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PATENTS ACT 1977 25 October 2005

APPLICANT Aeomica Inc

ISSUE Whether application number GB0218205.3 complies with sub-sections 1(1)(b), 1(1)(c) and paragraph 6 of Schedule A2

HEARING OFFICER P M Back

DECISION

Introduction

1 Patent application No. GB 0218205.3 ("the application") entitled "Human ZZAP1 protein" was filed on 6 August 2002 by Aeomica Inc ("the applicant") and claimed priority from an earlier application filed in the USA on 9 August 2001. The application was published on 9 April 2003 as GB 2380480 A.

2 The first examination report under section 18(3) was issued on 28 January 2003 as part of a combined search and examination. In this report the examiner raised an objection to lack of industrial application as the application did not demonstrate any specific function for the ZZAP1 gene or protein sequence. The application listed conditions that ZZAP1 may be involved in, but without any evidence of the actual function of the protein the examiner considered that the predicted uses of the ZZAP1 protein were merely speculative. The examiner also raised an objection under paragraph 6 of Schedule A2 to the Act as the industrial application of a gene sequence must be disclosed in the patent application as filed.

3 The examiner also raised an objection under inventive step on the basis of an earlier disclosure of a cDNA and hypothetical protein from *Macaca fascicularis* entered into GenBank with accession numbers AB 055276 and BAB21900 respectively ("the macaque sequences"). The hypothetical protein disclosed in BAB21900 displayed 93% identity at the amino acid level to ZZAP1. An objection under inventive step was also raised in view of the disclosure of WO 01/53455 A2 (HYSEQ) (and corresponding WPI accession number 2001-457603/49) ("HYSEQ"). The sequences represented by SEQ ID Nos 327 and 1066 of this document disclose human cDNA and protein sequences respectively, with the protein sequence represented by SEQ ID No 1066 having 85% identity with an approximately 500 amino acid segment of ZZAP1 . Objections relating to paragraph 3 of schedule A2 to the Patents Act and support were

also raised. On 14 November 2003 a meeting, requested by Amersham plc, was held to discuss general inventive step and industrial application objections raised by The Patent Office on this and related Aeomica applications. However, the inventive step and industrial application objections were maintained following this meeting. In a second examination report, issued 19 May 2004, the examiner upheld the industrial application and inventive step objections. A warning was also issued to the application regarding PCT application WO 03/008625 which is a potential novelty citation in the 2(3) field should it develop into either a UK application or a European application designating UK. The applicant was also warned of potential conflict under Section 73(2) with regards to corresponding European patent application EP 1285963. An objection to lack of support and lack of clarity was also made; the other objections having been overcome by amendment. The examiner suggested that the applicant request a hearing as an attempt to reach agreement over the industrial application and inventive step objections made in this report. The objections under lack of support and lack of clarity were not considered at hearing as these could be satisfactorily overcome by amendment. The applicant did not accept the examiner's view on this matter and requested a hearing.

4 The unresolved matters came before me at the hearing on 26 November 2004, at which Mr Richard Bassett of Eric Potter Clarkson, assisted by Dr Ian Bryan of Amersham plc, appeared for the applicant. On 25 November 2004 the applicant had submitted a declaration by Dr David Bentley, Head of Human Genetics at the Wellcome Trust Sanger Institute, Hinxton, Cambridge. In this declaration Dr Bentley commented on various aspects relating to the sequences claimed in the present application when considered in the light of the prior art and the knowledge and skills that would be available to one skilled in the art in 2001. Also submitted on 25 November 2004 was a skeleton argument.

The application

5 The application relates to the human ZZAP1 protein, so called because it contains two bZIP transcription factor motifs and similarity to V-ATPases. The ZZAP1 protein is a protein which is stated to function in protein-protein interactions, aberrant expression of which is likely associated with the development of certain types of cancer and other diseases. The application provides isolated nucleic acids that encode ZZAP1, variants having at least 65% sequence identity thereto and displaying the same biological and functional activities thereof, degenerate variants thereof, variants that encode ZZAP1 proteins, cross-hybridizing nucleic acids and fragments thereof. In particular the application relates to a ZZAP1 nucleic acid which comprises a specific nucleotide sequence (SEQ_ID_NO: 1 or SEQ_ID_NO: 2) and a ZZAP1 polypeptide which comprises a specific amino acid sequence (SEQ_ID_NO: 3). SEQ_ID_NO: 1 presents the cDNA of human ZZAP1 and includes the 5' and 3' untranslated (UT) regions and SEQ_ID_NO:2 presents the open reading frame from SEQ ID NO: 1.

6 It is stated that the nucleic acid sequences SEQ_ID_NO: 1 and SEQ_ID_NO: 2 were identified using bioinformatics algorithms, and that the deduced protein sequence contains domains that bear homology to the membrane-spanning α-subunit of V-ATPases. The application explains that such similarities imply that ZZAP1 plays a role similar to other proteins containing V-ATPase motifs in having protein-protein interaction activity. The ZZAP1 protein also comprises a leucine zipper motif, and a

number of additional motifs identified using the commonly available PROSITE database and PFAM database.

7 The claims of the application relate to various aspects of the invention as follows:

"1. An isolated nucleic acid that encodes a V-ATPase domain containing protein (ZZAP1), consisting of:
(a) a nucleotide sequence selected from the group consisting of:
(i) SEQ_ID_NO:1;
(ii) the complement of the sequences set forth in (i);
(iii) the nucleotide sequence of SEQ_ID_NO:2;
(iv) a degenerate variant of the sequences set forth in (iii); and
(v) the complement of the sequences set forth in (iii) and (iv);
(vi) the nucleotide sequence of the cDNAs having ATCC accession nos. PTA-3582; or
(b) a nucleotide sequence selected from the group consisting of:
(i) a nucleotide sequence that encodes a polypeptide having the sequence of SEQ_ID_NO:3;
(ii) a nucleotide sequence that encodes a polypeptide having the sequence of SEQ_ID_NO:3, with conservative amino acid substitutions; and
(iii) the complement of the sequences set forth in (i) and (ii).

2. The isolated nucleic acid of either of claims 1, wherein said nucleic acid, or the complement of said nucleic acid, is expressed in adult liver, brain, fetal liver, lung, placenta, testis, skeletal muscle, heart, bone marrow, as well as cell lines bf474 and hela

3. A nucleic acid probe, comprising:
(a) a nucleic acid of claim 1; or
(b) at least 17 contiguous nucleotides of SEQ_ID_NO:4 or SEQ ID NO: 6

4. The probe of claim 3, wherein said probe is detectably labeled.

5. The probe of either of claims 3 or 4, attached to a substrate.

6. A microarray, wherein at least one probe of said array is a probe according to claim 3.

7. The isolated nucleic acid molecule of any of claims 1 or 2, wherein said nucleic acid molecule is operably linked to one or more expression control elements.

8. A replicable vector comprising a nucleic acid molecule of any of claims 1 or 2 or 7.

9. A non-human host cell transformed to contain the nucleic acid molecule of any of claims 1 or 2 or 7 or 8, or the progeny thereof.

10. A method for producing a polypeptide, the method comprising: culturing the host cell of claim 9 under conditions in which the protein encoded by said

nucleic acid molecule is expressed.

