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## PATENTS ACT 1977

APPLICANT Aeomica Inc

ISSUE Whether application number GB0201819.0  
complies with sub-sections 1(1)(b)

HEARING OFFICER P M Back

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### DECISION

#### Introduction

- 1 Patent application No. GB 0201819.0 (“the application”) entitled “Human posh-like protein 1” was filed on 28 January 2002 by Aeomica Inc (“the applicant”) and claimed priority from an earlier application filed in the USA on 30 January 2001. The application was published on 19 March 2003 as GB 2379662 A.
- 2 The first examination report under section 18(3) was issued on 19 August 2002 as part of a combined search and examination. In this report the examiner raised an objection to lack of inventive step on the basis of an earlier disclosure of a mouse protein in a paper published in The EMBO Journal, Volume 17, 1998, Tapon, N. *et al.*, “A new Rac target POSH is an SH3-containing scaffold protein involved in the JNK and NF- $\kappa$ B signalling pathways”, pp.1395-1404 (“the Tapon paper”). Also raised in the first examination report was an industrial application objection and objections relating to paragraph 3 of schedule A2 to the Patents Act and support. In a second examination report, issued 01 September 2003, the examiner maintained the industrial application and inventive step objections; the other objections having been overcome by amendment. 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. Following this meeting the industrial application objection was waived in a letter issued 12 December 2003. In a third examination report, issued 09 March 2004, the examiner maintained an objection that the invention lacked an inventive step in view of the disclosure in the Tapon paper. The applicant did not accept the examiner’s view on this matter and requested a hearing in a letter dated 10 May 2004.
- 3 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 2000. Also submitted on 25 November 2004 was a skeleton argument.

### **The application**

- 4 The application relates to the human posh-like protein 1 (“POSHL1”), a protein which is stated to be an onco-protein which interacts with both small GTPases and the downstream effectors in the signal transduction pathway. The application provides isolated nucleic acids that encode POSHL1, variants having at least 65% sequence identity thereto, degenerate variants thereof, variants that encode human POSHL1 proteins having conservative substitutions which retain the biological and functional activities of human POSHL1 proteins, cross-hybridizing nucleic acids and fragments thereof. In particular the application relates to a POSHL1 nucleic acid which comprises a specific nucleotide sequence (SEQ\_ID\_NO: 1 or SEQ\_ID\_NO: 2) and a POSHL1 polypeptide which comprises a specific amino acid sequence (SEQ\_ID\_NO: 3). SEQ\_ID\_NO: 1 presents the cDNA of human POSHL1 and includes the 5’ and 3’ untranslated (UT) regions and SEQ\_ID\_NO:2 presents the genomic DNA of POSHL1.
- 5 It is stated that the nucleic acid sequences SEQ\_ID\_NO: 1 and SEQ\_ID\_NO: 2 were identified using the applicant’s own proprietary algorithm and that the deduced protein sequence shares certain domains and an overall structural organization with the mouse POSH protein. The application explains that such similarities imply that human POSHL1 plays a similar role to that of mouse POSH protein and therefore has a potential role as an onco-protein that interacts with both GTPases and effectors in the signal transduction pathway.
- 6 The claims of the application relate to various aspects of the invention as follows:
  - “1. An isolated nucleic acid that encodes a POSH-like onco-protein that interacts with both small GTPases and the downstream effectors in the signal transduction pathway, comprising: (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);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),wherein said isolated nucleic acid consisting of a nucleotide sequence selected from group (b) is no more than about 100 kb in length.
  2. The isolated nucleic acid of claim 1 wherein said nucleic acid, or the

complement of said nucleic acid, encodes a polypeptide having the ability to relay signals in a signal transduction pathway that is associated with tumor metastasis by interacting with both small GTPases and the downstream components in the pathway.

