model involving angiogenesis had not been shown at the time of filing, but angiogenesis was known to be a feature of RA. So with data showing the effectiveness of VEGF inhibition in an angiogenesis-dependent model, taking that together with the presence of angiogenesis in a disease such as RA, and indeed other diseases, I think that would have given you every confidence that blocking VEGF/VEGF receptor interactions would have had a therapeutic effect.

> Q. Doctor, you have taken my question which was not about RA back to RA. I get the impression ----
>
> A. I apologise, I was trying to answer the question more generally, like giving RA as an example, so other diseases in which, for example, VEGF expression had not been shown, but in which angiogenesis had been demonstrated to be a feature - increased blood vessels. As I said, I cannot comment on any specific disease, but I am just using RA here as an example. But in other diseases as well, I think that would have given you confidence that inhibiting angiogenesis, and specifically VEGF, would be a viable therapeutic option."

128. Further, at [177], the judge cited another passage from Dr Paleolog's cross-examination in which it was suggested to her that one might hypothesise that what holds for a tumour holds for RA, but it was not really scientific to go further. She responded:

> "I think it is a valid scientific hypothesis which underlies many scientific studies to try and extrapolate from disease condition to another."

129. The judge was required to weigh all of this evidence and I reject the appellants' submission that the conclusion at which he arrived in [180] is unsustainable. To the contrary, it seems to me to be a conclusion to which the judge was perfectly entitled to come and it is one which is entirely consistent with the evidence given by Professor Shima.

130. In summary, I am satisfied that the evidence did support the judge's conclusion that the patent discloses a principle of general application, namely that neovascular diseases are linked by the common thread of angiogenesis; that VEGF is necessary for pathological angiogenesis and that it was reasonable to predict that a strategy for treating excessive angiogenesis in neoplastic diseases would also be effective to treat such angiogenesis in non-neoplastic diseases.

131. Before leaving this topic I should, however, deal with some additional points raised by the appellants. First, they refer to RA and say it was the appellants' case, and largely common ground by the end of the trial, that the data in Example 6 of the patent did not demonstrate or prove that VEGF played a causative role in RA or the pathology it causes, or that its blocking would be in any way beneficial to patients.

132. This is true but it does not take the appellants very far. It has never been suggested that VEGF causes RA. Nor does the data in the patent demonstrate or prove that blocking VEGF will be beneficial to patients. However, as Genentech correctly says, this is not the correct question. For the reasons I have elaborated, a patent is not insufficient merely because it does not demonstrate or prove efficacy. It is enough that it is possible to make a reasonable prediction based upon the data in the patent that the invention will work across the scope of the claim.

133. The appellants also rely on atherosclerosis, psoriasis, ascites and pleural and pericardial effusion. They say that the presence of VEGF had not been

demonstrated in these conditions at the filing date. Accordingly, they continue, the skilled team would not have been able to make any sort of prediction that anti-VEGF therapy would be efficacious.

134. In my judgment this adds nothing to the points with which I have already dealt. The judge had ample evidence before him upon which to conclude that it was plausible that VEGF antagonism could be used to treat any non-neoplastic neovascular disease.

*Antagonists inactive against particular diseases*

135. The appellants contend that anti-VEGF therapy is in fact ineffective as a treatment of the following diseases:

i) atherosclerosis;

ii) ascites, and pleural and pericardial effusion.

I shall address them in turn.

136. At trial, the appellants argued that anti-VEGF therapy cannot be used to treat atherosclerosis because it will exacerbate rather than alleviate the patient's condition.

137. The judge dealt with this issue from [196]-[199]. As he explained, atherosclerosis is a disease 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 important in patients recovering from a stroke.

138. Professor Harris considered it would therefore be absurd to treat atherosclerosis with VEGF therapy. Professor Shima and Dr Paleolog adopted a more moderate position, explaining there were two schools of thought.

139. The judge reached his conclusion at [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."

140. The appellants say that the judge made two errors of principle. First, they say the judge thought it was sufficient for there to be an impact on angiogenesis, irrespective of any benefit in treating the disease. I disagree. The judge was considering, as he was bound to, whether VEGF antagonism would address the angiogenic aspect of the disease.