11. An isolated polypeptide produced by the method of claim 10.

12. An isolated polypeptide, comprising:
(a) an amino acid sequence selected from the group consisting of:
(i) SEQ_ID_NO_3;
(ii) the amino acid sequence of the cDNAs having ATCC accession nos. PTA-3582;
(b) an amino acid sequence having at least 65% amino acid sequence identity to that of (a)(i) or (a)(ii);
(c) an amino acid sequence according to (a)(i) or (a)(ii) in which at least 95% of deviations from the sequence of (a)(i) or (a)(ii) are conservative substitutions.

13. A transgenic non-human animal modified to contain the nucleic acid molecule of any one of claims 1 or 2 or 7 or 8.

14. A method of identifying agents that modulate the expression of human ZZAP1, the method comprising:
contacting a cell or tissue sample believed to express human ZZAP1 with a chemical or biological agent, and then comparing the amount of human ZZAP1 expression in said cell or tissue sample with that of a control, changes in the amount relative to control identifying an agent that modulates expression of human ZZAP1.

15. A method of identifying agonists and antagonists of human ZZAP1, the method comprising:
contacting a cell or tissue sample believed to express human ZZAP1 with a chemical or biological agent, and then comparing the activity of human ZZAP1 with that of a control, increased activity relative to a control identifying an agonist, decreased activity relative to a control identifying an antagonist.

16. A method of identifying a specific binding partner for a polypeptide according to claim 12, the method comprising:
contacting said polypeptide to a potential binding partner; and determining if the potential binding partner binds to said polypeptide.

17. The method of claim 16, wherein said contacting is performed *in vivo*.

18. A method for detecting a target nucleic acid in a sample, said target being a molecule according to any one of claims 1 or 2 or 7 or 8, the method comprising:
a) hybridizing the sample with a probe comprising at least 17 contiguous nucleotides of a sequence complementary to said target nucleic acid in said sample under high stringency hybridization conditions, and
b) detecting the presence or absence, and optionally the amount, of said binding.

19. A method of diagnosing or monitoring a disease caused by altered expression

of human ZZAP1, comprising:
determining the level of expression of human ZZAP1 in a sample of nucleic acids or proteins that derives from a subject suspected to have said disease, alterations from a normal level of expression providing diagnostic and/or monitoring information.

20. A diagnostic composition comprising the nucleic acid of any of claims 1or 2, said nucleic acid being detectably labeled.

21. The diagnostic composition of claim 20, wherein said composition is further suitable for *in vivo* administration.

22. A diagnostic composition comprising the polypeptide of claim 12, said polypeptide being detectably labeled.

23. The diagnostic composition of claim 22, wherein said composition is further suitable for *in vivo* administration.

24. A pharmaceutical composition comprising the nucleic acid of any one of claims 1 or 2 or 7 or 8 and a pharmaceutically acceptable excipient.

25. A pharmaceutical composition comprising the polypeptide of claim 12 and a pharmaceutically acceptable excipient.

26. Nucleic acid of any one of claims 1 or 2 or 7 or 8 for use in therapy.

27. Polypeptide of claim 12 for use in therapy.

28. A method of modulating the expression of a nucleic acid according to any of claims 1 or 2 or 7 or 8, the method comprising:
administering an effective amount of an agent which modulates the expression of a nucleic acid according to claim 1.

29. A method of modulating at least one activity of a polypeptide according to claim 12, the method comprising:
administering an effective amount of an agent which modulates at least one activity of a polypeptide according to claim 12."

The outstanding objection

8 The matters that remained unresolved at the time of the hearing before me were:

(a) whether the subject matter of claims 1-29 is capable of industrial application;

(b) whether the subject matter of claims 1-5, 7, 8 and 26 complies with paragraph 6 of Schedule A2; and

(c) whether the subject matter of claims 1-29 involves an inventive step.

Industrial application

The examiner's objection

9 The examiner's objection was based upon the fact that no function had been assigned to the ZZAP1 protein. The application indicates that ZZAP1 has a number of putative functional domains, and describes possible functions for the ZZAP1 gene in protein-protein interactions, acidification of intra- and extra-cellular compartments, and gene regulation. Diseases that ZZAP1 may be involved in were also listed.

10 In his first report of 28 January 2003 the examiner stated that the application had not disclosed any industrial application for the ZZAP1 protein. Whilst the application listed conditions that ZZAP1 may be involved in, in his opinion this was merely a speculative listing as the description provided no evidence of the actual function of the sequence. The examiner acknowledged that the application disclosed a number of possible functions for the ZZAP1 sequence (his emphasis), but considered that this wording of 'possible' functions suggested that the actual function of the isolated gene and/ or polypeptide was yet to be determined. He referred to Examples 5-8 of the specification and considered that these examples were merely common examples of laboratory procedures that would be obvious to undertake with such a sequence and did not exemplify the function or utility of the gene. In the examiner's opinion the predicted uses of ZZAP1 had not been identified, and consequently the disclosed industrial application was not considered to be specific. As the industrial application of a gene sequence must be in the application as filed the examiner also concluded that those claims that related to the gene sequence did not satisfy the requirements of paragraph 6 of Schedule A2 to the Act.

11 The examiner maintained this objection in his second examination report of 19 May 2004. He argued that in the present application there is no clearly demonstrated function of the protein, but merely a range of possible functions based on the apparent presence of certain domains. Whilst the apparent vacuolar ATPase function of the gene was considered to be a demonstration of function by the agent, the examiner pointed out that proteins with such domains have a range of cellular functions, and that this domain was merely one of a number of other conserved domains identified in the protein. In the examiner's opinion the application did not demonstrate or even suggest a function for the protein as a whole, other than a suggestion that it is involved in "protein-protein interactions", a function that, in his opinion, was too vague to be considered a credible assignment of function to the protein. The examiner therefore considered that the application did not disclose a specific, substantial and credible industrial application for the polynucleotides or polypeptides of the invention.

The applicant's position

12 Mr Bassett began by stating that there are two different aspects to looking at the industrial application for the present application; the first is the industrial application of the nucleic acid sequences, and the second is the industrial application of the protein sequences. He asserted that in the examiner's mind these objections come together, and consequently because there was no demonstration of a credible utility for the

protein there could not be a credible utility for the nucleic acid either. In Mr Bassett's opinion this presupposes that the only utility of the nucleic acid sequence is as an intermediate in the manufacture of the protein, and this is not the case. Therefore Mr Bassett proceeded to discuss the industrial application of the nucleic acid sequences independently of the protein sequences.

13 Mr Bassett referred to the decisions cited in the examination reports, namely *Chiron Corporation v Murex Diagnostics* [1996] RPC 535 and *Icos Corporation/ Seven transmembrane receptor* OJEPO 2002, 293 (EP-B-0630405). He noted that the *Icos* decision was a decision from the EPO Opposition Division and therefore should be regarded as having limited precedential value, but as Mr Bassett considered that the facts of the present case can be distinguished from both *Chiron* and *Icos* he agreed that, for the sake of argument, *Icos* could be accepted as being a legal precedent.