3. The isolated nucleic acid of either of claims 1 or 2, wherein said nucleic acid, or the complement of said nucleic acid, is expressed in fetal liver, adult liver, brain, lung, placenta, bone marrow, prostate, kidney, testis, adrenal gland, and/or skeletal muscle.
4. A nucleic acid probe, comprising: (a) a nucleic acid of claim 1; or (b) at least 17 contiguous nucleotides of SEQ\_ID\_NO:4.
5. The probe of claim 4, wherein said probe is detectably labeled.
6. The probe of either of claims 4 or 5, attached to a substrate.
7. A microarray, wherein at least one probe of said array is a probe according to claim 4.
8. The isolated nucleic acid molecule of any of claims 1-3, wherein said nucleic acid molecule is operably linked to one or more expression control elements.
9. A replicable vector comprising a nucleic acid molecule of any of claims 1-3 or 8.
10. A non-human host cell transformed to contain the nucleic acid molecule of any of claims 1-3 or 8 or 9 or the progeny thereof.
11. A method for producing a polypeptide, the method comprising: culturing the host cell of claim 10 under conditions in which the protein encoded by said nucleic acid molecule is expressed.
12. An isolated polypeptide produced by the method of claim 11.
13. An isolated polypeptide, comprising: (a) an amino acid sequence of SEQ\_ID\_NO\_3; (b) an amino acid sequence having at least 65% amino acid sequence identity to that of (a) and displaying the same biological and functional activities of (a); or (c) an amino acid sequence according to (a) in which at least 95% of deviations from the sequence of (a) are conservative substitutions.
14. A transgenic non-human animal modified to contain the nucleic acid molecule of any one of claims 1-3 or 8 or 9.
15. A method of identifying agents that modulate the expression of human POSHL1, the method comprising: contacting a cell or tissue sample believed to express human POSHL1 with a chemical or biological agent, and then comparing the amount of human POSHL1 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 POSHL1.

16. A method of identifying agonists and antagonists of human POSHL1, the method comprising: contacting a cell or tissue sample believed to express human POSHL1 with a chemical or biological agent, and then comparing the activity of human POSHL1 with that of a control, increased activity relative to a control identifying an agonist, decreased activity relative to a control identifying an antagonist.
17. A method of identifying a specific binding partner for a polypeptide according to claim 13, the method comprising: contacting said polypeptide to a potential binding partner; and determining if the potential binding partner binds to said polypeptide.
18. The method of claim 17, wherein said contacting is performed *in vivo*.
19. A method for detecting a target nucleic acid in a sample, said target being a molecule according to any one of claims 1-3 or 8 or 9, 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.
20. A method of diagnosing or monitoring a disease caused by altered expression of human POSHL1, comprising: determining the level of expression of human POSHL1 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.
21. A diagnostic composition comprising the nucleic acid of any of claims 1-3, said nucleic acid being detectably labeled.
22. The diagnostic composition of claim 21, wherein said composition is further suitable for *in vivo* administration.
23. A diagnostic composition comprising the polypeptide of claim 13, said polypeptide being detectably labeled.
24. The diagnostic composition of claim 23, wherein said composition is further suitable for *in vivo* administration.
25. A pharmaceutical composition comprising the nucleic acid of any one of claims 1-3 or 8 or 9 and a pharmaceutically acceptable excipient.
26. A pharmaceutical composition comprising the polypeptide of claim 13 and a pharmaceutically acceptable excipient.
27. Nucleic acid of any one of claims 1-3 or 8 or 9 for use in therapy.

28. Polypeptide of claim 13 for use in therapy.
29. A method of modulating the expression of a nucleic acid according to any of claims 1-3 or 8 or 9, the method comprising: administering an effective amount of an agent which modulates the expression of a nucleic acid according to any one of claims 1-3 or 8 or 9.
30. A method of modulating at least one activity of a polypeptide according to claim 13, the method comprising: administering an effective amount of an agent which modulates at least one activity of a polypeptide according to claim 13.”

### **The outstanding objection**

- 7 The matter that remained unresolved at the time of the hearing before me was whether the subject matter of claims 1-30 involves an inventive step.