141. Second, they contend the finding that regulatory approval of such a treatment is unlikely means that VEGF antagonism is not suitable for the treatment of atherosclerosis. In my judgment the answer to this point is that the patent does not promise that all VEGF antagonists will pass clinical trials and achieve regulatory approval for the treatment of all neovascular diseases. In some cases the side effects may, in the view of the regulatory authorities, outweigh the benefits. But that does not mean to say that anti-VEGF therapy will not treat the disease by addressing its angiogenic component. In other cases the neovascularisation may be beneficial. But such a disease state will not fall within the scope of the claim at all because it will not be one characterised by undesirable excessive neovascularisation.

142. The attack in relation to ascites and pleural and pericardial effusion followed similar lines. The appellants contended at trial that the treatment of these conditions with anti-VEGF therapy would, in some circumstances, be dangerous to patients.

143. The judge did not deal with this particular issue in his judgment. However, there was no evidence to suggest that VEGF antagonism would not address the angiogenic component of these conditions. The debate was whether it would be good clinical practice to treat particular patients with a VEGF antagonist. The effect of the evidence was that this would depend on the individual diagnosis of each patient. But that does not render the patent insufficient. There is no requirement in law that a product for use in therapy should be suitable for all patients.

144. The appellants' next category of complaints is that certain claimed VEGF antagonists are not effective in the treatment of particular non-neoplastic neovascular diseases. For the purpose of this appeal, they rely upon the following:

i) the treatment of RA by anti-flk-1 antibodies;

ii) the treatment of RA by anti-VEGF antibodies; and

iii) the treatment of atherosclerosis by anti-flk-1 antibodies.

Again, I shall address them in turn.

145. The appellants contended at trial that two papers, Luttun published in 2002 and De Bandt published in 2003, showed that antibodies to one of the known VEGF receptors were ineffective at treating RA in a mouse model of the disease.

146. The judge summarised the teaching of these papers and the expert evidence that he heard in relation to them from [211]-[214]. They suggest that inhibition of flk-1 driven angiogenesis does not halt disease progression. Genentech had two answers. The judge rejected the first and explained the second and the evidence relating to it at [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."

147. It was therefore hardly surprising the judge reached the conclusion he did at [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."

148. The appellants contend that this analysis was predicated upon the judge's approach to the construction of the claim. They say he ought to have found that anti-flk-1 therapy is ineffective against RA.

149. Once again, this submission depends upon the proper interpretation of the claim. For the reasons I have given I am satisfied that there is no requirement that the patented invention must treat all aspects of any particular disease. It is enough for it to treat the disease by addressing its angiogenic component. The judge was therefore right to dismiss this allegation.

150. The next attack, the treatment of RA by anti-VEGF antibodies, is similar. It was based upon the paper by De Bandt and a further paper by Lu published in 2000. The judge summarised the disclosure of these papers and expressed his conclusion at [217]-[218]:

> "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."

151. The appellants contend that the judge, having concluded that the De Bandt antibodies were ineffective to treat the disease and those in Lu were ineffective in established disease, should have held the patent insufficient.

152. The answer to this submission is that, as the judge explained in dealing with the allegation concerning anti-flk-1 treatment, the De Bandt paper was measuring swelling, not angiogenesis. Further, the appellants made no attempt to establish that the Lu paper was measuring angiogenesis either. Overall I am satisfied the judge was entitled to reach the conclusion he did.

153. Finally then I come to the use of anti-flk-1 antibodies in atherosclerosis. This allegation was based upon the Luttun paper which reported experiments into the effect of antibodies to flk-1 and flt-1 receptors in a mouse model of atherosclerosis.

154. The judge summarised the position in this way at [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."

155. The appellants led no evidence from Professor Harris in relation to this allegation and they relied simply upon a few questions put to Dr Paleolog in the course of cross-examination. But she was not invited to comment upon or express her agreement with the conclusions in the paper, nor to accept that they demonstrated that anti-flk-1 antibodies would be ineffective in treating the angiogenic component of atherosclerosis. I am therefore satisfied that the judge was entitled to reject the allegation in the way that he did.

*Undue research and experimentation*

156. The appellants ran two separate points at trial. First, they contended that it would require undue effort to determine which antagonists were therapeutically effective against any particular neovascular disease. So, for example, it involved too much by way of research and experimentation to get the invention to work in the form of an approved treatment for a disease such as RA.

157. The judge dealt with this allegation at [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."

158. I think the judge was right in reaching this conclusion. As the Board of Appeal said in T609/02 *Salk*, proving the suitability of a given compound as an active ingredient in a pharmaceutical composition might require years and very high development costs. For this reason, the patent system does not require absolute proof that the

compound is approved as a drug before it may be claimed as such. Furthermore, there may be many commercial reasons why a patentee chooses not to carry a particular treatment through to final approval. Indeed, Professor Shima explained in cross-examination that developing drugs involves both a business decision and a major clinical trial. But that does not render a patent insufficient.