14 Mr Bassett stated that section 4(1) of the Act says that something shall be regarded as being capable of industrial application if it is capable of being made or used in industry. In the *Chiron* decision, Mr Bassett considered that the Court of Appeal emphasized the word "industry" by stating that industry only exists to make useful things, and therefore it is not enough for it to be physically capable of being made or used, it has to be useful, otherwise it cannot be regarded as being made in industry. The only claim lacking industrial applicability in *Chiron* was a claim to a class of polypeptides encoded by polynucleotides that would hybridize to some or all of the hepatitis C genome. Mr Bassett proceeded to explain that simply because one polynucleotide hybridizes to a second polynucleotide, it does not necessarily follow that the protein encoded by the second polynucleotide will have a similar amino acid sequence or the same function. Consequently the polypeptides embraced by that claim bore no functional relation to what had been disclosed in the *Chiron* patent. Mr Bassett asserted that the situation with the present application was entirely different to that of *Chiron*, and he explained that in the present application the claims to nucleic acid sequences were specifically directed towards those nucleic acid sequences that had been shown to be expressed in human tissue and encode a protein.

15 Mr Bassett then referred to the Invitrogen® online catalogue ("the Invitrogen® internet pages"), which he considered to provide evidence of a utility for the polynucleotide sequences in their own right. The "GeneStorm" products sold by Invitrogen® are a number of clones that have been shown to be expressed in human tissue. There is no proof that any particular clone encodes a particular protein that has a proven utility or function, although similarities of each clone to known polynucleotide or polypeptide sequences are listed. Mr Bassett asserted that this is the same situation as in the present application. He stated that the present application provides nucleic acid sequences that have been shown to be expressed, and that certain utilities of the nucleic acids are predicted based upon the chromosomal location and the sequence motifs found in the encoded proteins and their similarities to known proteins with similar motifs. Even though the gene claimed in the present application is not on the market in the same way as the GeneStorm clones are being sold by Invitrogen® , Mr Bassett asserted that the GeneStorm clones are directly comparable to the polynucleotide sequences claimed in the present application as they have the same level of information pertaining to them, i.e. they have been shown to be expressed and there is some similarity to a known protein. As the GeneStorm clones, which in Mr Bassett's opinion are similar to the polynucleotide sequences of the

present invention, are on sale for £530 each in the Invitrogen® catalogue, Mr Basset concluded that it is not possible to say that the claims of the present application are incapable of industrial application. He went on to explain that this was independent of whether or not any utility had been shown for the protein encoded by these nucleic acid sequences.

16 Mr Bassett submitted that it is not possible to draw a distinction between the nature of the nucleic acid claimed in the present application and the nucleic acids for sale by Invitrogen® , and as they could be sold in the same way as the GeneStorm clones they are capable of industrial application according to the definition in *Chiron*. In Mr Bassett's opinion if the view was taken that the nucleic acids according to the present invention were not capable of industrial application then it would follow that the GeneStorm clones sold by Invitrogen® are also not capable of industrial application. Mr Bassett agreed that it is possible to sell rubbish if it is marketed properly, but considered that this was not the case in the present situation. He used the example that it is possible to sell broken plant pots for use as drainage in other plant pots, but you could break your own plant pots rather than pay good money for that broken plant pot. However, Mr Bassett considered that the present situation was not in the same league, as Invitrogen® is a serious company selling serious research materials, and serious people who are conducting research are prepared to buy them. The clones sold by Invitrogen® were something physical that can be used as research reagents in any laboratory.

17 In his arguments relating to the claims for the proteins, Mr Bassett referred to the *Icos* decision that had been cited by the examiner in his examination reports. In particular, Mr Bassett referred to a passage within the headnote of this decision which stated that "*The disclosure of a predicted function of a protein in combination with a method of verification of this function is not necessarily adequate to sufficiently disclose the function of the protein.*" Mr Bassett placed emphasis upon the word "necessarily" towards the end of the passage, and asserted that the use of this word implied that in certain circumstances a predicted function would be sufficient. In *Icos* the predicted function was not enough as the protein in question was a receptor and no ligand had been identified for the receptor. Furthermore, without any guidance from the application, the task of identifying the ligand would be an undue burden.

18 Mr Bassett referred to a second passage within the *Icos* decision, where it stated that "*Indeed there are cases where a predicted function of a protein may be demonstrated in a technically undemanding way (e.g. predicting a specific enzymatic activity), in which case the disclosure of predicted function in combination with a method of verification of said predicted function amounts to sufficiently disclosing the function of said protein."* Mr Bassett asserted that the particular situation where the EPO opposition division considered that a predicted function would be sufficient would therefore be in the case of a protein with a specific enzymatic activity. In this regard, he referred to pages 134 to 136 of the application, where it states that the ZZAP1 protein has ATP hydrolysis activity, and specifically referred to line 5 of page 135 of the application, where it states that "*V-ATPase domains are involved in hydrolyzing ATP to ADP and an inorganic phosphate and operating as ATP dependent proton pump*". According to Mr Bassett, as ATPase triphosphate hydrolysis activity is an enzymatic function it is well within the scope of abilities of a person skilled in the art to determine whether the protein has this activity. In his opinion, this is the precise

situation that the Opposition Division in *Icos* would recognize a sufficient disclosure of activity.

19 Mr Bassett referred to the abstract by Muroi, M. *et al* published in Cell Structure and Function, Volume 18, 1993 "Folimycin (concanamycin A), a specific inhibitor of V-ATPase, blocks intracellular translocation of the glycoprotein of vesicular stomatitis virus before the arrival to the Golgi apparatus", pp 139-149 ("The Muroi paper"), which discloses a vacuolar type ATPase, which is the function ascribed to ZZAP1 in the present application. This paper discusses the prevention of the movement of a viral protein across the cell membrane by folimycin, and according to Mr Bassett this could have a therapeutic utility in preventing the development and spread of viral disease. Mr Bassett asserted that the utility of this protein was therefore in the screening of compounds to inhibit its activity, and that this may have a therapeutic value to it.

20 Mr Bassett compared the function of the protein of the application to the function of the protein disclosed in the Muroi paper. He specifically referred to pages 3 and 4 of the application, which discloses various properties and utilities of v-ATPases. In particular, the passage on page 4, line 12 states that "*Other recent studies have implicated the endocytotic role of v-ATPase domains in the development of acquired immunodeficiency syndrome (AIDS). Specifically the catalytic subunit of v-ATPase is believed to facilitate internalization of the accessory protein negative factor from human immunodeficiency virus (HIV), a key step in the progression from HIV to AIDS*". This, in Mr Bassett's opinion, demonstrates that the protein of the present invention has a close connection with the protein of the Muroi paper, as the inhibition of both enzymes can lead to the inhibition of internalization of viruses and viral particles. According to Mr Bassett the association of ZZAP1 with the protein disclosed in the Muroi paper demonstrates that the utility of the ZZAP1 protein is something that people are clearly interested in and furthermore would wish to screen for inhibitors.

21 Mr Bassett asserted that the present situation was a conventional situation where the claims are directed to chemical compounds with a predicted utility, and that in any application for chemical compounds the large majority of the scope of the claim is going to be based upon a prediction of utility. Not every compound would be tested in a human pharmaceutical context, it is quite rare even to have animal data let alone human data, and in Mr Bassett's opinion everything is based upon prediction, and it is a question of whether it is a reasonable prediction. Mr Bassett asserted that in the present situation a reasonable prediction of the activity of the protein had been provided, based upon similarities to known sequences and a recognition of sequence motifs. The application provides an indication of the particular property of the protein, and according to Mr Bassett one can test and confirm that the protein has this particular utility. In Mr Bassett's opinion the fact that the Muroi paper discloses a similar protein, demonstrates that the ZZAP1 protein has a real life utility.