### **Inventive step**

#### *The examiner's objection*

- 8 The examiner's objection was based on the disclosure in a paper published in The EMBO Journal, Volume 17, 1998, Tapon, N. *et al.*, “A new Rac target POSH is an SH3-containing scaffold protein involved in the JNK and NF-κB signalling pathways”, pp.1395-1404 (“the Tapon paper”). This paper was published in March 1998 and describes the POSH protein from the mouse. POSH (Plenty of SH3 domains) is named for the four SH3 (Src Homology 3) domains present in the protein. The paper describes a full-length open reading frame coding for a protein of 892 amino acids. The nucleic acid and polypeptide sequences of mouse POSH identified in this paper were submitted to the NCBI database on 01 April 1998 and given the accession number AF030131.
- 9 In his first report of 19 August 2003 the examiner stated that the invention was obvious given the POSH sequences disclosed in the Tapon paper. It was obvious, in his opinion, to look for POSH orthologs in species other than mouse and therefore the identification of human POSHL1 sequences did not involve any inventive step. The examiner maintained this inventive step objection in both his second and third examination reports of 01 September 2003 and 09 March 2004. He argued that since the goal was known (the human POSH ortholog) and that the relevant materials were readily available (the mouse POSH sequences and the human genome sequence) there would be no inventive step in isolating POSHL1. The examiner also stressed that the method the applicants had used to identify POSHL1, their proprietary algorithm, was immaterial and could not provide an inventive step since the claims were not directed to the method of identification.

#### *The applicant's position*

- 10 Mr Bassett began by stating that in the examination reports the examiner had not

specified a particular identity between the amino acid sequence in the prior art and that claimed in the application and that he had not actually alleged that it was necessarily obvious to go from the prior art sequence to the claimed sequences. From this, Mr Bassett concluded that it was implied that the principal inventive step objection was that of general data-mining. However, he began by looking in some detail at how the prior art sequence may have been used to identify the claimed sequences.

- 11 Mr Bassett proceeded to explain the process by which the prior art sequence in the Tapon paper may have been used as a starting point to identify a human homologue; the results of which process formed a part of the declaration by Dr David Bentley. Such a homologue would, in Mr Bassett's view, be the most closely corresponding sequence. Dr Bentley had used BLAST software to identify sequences in the human genome that were similar to the prior art sequence and found that the most similar sequence was on chromosome 4, the next on chromosome 8 and a third on chromosome 5. Mr Bassett stressed that Dr Bentley noted that the matches between the prior art sequence were lower to the chromosome 8 and chromosome 5 sequences and that each one represented a significant effort to characterise the gene structure. Since the sequence that was being claimed was the one on chromosome 5, Mr Bassett suggested that it was not the obvious one and that the obvious, easiest, most routine, unimaginative thing to have done would have been to arrive at the chromosome 4 sequence and to regard that as the human homologue and to develop that. According to Mr Bassett, extending the search to less similar sequences should be characterized as an open-ended research program requiring substantial input and some months of work and was not something that represents the routine and unimaginative extension of the prior art to the next step. Mr Bassett acknowledged that the skilled person could have located the claimed sequence by using the prior art sequence in the Tapon paper but not that he would have done.
- 12 Mr Bassett asserted that there was an error in the application relating to the sequence comparisons between the claimed amino acid sequence and that of the mouse POSH sequence. He explained that the figures of 33% amino acid identity and 49% amino acid similarity were incorrect and that the latter figure should relate to nucleotide similarity. Following re-alignment of the two sequences an amino acid identity of 29% and a nucleotide similarity of 48% were obtained. Mr Bassett submitted that such figures were too low for there to be any demonstrable homology between the mouse and human sequences and that it would not have been straightforward to have moved from the prior art sequence to the claimed sequences.
- 13 Mr Bassett then referred to the official letter of 09 March 2004 in which the examiner had cited from an article by Dr Kellis in The Wall Street Journal of 03 May 2003. Dr Kellis had stated (on the subject of identifying genes in the human genome) that:

“What you do, instead, is look for sequences that spell genes in other creatures and hope they spell genes in humans, too.”

Mr Bassett submitted that a mere hope is not enough to establish inventive step. He continued, again quoting from the official letter of 09 March 2004, this time not from Kellis but from the Office itself:

“...this would therefore suggest that once a gene is known in one organism, e.g.

a mouse, it would be obvious (and is also common practice, given the above quote) to search for its human homologue”

Mr Bassett stressed that the words were couched in the singular and that, given the declaration by Dr Bentley, its human homologue, the human homologue of the mouse gene, the one that is most similar, is not the one that is being claimed.