159. The appellants advanced a further argument that the claims were ambiguous and did not adequately define "non-neoplastic disease or disorder characterised by undesirable excessive neovascularisation".

160. The judge addressed this argument at [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."

161. The appellants contend that the judge fell into error here and that it is plain in the light of Professor Shima's evidence that identifying the diseases which can be treated, and which antagonists can be used to treat those diseases, would require clinical trials.

162. In my judgment the conclusion reached by the judge was correct. The evidence of Professor Shima does not begin to establish that there is any difficulty in identifying treatable diseases. Further, the suggestion that it is necessary to establish efficacy by carrying out clinical trials is founded upon the same misunderstanding of what amounts to a sufficient disclosure of a therapeutic application and I reject the submission for the reasons I have already given.

*Infringement – insufficiency squeeze*

163. The appellants accepted at trial that it would be within the capability of the skilled team armed with the patent to make an isolated hVEGF receptor for use in accordance with the invention. But they contended that it would involve an undue burden to discover truncated sections of the isolated VEGF receptor which would work as VEGF antagonists.

164. The judge summarised the evidence given by the experts and in particular Professor Harris on this issue and reached his conclusion at [206]-[207]:

> "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."

165. The appellants do not challenge that finding. Their case did not, however, rest there. They also alleged that the specification does not provide directions as to how to make VEGF-Trap.

166. Professor Harris gave evidence that he regarded aspects of VEGF-Trap as very clever and said that the combination of high affinity which it achieves and its improved pharmacokinetics could not have been predicted. Further, he said it was the result of a major research effort. All of that evidence was accepted by the judge. However, he rejected the allegation that the claim was insufficient:

> "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."

167. The appellants now challenge this finding. They argue that chimeric proteins such as VEGF-Trap involve combining together parts of one protein with a particular function with parts of another protein with a slightly different function to produce a new therapeutic. Production of chimeric molecules of this kind did not form part of the common general knowledge and are not described in any way in the patent. Further, they could not be made without undue effort. It follows that these molecules are altogether different inventions and so do not fall within the scope of the claim or, if they do, then the claim must be insufficient.

168. This is something of a refinement of the case presented by the appellants at trial which focused first, on truncated forms of receptors and second, on VEGF-Trap. The appellants now seek to contend that the patent is insufficient in relation to chimeric molecules which bind VEGF, of which VEGF-Trap is but one example, albeit a highly effective one.

169. In considering this submission it is helpful to have the following points in mind. First, as I have said, the appellants do not seek to challenge the finding of the judge that the patent is sufficient in relation to truncated receptors, including fragments of the ECD.

170. Second, the patent specifically contemplates fusion proteins in which non-hVEGF polymers or polypeptides are conjugated to truncated forms of VEGF receptors. One such non-hVEGF polymer is the constant (Fc) domain of immunoglobulin, just as depicted at [51] above, and by its nature, when used to produce a fusion protein with VEGF receptor proteins, it will have attached to it two such receptor proteins to produce a molecule having two arms and the general appearance of VEGF-Trap.

171. Third, Professor Shima explained in his second report that the recombinant production of chimeric receptors was a known concept at the date of the patent. For example, chimeric receptors that combined sequences from different receptors had been used to assist in localising the receptor subdomains involved in ligand binding for a number of growth factor receptors. He therefore thought that the chimeric approach was something the skilled team would have thought about and that the production of such a chimeric receptor was something within the grasp of the skilled team using standard molecular biology techniques. In cross examination he elaborated that this was something the skilled team could readily have done and that it would have been a simple cloning exercise.

172. It follows from all of the foregoing that the skilled team would have regarded chimeric molecules as variants falling within the scope of the claim. The skilled team would have had them well in mind in the light of the teaching in the patent and the common general knowledge and would have been able to produce such molecules across the scope of the claim without any great difficulty. That is not to say they could have produced VEGF-Trap, for I accept this would have required a good deal of ingenuity.

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

*Insufficiency – conclusion*

174. I believe the judge was right to reject all the allegations of insufficiency. It follows he was also right to reject the allegation that the invention is obvious because it does not work and solves no technical problem.

**Conclusion**

175. For all the reasons I have given I would dismiss this appeal.

**Lord Justice Moses:**

176. I agree.

**Lord Justice Longmore:**

177. I also agree.