22 Mr Bassett referred to the Examination Guidelines for Patent Applications relating to Biotechnological Inventions ("the Guidelines") published by the UK Patent Office, and the reference within these that stated that it was necessary to demonstrate a specific, substantial and credible utility for what is claimed. He acknowledged, as did the Guidelines, that this test has been adopted from the USPTO Utility Guidelines, and had not yet been tested in the UK courts. Nevertheless, Mr Bassett asserted that a

specific, substantial and credible utility had been demonstrated with respect to the application. In Mr Bassett's opinion, the fact that the Muroi paper disclosed a similar protein with experimental data demonstrated that the protein had a substantial utility; the properties of the protein were considered to be specific; and the utility was considered to be credible as it can be tested in the manner suggested by the opposition division in *Icos*. Mr Bassett asserted that the polynucleotide claims would inherently pass the standard of a specific, substantial and credible utility as similar polynucleotides are being sold by Invitrogen® .

23 In order to demonstrate that the specification complies with paragraph 6 of Schedule A2, Mr Bassett referred to the passage on page 37-43 of the application. In his opinion, this passage provides extensive use of nucleic acids for diagnostic purposes, and therefore demonstrates that the industrial application of the polynucleotide was in the application as filed. For example, Mr Bassett referred the a passage on page 40 line 8, which disclosed the use of nucleic acid probes for measuring the level of ZZAP1 expression in tissues, and that such expression had already been confirmed. This, in Mr Bassett's opinion was a further demonstration of a specific, substantial and credible utility.

The Law

24 Section 1(1)(c) states that a patent may only be granted for an invention if it is capable of industrial application. This is expanded in section 4(1) which states:

> "….an invention shall be taken to be capable of industrial application if it can be made or used in any kind of industry, including agriculture"

In addition, paragraph 6 of Schedule A2 states that:

> "The industrial application of a sequence or partial sequence of a gene must be disclosed in the patent application as filed"

25 Therefore, where a patent application comprises claims to a polynucleotide sequence, the industrial application of that polynucleotide sequence must be in the application at the filing date and cannot be provided as evidence at a later date.

26 In *Chiron Corp* the Court of Appeal considered that sections 1(1)(c) and 4 of the Act require that (my emphasis):

> "…the invention can be made or used 'in any kind of industry' so as to be 'capable' or 'susceptible of industrial application'. The connotation is that of trade or manufacture in its widest sense and whether or not for profit. **But industry does not exist in that sense to make or use that which is useless for any known purpose**"

In considering industrial application, the Court of Appeal stated that the Act (and the European Patent Convention) was manifestly intended that monopoly rights should be confined to that which has some useful purpose.

27 Industrial application was also dealt with in the decision of the EPO Opposition Division in *ICOS Corp*. The Opposition Division considered that the evidence in the

application did not explicitly or implicitly indicate the involvement of the protein of the invention in the proposed biological processes, thus indicating that the invention was not capable of exploitation in relevant industrial applications. In their reasoning the Opposition Division stated that (my emphasis):

> "Potential uses of the invention are disclosed in the specification which however are based on a proposed function of the V28 protein as a receptor which is not sufficiently disclosed in the specification. Thus, **the potential uses disclosed in the application are speculative, i.e. are not specific, substantial and credible and as such are not considered industrial applications**."

28 In *ICOS* the Opposition Division were of the opinion that the industrial application of the protein was not 'specific, substantial and credible' in light of the speculative uses disclosed in the application. The 'specific, substantial and credible' test was introduced by the USPTO, and published in their Utility Guidelines in 2001, and can be summarized as follows:

> *Specific*: An industrial application is specific if it is particular to the subject matter claimed. For example, a claim to a probe *per se* would not be specific unless a particular gene or chromosomal target has been identified. Similarly, a claim to a diagnostic or therapeutic would not be specific unless the condition that is to be diagnosed or treated is identified.
>
> *Substantial:* A substantial industrial application is one which defines a 'real world' use. In other words, utilities that require further research in order to identify or confirm the use of a gene or its product are not considered to be substantial. Therefore the industrial application cannot be considered to be substantial if the only confirmed use of an invention is as a tool in studying its own properties. An example of such a situation is where the precise function of a gene or its encoded protein is unknown or merely speculative and further research is required in order to confirm this function.
>
> *Credible*: An invention can be considered to have a credible industrial application if a person skilled in the art would accept that the invention could realistically be given such a use. For example, the use of a gene sequence as a probe is a credible utility as such uses of gene sequences are common.

29 Therefore, following the 'specific, substantial and credible' test for the industrial application of a gene sequence, it is necessary to provide information and/ or evidence of (i) the particular gene/ gene product claimed (the specific test); (ii) the particular use of the gene/ gene product, based upon its function, wherein the use is not speculative and does not need confirmation by means of further research (the substantial test); and (iii) a use of the gene/ gene product that would be accepted by a person skilled in the art.

30 As an assessment of industrial application, the examiner used the "specific, substantial and credible" test referred to in the USPTO Utility Guidelines. This test has also been incorporated into the Guidelines published by the UK Patent Office, and I have noted that this was also used by the EPO opposition division in *Icos*, which would suggest to me to be a standard also used by the EPO. I am aware that this has not yet been tested

in the UK courts, but in the absence of such a decision I agree that it is a method of consistently assessing the industrial application of inventions. Consequently I have used the specific, substantial and credible test when considering the industrial application of the ZZAP1 polynucleotides and polypeptides. I have also noted Mr Bassett's point that decisions of the opposition division are not binding in UK law, however I have considered the *Icos* decision when reaching my conclusion on industrial application because these can offer guidance.

Assessment and conclusion on industrial application

31 The examiner's objections were based upon the fact that no function had been provided for the polynucleotides or the polypeptides of the application. On looking at the facts of the case, it is clear to me that at the time of filing the applicant did not know for certain what the function of the ZZAP1 protein actually was. The applicant has ascribed the function of V-ATPase to ZZAP1 due to the V-ATPase motifs that are present in the protein, and consequently predicts that ZZAP1 will play a role similar to that of other proteins containing V-ATPase motifs. However, the application does not suggest any role for the other motifs found in the ZZAP1 protein, as described on page 7 line 16-22 of the application, and in my opinion these motifs may play an important role in the determination of the precise function of ZZAP1. It is clear to me that further research is required in order for the proposed function of ZZAP1 to be verified. Consequently, in my opinion the proposed industrial application is not substantial. I have also considered the passages on pages 2- 4, which discuss the role of V-ATPases in a variety of celluar processes and disorders. These roles are related to a variety of different functions for the V-ATPases, such as endocytosis, osteoclast acidification, and cell growth and differentiation, and this diversity in functions suggests to me that merely assigning the function of "V-ATPase" to a protein is not necessarily sufficient to identify the role of that particular protein in its natural environment; the proposed utility of ZZAP1 would therefore appear to not be specific in light of this. I have also noted that the application has mapped the ZZAP1 gene to chromosome 17q23, and lists several diseases that are also mapped to this region. However, none of these diseases are related in terms of their underlying mechanisms and none have been previously associated with V-ATPases, and I also do not consider that the association of a V-ATPase, such as ZZAP1, with these diseases is specific. I accept that the proposed uses of the gene as probes and in diagnostics etc are common uses of gene sequences and therefore they are uses that a skilled man would consider to be credible. However, without a definitive role for these probes/ diagnostics etc in diseases such uses are agin clearly not specific. Therefore I do not believe the application demonstrates a specific, substantial and credible industrial application for the ZZAP1 gene or protein, and I will now expand upon the reasons for this belief.