14 Mr Bassett also considered the fourth step in assessing inventive step used in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59; that is whether it was obvious to go from the prior art to the invention. He concluded that, starting from the prior art sequence in the Tapon paper, it was not obvious to go to the particular sequence that was claimed: if it was obvious to go to a sequence at all, he suggested, one would not have ended up with the one claimed.

15 Mr Bassett also made reference to an official letter on another, related application (GB0217548.7) wherein the examiner had suggested that:

“It is not the case that the gene MDZ3 could have been isolated but in time would have been isolated.”

16 Although Mr Bassett agreed that a distinction should be drawn between what could be done (which might not be obvious) and what would be done (that which should be regarded as being obvious), he suggested that the key words in the phrase were “...in time...”. In time, he argued, all inventions will be made but, simply because an invention will ultimately be made, does not mean that it is obvious. The time scale has to be considered: it has to be the logical consequence of following prior art teachings. Mr Bassett wondered whether, underlying the inventive step objection, was the examiners feeling that, in time, the human genome will be completely characterized and that therefore it should all be regarded as obvious at the priority date. He submitted that this was not the way to approach the question. Rather the question was what is the immediately obvious thing to flow from the prior art .

17 Mr Bassett also commented on the period of time that had elapsed between the publication of the Tapon paper and the priority date of the application. That three years had elapsed, a length of time which in his view was a long period in the field of human genomics but not a particularly long period in many areas of art, should be regarded as significant since if it was obvious to go from the mouse sequence in the Tapon paper to the claimed sequence then it would have occurred sooner than three years.

18 Mr Bassett then moved on to the question of whether it was obvious to use general data-mining techniques at the priority date and whether any gene that was found using these techniques should itself be regarded as obvious. On this point Mr Bassett referred to the analogy of an attempt to find an oil-eating bacteria. He explained that one might easily regard it as being an obvious and logical thing to do to take soil samples from near a well established oil well and to screen those samples in order to find a bacterium that survives in an oily environment and can actually consume the oil and grow on it. But the particular bacterium that you find would not be regarded as obvious, because you could not have written down the claim for it before you had actually done the work. You would need to find the organism, and characterize it but

you would need to have done the work, you would need to have something in your hands that you could define in some way. In relation to the present case, Mr Bassett agreed that the human genome had been screened, but the result of such a screening could not have been predicted in advance: it would not have been possible to write the claims, which are based around particular nucleic acid and protein sequences, until the screening had been undertaken. In both cases, he argued, the approach could be regarded as obvious but the results should not be regarded as being obvious: nobody would have realized that the sequences that are claimed existed as an entity nor that the gene was expressed.

- 19 Mr Bassett then cited the CIPA Guide to the Patents Act, at page 83, where Judge G.S. Rich is quoted as saying ((1978 60 JPOS 271 at 288) that:

“The good patent gives the world something it did not truly have before, whereas the bad patent has the effect of trying to take away from the world something which it effectively already had”.

Mr Bassett argued that what the applicant's were giving to the world in their application is new human gene sequences which have been identified from the human genome.

- 20 Mr Bassett also expanded on a further part of Dr Bentley's declaration that dealt with the assessment of gene prediction programs. The Genescan program was shown to detect approximately 90% of the protein coding genes but was accompanied by an overprediction of approximately fourfold. Combining Genescan with another program such as FGenes leads to a halving of the overprediction but nevertheless still a 50% failure rate; half of the genes identified using these two programs would not turn out to be expressed. Dr Bentley's declaration acknowledged that to restrict false positives by altering the parameters of these programs results in a substantial number (70-75%) of real genes being missed. Mr Bassett submitted that there were therefore limitations in using these programs and that they do not simply and inevitably guide you to the human homologue of the prior art sequence, or even to a true gene.
- 21 From the point of view of general data mining techniques Mr Bassett submitted that it was not obvious to arrive at the claimed sequences because they were not attained simply by the application of computer programs, but that human effort and ingenuity were involved. He suggested that the effort and ingenuity represented by the application represents at least as much ingenuity and effort and cleverness as the sort of inventions in other arts - such as the mechanical art - where a relatively small alteration can be made to a mechanical device and that can be considered worthy of a patent. Paying particular regard to the expression data, as discussed in Dr Bentley's declaration, Mr Bassett considered that the application represented comparable quality and was of comparable benefit to mankind and he suggested that unless there was some incentive to do what had been done in this application then the human genome would lie fallow and would not be beneficially exploited.
- 22 The expression of the genes was stated by Mr Bassett as being important since it was the detection of this expression, and in some cases differential expression between different human tissues, that was proposed to take the claimed invention beyond mere data-mining. It was stressed by Mr Bassett, that in his declaration, Dr Bentley put