32 At the hearing, Mr Bassett began by distinguishing between the industrial application of gene and protein sequences, and disagreeing with what he considered to be the examiner's opinion that you cannot have one without the other. However, I do not agree with this. The central dogma of biochemistry is that "DNA makes RNA makes protein", and it is this relationship between the DNA and the protein that links them together in function and use. The application relates to a gene sequence, the ZZAP1 gene, and as the gene itself is expressed and a protein is produced, the two are clearly linked. It is the protein that has the role in the cell, and therefore it is the function of this that, in my opinion, determines the underlying utility of the gene.

33 Mr Bassett discussed the decision of the Court of Appeal in *Chiron* with respect to industrial application, and considered the facts of present case in relation to the facts of the *Chiron* case. He explained that the claim lacking industrial application in *Chiron* was to a class of polypeptides encoded by polynucleotides that would hybridize to some or all of the hepatitis C genome, and that these polypeptides may not bear any functional relationship to the hepatitis C polypeptides defined as the invention. I agree that the facts of the present case are different to those of *Chiron* as the polypeptides and polynucleotides claimed are related structurally and functionally to ZZAP1. However, the arguments made by the examiner in his reports are based upon the fact that no function of the ZZAP1 polypeptide has been verified, and therefore whilst the polypeptides and polynucleotides of the present application do bear a functional relationship to ZZAP1, it is unclear what this functional relationship might be. In my consideration of *Chiron*, I have taken into account the principle behind this decision. In particular, I have considered the section specifically referred to by Mr Bassett the section of the decision that stated that "*industry does not exist in that sense to make or use that which is useless for any known purpose*", which was also referred to by the examiner in his examination reports. In *Chiron* it is clear that the polynucleotides and polypeptides claimed do not have any known purpose. Indeed it is unclear what the polynucleotides and polypeptides might be, let alone what use they might be. In the present application it is clear that the polypeptides and polynucleotides claimed are ZZAP1, and therefore the facts are clearly different in this regard. The applicant has also suggested a use for ZZAP1, based upon a predicted function for the polypeptide. However, it is this predicted function that makes the industrial application of these polynucleotides and polypeptides uncertain, and consequently it is unclear to me what useful purpose these polypeptides and polynucleotides might have in industry.

34 Before this hearing, Mr Bassett submitted details of the GeneStorm clones, which are for sale by Invitrogen® on their web site. These GeneStorm clones are merely expression tested polynucleotides representing 1,800 human open reading frames, and in Mr Bassett's mind these clones are similar to the polynucleotide of the application yet are for sale by a reputable company. Consequently, in his opinion the fact that these similar clones are for sale means that they have a use in industry. I have looked at the GeneStorm clones, and agree that the information relating to these clones suggests that they are similar in nature to the polynucleotides of this application. No function has been ascribed to these clones, all that is provided is a description of the human gene most similar to each clone. They are merely cDNA sequences that have been cloned and expression tested, and in this regard they do bear a similarity to the polynucleotides of this application. However, in my mind, just because something is for sale does not necessarily mean that anybody will purchase that item and find a use for it. Selling an item does not necessarily make it "useful" for the purposes of industry or otherwise. Even if these clones are purchased, they are, as Mr Bassett suggested, sold as research materials; they are a starting point in a research program. In my opinion such research materials do not have an industrial application. The industrial application comes later, following the research, when the polynucleotides and their expressed products have been properly characterized and their function determined. Therefore, I do not consider that simply because clones similar to the ZZAP1 gene of this application are for sale on the Invitrogen® web site this inherently gives the polynucleotides an industrial application.

35 Referring now to *Icos*, the opposition division also considered that "*…the potential*

uses disclosed in the application are speculative, i.e. are not specific, substantial and credible and as such are not considered industrial applications". In my opinion the framework of the *Icos* patent is very similar to the present application. Both applications relate to the identification and isolation of novel genes, yet the applications contain little more than an expression profile of the gene and a predicted function based upon a similarity to an exisiting protein. Consequently, as the opposition division decided in *Icos,* I believe that the present application also fails to demonstrate a specific, substantial and credible industrial application for the ZZAP1 polynucleotides and polypeptides

36 In *Icos,* the opposition division found that "*the disclosure of a predicted function of a protein in combination with a method of verification of this function is not necessarily adequate to sufficiently disclose the function of the protein*", and I have considered Mr Bassett's assertion that the term "necessarily" within that phrase suggests that in certain circumstances the EPO would accept that a predicted function would be sufficient. The example used in *Icos* was that of predicting a specific enzymatic activity, and the opposition division stated that this predicted function in combination with a method of verification of said predicted function would be sufficient. In my opinion, the situation that the opposition division was envisaging in this example is where the newly identified protein was highly homologous to a previously characterized protein, and was a member of a family of enzymes with highly specific activities with highly similar targets and downstream effects. That is not the situation that we have here as not only does ZZAP1 bear no homology to existing V-ATPases other than at its V-ATPase domain, it is also clear that V-ATPases have a wide range of cellular activities that have varying downstream effects. Even if my interpretation of the opposition division is incorrect, then I would still find that the predicted function is not sufficient in this case. The opposition division made it clear that they would require a method of verification of the predicted function, yet there is no such method disclosed within the application. Whilst the application contains methods for cloning, expression analysis, production of proteins and antibodies, and proposes therapeutic uses and diagnoses, there is no disclosure whatsoever of a method to verify the predicted enzymatic function of ZZAP1. Therefore, even if I accepted the predicted enzymatic function for ZZAP1, the application does not provide enough information to verify this, and therefore I cannot see how this predicted function would be sufficient in light of the requirements suggested by the opposition division in *Icos*.

37 I have also noted that, again in *Icos,* the opposition division did not agree with the patentee that the specification fulfilled the requirements of industrial application as the receptor could be made and used, as per Article 57 EPC. They considered that as the uses of the receptor were merely speculative they could not be considered to be industrial applications. In my mind this appears to be along the same lines as *Chiron*, where the Court considered that industry did not exist to make something that was useless. It is this situation that we have in the present application. With only a speculative function, it is difficult for me to see how the polynucleotides and polypeptides of the present invention can be anything other than useless. Clearly they could be used, but I cannot see how they could be used in a useful manner without any knowledge of what the polynucleotides or polypeptides actually do.

38 I turn now to the Muroi paper, which discloses a vacuolar type ATPase, which is the proposed function of the ZZAP1 protein of this application. This paper demonstrates

the inhibition of the excretion of glycoprotein G from vesicular stomatitis virus by folimycin, which is a specific inhibitor of V-ATPase. Mr Bassett compared the disclosure of this paper with a passage on page 4 line 12-20 of the application, which stated a role of V-ATPase domains in the development of AIDS, specifically in the internalization of Nef. It is clear from the Muroi paper and the references referred to on page 4 of the application that a role of V-ATPases in the pathogenesis of viral infections has been demonstrated. However, none of these papers disclose such a role for the ZZAP1 protein, and moreover they do not suggest that all members of the V-ATPase family have such a role. Indeed, it is clear to me from what is disclosed on pages 3 and 4 of the present application that V-ATPases serve a wide variety of roles in different cellular processes and in different cell types and therefore I cannot accept that all V-ATPases, including ZZAP1, would have such a role in a viral infection

39 If, for the sake of argument, I accepted that role of the ZZAP1 protein is as a V-ATPase, would this be enough to provide an industrial application for the protein? I would have to answer no to that question because of the many different roles that these V-ATPase proteins play in a cell, and these roles differ between different cell types and V-ATPase family member. There is nothing within the application that says exactly what role the ZZAP1 protein plays. The only experimental data provided is the expression profile of ZZAP1, and this demonstrates that the gene is expressed in brain, liver, testis, skeletal muscle, heart and bone marrow. This does not provide any guidance towards the precise role of the ZZAP1 protein in these cells.

40 I have considered Mr Bassett's assertion that the present situation was analogous to a conventional situation with chemical compounds with a predicted utility. I agree with Mr Bassett that not every compound falling within a scope of a claim would be tested in a human pharmaceutical context, and it is rare to have human or even animal data. However, in any application I would expect some evidence that the compound displays the properties claimed and all of the compounds claimed would be expected to display the same properties and have the same effect in a pharmaceutical context. In other words I would expect a specification to identify at least one compound that had been shown to work. Such evidence would usually be in the form of *in vitro* experimental data, and this data is lacking in the present application. However, I have noted that application maps the ZZAP1 gene to chromosomal region 17q23.3, and lists diseases that are also mapped to this region. These diseases include hypertension, psoriasis, malignant hyperthermia and Meckel syndrome. However, there is no suggestion in the prior art that V-ATPases are associated with any of these diseases, and therefore in my opinion this sheds further doubt upon the function of the ZZAP1 protein.

41 Mr Bassett referred to pages 37-43 of the application as demonstrating that the application complies with paragraph 6 of Schedule A2 to the Act. These pages list uses of the ZZAP1 gene and its fragments as probes, primer, on microarrays, or in expression analysis. Each use is for the detection of expression or amplification of the ZZAP1 gene, and without a disclosed utility for the ZZAP1 gene or its expression product, I cannot see what use these techniques would be. Consequently I do not believe that the application discloses an industrial application for the polynucleotide sequences.

Finding on industrial application

42 Thus I have found, for the above reasons, that the human ZZAP1 nucleotide sequences of SEQ ID_NO: 1 or SEQ ID_NO: 2 or one encoding the amino acid sequence of SEQ_ID_NO:3, the complements of SEQ_ID_NO:1 and 2, and the polypeptide of SEQ_ID_NO:3 as claimed in claims 1 and 12 do not have an industrial application according to section 1(1)(c) of the Act. There is no disclosed function of the ZZAP1 gene or its expression product, and as the industrial application of a gene flows from its function then there cannot be any industrial application for ZZAP1. It is also considered that variants of these sequences, uses of these sequences, and antibodies raised against these sequences are also lacking an industrial application as their industrial application would flow from that of the ZZAP1 gene and polypeptide themselves. Consequently claims 1-29 are not capable of industrial application.

43 As I have found that the polynucleotide sequences of claims 1-5, 7, 8 and 26 are not capable of industrial application according to section 1(1)(c) of the Act, these claims therefore do not comply with paragraph 6 of Schedule A2 to the Act.

Inventive step

The examiner's objection

44 The examiner's objection was based on the disclosure of a cDNA and hypothetical protein from *Macaca fascicularis* entered into GenBank with accession numbers AB055276 and BAB21900 respectively, both of which were available from 6 February 2001. The hypothetical protein displayed 93% identity at the amino acid level to ZZAP1. The objection was also based upon the disclosure of WO 01/53455 A2, specifically the sequences represented by SEQ ID Nos 327 and 1066, which was published on 26 July 2001. The sequences represented by SEQ ID Nos 327 and 1066 disclose human cDNA and protein sequences respectively, with the protein sequence as represented by SEQ ID no 1066 having 85% identity with an approximately 500 amino acid segment of ZZAP1.

45 In his first report of 28 January 2003 the examiner stated that the invention was obvious given the prior disclosure of the Macaque sequences and the HYSEQ sequences. It was obvious, in his opinion, to identify a human gene with such close identity to these proteins. The examiner maintained this inventive step objection in his second examination report of 19 May 2004. He argued that given the 93% identity to the macaque sequence it would be obvious to look for a human counterpart with a reasonable expectation of success, and that given the level of identity any attempt to identify the human homologue of the macaque gene would lead directly to ZZAP1. He also argued that given the 85% identity of protein of the application to the HYSEQ protein, it would be obvious to search for closely related human genes, and that this was despite the fact that no function had been ascribed to the HYSEQ sequence, or that there was no suggestion that this human sequence encoded a vacuolar ATPase.

The applicant's position

46 Mr Bassett began by stating that neither the macaque sequence or the HYSEQ sequence gave any indication of the function of the gene or the protein that it encodes. He therefore suggested that there was no incentive to even look for a human corresponding gene. Mr Bassett referred *Genentech Inc.'s Patent* [1989]RPC 147-287

and *Brugger and Others v. Medic-Aid Ltd* [1996] RPC 635-666, and submitted that in each of these cases there was a great emphasis on the motivation in those cases to arrive at what was claimed, and that such motivation was absent in relation to this particular application. In Mr Bassett's opinion the only motivation was a general desire to ultimately make sense of the human genome, and that was not sufficient motivation to render everything identified as a result as obvious.

47 Mr Bassett elaborated upon the question of motivation, and drew an analogy with the art of pharmaceutical chemistry where a compound may have been synthesized out of chemical curiosity but no function had been ascribed to it. A patent applicant may then synthesise compounds with a structural similarity to the prior art compound, and characterize and give an indication of utility for the compounds. In Mr Bassett's opinion he would be granted a patent for those similar compounds as the mere structural similarity between his compounds and the prior art compounds would not prevent them from being inventive. Whilst it would be necessary for him to exclude the prior art compound *per se* for purposes of novelty, Mr Bassett asserted that inventive step would not be a problem as he had indicated a utility for his compounds whereas the prior art did not.

48 Referring to the macaque sequence, Mr Bassett pointed out that there was no indication of utility for either the polynucleotide or polypeptide of this sequence. He then referred to the HYSEQ sequence, where the examiner had stated that the polypeptide sequence had about 85% sequence identity to the polypeptide sequence of the application, and accepted that the reverse complement of the HYSEQ polynucleotide sequence had a 99% similarity to the polynucleotide of the application. Mr Bassett pointed out that there were 739 polynucleotide sequences listed in the HYSEQ document, and a corresponding number of polynucleotide sequences, which he considered to be a huge disclosure of sequences.