great emphasis on the fact that gene expression had been demonstrated and that detection of such expression rules out the possibility of the sequence being a false positive, and furthermore that the evidence of expression takes the work beyond any routine application of computational data-mining techniques.

- 23 In a further reference to *Windsurfing* and also to *Genentech Inc. 's Patent* [1989]RPC 147-287, *Brugger and Others v. Medic-Aid Ltd* [1996] RPC 635-666 and *Farber/Monokine MIG induced by IFN-GAMMA* T 0111, Mr Bassett submitted that in each of these cases there was a considerable and identifiable incentive to arrive at what was claimed, yet in the present application there was no such specific incentive. In the present application, he argued, there was no incentive to move from the prior art because the therapeutic value of the prior art had not been characterized in the way that it had been in the *Farber* or *Genentech* decisions and it was not possible to write the claim before you had actually done the work, which was the case for the *Brugger* and the *Windsurfing* cases.

#### *The Law*

- 24 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.”

- 25 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, which has already been referred to in part by Mr Bassett.

#### *Assessment and conclusion on inventive step*

- 26 Since I intend to make my decision on inventive step based on the sequences provided in the prior art I do not consider that I need to address points raised relating to general data-mining techniques and the probability of finding the claimed sequences from the published human genome alone.
- 27 It has been accepted by the applicants that the Tapon paper shows a mouse ortholog of human POSHL1 since this prior art was used to infer a function for the human protein (application page 6, lines 8-14):

“...the newly isolated gene product shares certain protein domains and an overall structural organization with mouse POSH protein. The shared structural features

strongly imply that human POSHL1 plays a role similar to that of mouse POSH protein...”.

It has also been acknowledged by Mr Bassett that the skilled person could have located the claimed sequence by using the prior art sequence in the Tapon paper. However, it is for me to decide whether the skilled addressee would have located the claimed human POSHL1 sequence given the sequence of the mouse POSH protein in the prior art.

- 28 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.
- 29 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 from different species 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.
- 30 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 Tapon paper, must be identified. The Tapon paper discloses work done to identify a murine Rac-interacting protein comprising 892 amino acids and containing an N-terminal RING finger domain (a potential zinc finger structure), four SH3 domains and a Rac-binding site. By 01 April 1998 the nucleic acid and polypeptide sequences of mouse POSH identified in this paper were accessible *via* the NCBI database with accession number AF030131. Thus, the Tapon paper and the alleged invention both concern Rac-interacting proteins but they have their origins in different species, namely mice and humans. Not surprisingly, the nucleotide and amino acid sequences of POSH, which are the subjects of the Tapon paper, are different from the nucleotide and amino acid sequences of the present inventive concept.
- 31 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?
- 32 The question of whether it would have been obvious to the addressee to obtain a human ortholog of the mouse POSH must first be considered. In the agent’s letter of 13 August 2003 it is stated that (emphasis added):

“...the Tapon paper...does not teach or suggest modification of genes in general to arrive at novel POSH encoding genes, nor of specific modification necessary

to identify the particular sequences of the claimed invention. Thus, it is submitted, the prior art fails to address the problem addressed by the claimed invention **and provides no incentive** or guidance for the skilled person to do so.

proteins Furthermore, there is no disclosure in the prior art of the specific gene or of the claimed invention. Thus, it is submitted, **the cited art offers no guidance** to the solution provided by the claimed invention.”