49 Mr Bassett referred to page 152 of the HYSEQ document, which is part of Table 2, headed "The nearest neighbour results", which listed the human fragments identified in the HYSEQ application along with what the sequences might represent based upon similarity searching. He pointed out that the polynucleotide cited against the application was from *Schistosoma japonicum*, and only displayed 28% identity with the polynucleotide of the application. Furthermore, Mr Bassett pointed out that there was no information regarding the polypeptide sequence SEQ ID No 1066 other that its association with nucleic acid sequence SEQ ID No 327. Therefore, in Mr Bassett's opinion, the polynucleotide and polypeptide sequences cited against the application were hidden amongst the other seven hundred sequences within the HYSEQ application, and the only function ascribed to it was a myosin from *Schistosoma* which he did not consider to be meaningful as the similarity was so low Mr Bassett thought it unlikely that anybody would attach any importance to it.

50 Mr Bassett submitted that given the lack of homology with any human gene, the sequence represented by the HYSEQ application would not provide any motivation for the search for a corresponding human gene. In addition, Mr Bassett asserted that as they had looked for a corresponding gene in the HYSEQ application and the closest result they had obtained was a gene from *Schistosoma* with a low level of identity, this would also not provide any motivation for the search for a human gene. In Mr Bassett's opinion, the HYSEQ document teaches away from the possibility of a human

gene corresponding to the fragment represented by SEQ ID No 327.

51 In contrast, Mr Bassett stated that the sequence of the present application was a specific sequence representative of a true gene. The application demonstrated expression in various tissues, with different levels of expression in different tissues, which in his opinion would facilitate the use of the sequences in, for example, diagnostic arrays, and Mr Bassett submitted that this went beyond anything that was disclosed in either of the prior art sequences. Consequently, in his opinion, there was no motivation whatsoever to even start down the path, let alone arrive at the specific sequences claimed in the application.

The Law

52 Section 1(1)(b) states that a patent may only be granted for an invention if it involves an inventive step. This requirement is developed in section 3 which states:

> "3. An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 2(2) above (and disregarding section 2(3) above."

53 The test for obviousness should be an objective one as was made very clear by the Court of Appeal in *Windsurfing* when it stated that the question of obviousness:

> "…has to be answered, not by looking with the benefit of hindsight at what is known now and what was known at the priority date and asking whether the former flows naturally and obviously from the latter, but by hypothesizing what would have been obvious at the priority date to a person skilled in that to which the patent in suit relates…"

This led the Court of Appeal to formulate its structured approach to the question of obviousness in the four steps of the *Windsurfing* approach.

Assessment and conclusion on inventive step

54 It has been accepted by the applicants that the macaque sequence displays a high level of identity, 93% identity to be exact, to the ZZAP1 sequence. The applicants also accept that the reverse complement of the HYSEQ polynucleotide sequence, which is a human gene, displays a 99% similarity to the polynucleotide sequence of the application. However, in Mr Bassett's opinion neither of these sequences provide any motivation to look for the corresponding human gene as there was no disclosure of the function of these sequences, and he referred to *Genentech* and *Brugger* as placing great emphasis upon motivation to arrive at what was claimed. As Mr Bassett stated, the only motivation was a general desire to make sense of the human genome, and in my mind this alone is a sufficient motivation to arrive at the present invention given that the human genome has been sequenced and the logical next step is to determine what genes exist and what functions these genes have. However, I will also consider whether the prior art sequences would have provided a further incentive to arrive at the sequences of the invention when I am deciding whether the skilled addressee would have located the claimed human ZZAP1 sequence given the sequences available in the prior art.

55 Applying the first step of the *Windsurfing* approach, the inventive concept is identified as an isolated polynucleotide of SEQ_ID_NO:1 or SEQ_ID_NO:2 or one encoding the amino acid sequence of SEQ_ID_NO:3, the complements of SEQ_ID_NO:1 and 2, and the polypeptide of SEQ_ID_NO:3. It seems that this is what the applicant was seeking and once found would provide a foundation for everything else that is claimed.

56 Taking into account the second *Windsurfing* step, it is considered that the notional skilled person or addressee would be one trained in the field of molecular biology and would be familiar with the bioinformatics tools and web-based genomic resources of the time. I would also consider that the skilled person would be aware that the overall similarity between full-length genes and proteins can be low but that the majority have conserved regions within their functional domains that are indicative of similar function. This last consideration was raised at the meeting held with Amersham in November 2003 and was accepted by both parties.

57 Now that the common general knowledge of the skilled addressee has been established the third *Windsurfing* step, the critical difference between the invention in suit and what was known from the macaque sequence and HYSEQ sequence must be identified. The macaque sequence discloses a polynucleotide sequence that displays 97% identity to the polynucleotide sequence of the application, across its entire sequence, and a polypeptide sequence that displays 93% sequence identity to the polypeptide sequence of the present application. The macaque sequence is merely an entry in GenBank of a cDNA clone isolated from the brain of *Macaca fascicularis*, which encodes a protein of 590 amino acids in length. This sequence was first accessible *via* the NCBI database on the 6th of February 2001, with the accession number BAB21900. The reverse complement of the HYSEQ polynucleotide sequence displays a 99% identity to the polynucleotide sequence of the present application across a 995bp section, and the sequence of the HYSEQ polypeptide displays an 85% identity to the polypeptide of the invention across a 496 amino acid section. The HYSEQ sequence has also not been characterized, but Table 2 of the HYSEQ application suggests a similarity to a myosin from *Schistosoma japonicum*.

58 I can now move on to the fourth and final *Windsurfing* step: whether, when viewed without any knowledge of the alleged invention, the differences constitute steps which would have been obvious to the skilled person or whether they require any degree of invention? The question of whether it would have been obvious to the addressee to obtain a human ortholog of the macaque protein must be considered, and whether it would have been obvious to further characterize the HYSEQ sequence. Mr Bassett made the point at the hearing that, unlike that shown in *Windsurfing, Genentech, Brugger* and *Farber,* there was no incentive to go from the macaque sequence or the HYSEQ sequence to the sequence of the invention. However, I believe that there was such an incentive, and will now expand my reasons for this belief.

59 I will discuss the HYSEQ sequence first of all, which is the human gene sequence with similarity to the ZZAP1 sequence. The polynucleotide sequence, SEQ_ID_No: 327, listed in the HYSEQ application is in fact the reverse complement of the sequence of the present application, and was identified by the examiner as BLAST searching looks for the complementary and the reverse-complementary sequences of the query sequence. Despite being the reverse complement, the polypeptide sequence,

SEQ_ID_No: 1066 does bear a share degree of homology with the ZZAP1 polypeptide sequence, which would suggest that the applicant considered the reading frame on the reverse strand. Looking at the polypeptide sequence on page 215, it appears to me that there is an uncertainty over the precise sequence, for example there are possible stop codons at positions 120 and 450. Furthermore, the sequence has not been characterized and therefore its function is unknown. As Mr Bassett pointed out, a database search using the polynucleotide SEQ_ID_No: 327 revealed a relatively weak similarity to a myosin from *Schistosoma japonicum*, and this is detailed on page 152 of the HYSEQ application; no search was performed using the reverse complement. Given the lack of characterization of the gene product, and the result of homology searching on page 152, I would agree with Mr Bassett that there was little motivation for a skilled person to further characterize this gene. Therefore, I do not think that it would be obvious for the skilled man to arrive at the sequence of the present application from looking at document WO 01/53455, and consequently the inventive step objection in relation to this document is not well founded.