33 Mr Bassett also made the point at the hearing that, unlike that shown in *Windsurfing, Genentech, Brugger* and *Farber*, there was no incentive to go from the mouse POSH sequences in the Tapon paper to the human sequences now being claimed. I believe that there was such an incentive and I shall now expand my reasons for this belief.

34 The Tapon paper states that a new target of Rac, the POSH protein, has been identified in mice and that the expression of this protein leads to both the Rac-mediated activation of the JNK pathway and to nuclear translocation of NF- $\kappa$ B. The skilled person, on reading the Tapon paper and references contained therein, would be aware that activation of the JNK pathway is associated with a wide variety of responses ranging from cell growth, proliferation, differentiation, and cell death and that this pathway has been implicated in the pathogenesis of human malignancies as well as diseases associated with abnormal cell death. Furthermore, this paper would teach the skilled person that activation of the NF- $\kappa$ B pathway has been implicated in *e.g.* oncogenesis. Identifying components that activate these pathways would therefore allow determination of the role of JNK and NF- $\kappa$ B in various cellular events such as cancer. In this regard it is stated that many groups are attempting to identify Rac targets in order that the GTPase pathways may be explained:

“To characterize the biochemical pathways mediating the various cellular responses induced by GTPases, **many groups** have used yeast two-hybrid and affinity chromatography techniques to identify target proteins **and approximately ten candidate targets for Rac have been isolated so far.**”

35 Importantly, functional assays described in the Tapon paper also clearly demonstrated that POSH was a potent inducer of apoptosis. It is my opinion that the essential role that apoptosis plays in normal growth and development, and the abnormalities in this pathway that have been linked to the pathogenesis of a number of diseases, would be common general knowledge to the skilled man. For example, failure of cells to undergo apoptosis has been associated with the development of a large number of malignancies. Owing to the central role played by apoptosis in the pathogenesis of human diseases, the apoptotic pathway and therapies that can modulate this pathway would be known to be the focus of extensive research.

36 The Tapon paper also describes p67<sub>phox</sub>, an SH3 domain-containing protein found in phagocytes and which is a target of Rac. This protein consists of two SH3 domains (the second of which shows close similarity to the first and fourth SH3 domains of POSH) and forms part of a complex responsible for the pathogen-killing mechanism of professional phagocytes. Both Rac and p67<sub>phox</sub> are essential for the activity of the complex. The paper also states that although the biochemical mechanism through which over-expression of POSH leads to activation of JNK in fibroblasts is unclear, expression of other adaptor-like molecules with SH3 domains can have profound

cellular effects: the SH2/SH3-containing protein v-Crk, for example, can induce malignant transformation.

- 37 The knowledge that POSH is involved in cellular pathways associated with malignancy and apoptosis would provide more than enough incentive to identify related human proteins that would be expected to function in a similar manner. Moreover, given the large number of groups attempting to identify potential Rac targets and also the association of some SH3 domain-containing proteins with pathogen killing, I believe that the skilled addressee would have considered it obvious at the relevant time to try and obtain a human ortholog of mouse POSH. Although any potential therapeutic value of the prior art has not been characterized, in the way that it was in the *Farber* or *Genentech* decisions, the above incentives would be sufficient for the skilled man to attempt to identify POSHL1. It should also be noted that in the Tapon paper two potential Rac targets (p65<sup>PAK</sup> and MLK), previously thought to activate the JNK pathway, were found not to have this function. This discovery would give the skilled addressee further incentive to identify the correct targets in humans and hence lead to the identification of POSHL1. While it would not be possible to write the claims of the present invention before any work had actually been carried out, as was asserted by Mr Basset to be the case in *Brugger* and *Windsurfing*, I consider that the knowledge of the mouse sequences would allow the skilled man to make a postulation that a human ortholog would have a similar sequence and would be found by using the mouse sequence as a starting point.
- 38 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 Chemical 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.”
- 39 Consistent with Dillon’s judgement I consider that the person skilled in the art would have assessed there to be a reasonable expectation of success in identifying human POSHL1 to warrant a trial and such a step would therefore have been obvious to try. Whilst I accept that success would not have been certain, I consider that the potential major benefits, which would come from success, would have outweighed any thought of failure.
- 40 Now I am confident that the disclosure in the Tapon paper would have led the skilled person to look for a human ortholog of POSH 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.
- 41 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 used 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.”