60 It is well known in the art to isolate a gene from one species based upon its previous identification in another species, and I have considered this common general knowledge in my assessment of the inventive step of the ZZAP1 sequence in light of the published macaque sequence. It is also well known that there is a significant homology between genes of functional importance in different species. However, I am aware that at the priority date of the present application the function of the macaque gene was not known, and therefore its importance as a gene could not have been assessed. Nevertheless, macaques and humans have a very close phylogenetic relationship, both belonging to the order primates, and therefore in my mind there would be a very good chance of finding a human ortholog of a macaque gene. As Mr Bassett pointed out, there was a general motivation to determine the structure of the human genome, and it is necessary for me to consider whether this motivation, in combination with the sequence of a gene from a closely related species, would be sufficient to encourage a skilled man to search for the human equivalent.

61 In coming to a judgement on inventive step in *Genentech*, Dillon, L.J. used the tests set out by Diplock, L.J. in *Johns-Manville Corp.'s Patent* [1967] RPC 479 and Graham, J. in *Olin Mathieson Chenical Corp*. v. *Biorex Laboratories Ltd*. [1970] RPC 157. Referring to Diplock, L.J. in *Johns-Manville* he stated that:

> "…he expressed the view that the case that an allegedly inventive idea was at the priority date 'obvious and clearly did not involve any inventive step' would have been made out if before the priority date the man skilled in the art would have thought the idea well worth trying out in order to see whether it would have beneficial results. He took the view that it would be enough that the person skilled in the art would assess the likelihood of success as sufficient to warrant actual trial, without postulating prior certainty of success."

62 Consistent with Dillon's judgement I consider that the person skilled in the art would have assessed that, given the high degree of sequence similarity between human and macaque gene sequences, there would be a reasonable expectation of success in identifying the human equivalent of the macaque sequence to warrant a trial. Such a step would therefore have been obvious to try. A successful outcome to this trial would provide another piece of the jigsaw that is the human genome, and would move

the scientific community one (albeit small) step closer to the understanding of the entire human genome. This elucidation of the human genome would provide a necessary foundation for the understanding of many human diseases and disorders. I accept that success would not have been certain, and that without a function for the macaque sequence the importance of this gene could not be known at the priority date of the present application. Nevertheless I consider that the potential major benefits, which would come from success, would have outweighed any thought of failure.

63 Now I am confident that the availability of the macaque sequence would have led the skilled person to look for a human ortholog, the question of whether the techniques for obtaining these sequences would have required any inventive ingenuity on the part of the addressee must now be considered.

64 It has been common practice for many years to use the BLAST tools to identify orthologues of known nucleotide and polypeptide sequences. The BLAST software was widely available at the priority date and would have been well known to the skilled addressee. Dr Bentley describes in his declaration how the BLAST tool may be use to detect genes in genomic sequences:

> "…the Basic Local Alignment of Sequences Tool ('BLAST') program…would be used to align the sequence of interest to all sequences in Genbank, and the program would return to the user all matches, ranked in order of % identity. The results could be examined directly, or visualised all together using a number of commonly available viewing tools…The search could also be carried out at the protein level, by first translating the sequence of interest in all six reading frames and then taking the resulting putative protein sequences and matching them (using BLAST) to all known protein sequences in the public databases. Using these approaches, any clues to the existence of a gene or part thereof, such as an exon, would form the basis for identifying a gene."

65 Dr Bentley therefore establishes that gene identification can be carried out using either nucleotide or protein sequences as the searching tool.

66 Looking at page 134 of the application, it is evident that a BLAST search using the sequence of the invention identified multiple human, mouse, chicken and cow ESTs with a sequence closely related to ZZAP1. Given the sequence identity between the macaque and human polynucleotide sequences, a BLAST search using the macaque sequence would produce the same ESTs. Therefore, even though the human gene had not been identified at the priority date of the application it is clear that the search of a human EST database using the macaque sequence would identify human ESTs with sequences closely related to the macaque gene, including ZZAP1. The identification of such sequences would, in my opinion, provide further motivation for the isolation of the human ortholog of the macaque gene.

67 In *Genentech* at page 243, lines 5-8, Dillon L.J. cites the judgement of Whitford J. in *Philips (Bosgra's) Application* [1974] RPC 241 and states that:

> "…to render an invention obvious it was not necessary that the materials in question should have been the first choice of the notional research worker; it was enough that the materials were 'lying in the road' and there for the research

worker to use".

68 In the present case the material, the sequence of the human genome containing the ZZAP1 sequence was indeed "lying in the road" for the skilled man to use. Moreover, human ESTs comprising sequences related to the macaque sequence were available at the priority date of the invention, thus providing the skilled man with a starting point in his search for the human ortholog of the macaque gene. Consequently, it is sufficient for me to accept that the skilled addressee would have found the sequences of SEQ_ID_NOs 1-3 of ZZAP1 using the macaque DNA and protein sequences as a springboard, without the need for inventive ingenuity.

69 In the agent's letter of 30 January 2004 the method of gene identification is described and the apparent difficulty in obtaining genes from published sequences is addressed. The letter stated that:

> "…the applicant adopted a different approach to identifying the polynucleotides and polypeptides of the invention than had hitherto been used; this approach is described in Example 1 of the application. Potential exons were identified by data mining of the human genome and a selected group then screened for tissue specific expression by linking these genomically-derived single exon probes to microarrays. Those polynucleotides which hybridised to the probes were then cloned and sequenced to identify the full length genes. BLAST searches were subsequently conducted to identify known polynucleotide and polypeptide homologues of this gene.
>
> The inventiveness of this approach lies not only in the selection of which exons to screen for tissue specific expression but also in the selection of which exons to clone following expression analysis.
>
> This approach is therefore totally different to that of selecting a polypeptide of interest and conducting a homology search of the human genome to identify an equivalent human gene."

70 That the applicants have used a different, "proprietary" method to identify the human ZZAP1 gene is of no significance and does not provide the claimed sequences with an inventive step since the claims are not directed to the method of identification nor to the product of such a method. Rather than carry out the applicants proprietary method to isolate ZZAP1, the skilled person would have concentrated on the macaque polynucleotide sequence, and used that in BLAST searches to identify related genes in humans.

Finding on inventive step

71 Thus I have found, for the above reasons, that the human ZZAP1 polynucelotide sequences of SEQ_ID_NO:1 or SEQ_ID_NO:2 or one encoding the amino acid sequence of SEQ_ID_NO:3, the complements of SEQ_ID_NO:1 and 2, and the polypeptide of SEQ_ID_NO:3 as claimed in claims 1 and 12 do not have an inventive step having regard to the prior disclosure of the macaque sequence and the common general knowledge at the priority date. It is also considered that variants of these sequences, inasmuch as such variants must share a common, specific activity to the sequences of SEQ _ID_NOs 1-3, also lack an inventive step. The skilled person

would be able to routinely determine the function of any human sequence identified using the macaque sequence as a starting point, and once this function is determined he would appreciate exactly what the possible variations could be. The test he would have to carry out in order to determine whether the variations produced, for example, a polypeptide having the activity of the protein of SEQ_ID NO-3 would be a routine exercise. The remaining claims 2-11 and 13-29 all relate to standard features or applications of polypeptides and polynucleotides which would be considered when any gene and/or protein is identified. Therefore since none of these claims amount to an inventive use of the sequences of SEQ ID NOs 1-3 these claims also lack an inventive step.

72 Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days

P M Back
Divisional Director acting for the Comptroller