- 42 Dr Bentley therefore establishes that gene identification can be carried out using either nucleotide or protein sequences as the searching tool. At page five of his declaration Dr Bentley describes how he arrived at the BLAST results given at page 6, obtained by searching the *Homo sapiens* database, (note that the term PB0178 in the passages below relates to the sequences in the application in suit):

“I searched Genbank and retrieved the sequence AF030131, which is described as a mouse sequence and referenced to Tapon et al. In addition to a range of cDNA matches, the top scoring matches to genomic sequence were to AC096741 (blast score 498), AC104783 (score 266) and AC021151 (score 240; earliest date available 14<sup>th</sup> Jan 2000), which are overlapping BACs on chromosome 4 that are not cited in the PB0178 specification. The next genomic matches are to chromosome 8 sequences AC084128, AC103409 and AF165424 (each with individual blast scores of 46; AF165424 has an earliest available date of 6<sup>th</sup> July 1999) and then chromosome 5 sequence AC005216 (also with a blast score of 46; earliest available date 1<sup>st</sup> July 1998).”

- 43 At page four, Dr Bentley states that using the nucleotide sequence from the Tapon paper (AF030131) one skilled in the art would have identified several distinct regions in the human genome sequence:

“Sequence AF030131 would lead one skilled in the art to identify matches to several distinct regions in the human genome sequence. The closest match was to a place on human chromosome 4 (earliest date 14<sup>th</sup> January 2000), then one on chromosome 8 (earliest date 6<sup>th</sup> July 1999) and then one on chromosome 5 (earliest date 1<sup>st</sup> July 1998). If the skilled person wished to characterise the gene most related to AF030131, the subject of this investigation would be the chromosome 4 sequence. If the skilled person wished to characterise other genes that would be expected to be related to AF030131 and to the chromosome 4 gene, he/she would then know to extend the work to the chromosome 8, chromosome 5 and possibly other loci. He/she would know that the matches between AF030131 were much lower to these sequences, and that each one represented a significant effort (2-3) months to characterise the gene structure. The match of AF030131 to chromosome 5 does include sequence referred to in the PB0178 claim.”

44 Thus, the sequences claimed in the present application - those contained on chromosome 5 - **would** have been identified following the nucleotide BLAST of the AF030131 sequence, as has been demonstrated by Dr Bentley. However, it could be argued that since the chromosome 5 sequence was not the 'top' hit it should be disregarded. Indeed, Mr Bassett tried to persuade me that extending the search to less similar sequences (*i.e.* other than those on chromosome 4) should be characterized as an open-ended research program requiring substantial input and some months of work and was not something that represents the routine and unimaginative extension of the prior art to the next step. This cannot be right: it does not matter how long it might take or how much effort is involved to identify a sequence so long as sufficient of the theory and practice is known for the skilled man to predict where he is going without there being an original step. In this regard, Mustill, L.J. in *Genentech* stated that:

is “Quite plainly, the longer the odds against mere repetition of established techniques yielding the derived answer, the more likely it is that success was achieved by intellectual activity beyond the norm or by good luck (if good luck is enough to make a patent). But this does not itself show that what made for success is anything other than the proper reward for diligent and skilled labour. It may be that such labour and the resulting success deserve a prize, but the law, as I read it, calls for something more.”

45 Mr Bassett also asserted that three years was a long period in the field of human genomics and that it should be regarded as significant that if it was obvious to go from the mouse sequence to the claimed sequence then it would have occurred sooner. Again, I cannot see that it matters how long it takes to find a sequence given a similar sequence as a starting point. The human genome is very large and only a finite number of researchers can work on a limited number of genes within a given time. It would therefore be anticipated that it would take a long time to investigate the entire genome and it cannot be expected that all of this research would be done in a time frame of Mr Bassett's liking.

46 Consequently, in my view, the skilled addressee, given a task of identifying genes related to mouse POSH, would have carried out substantially more work than merely running a single BLAST search using the mouse POSH nucleotide sequence. Since it has been acknowledged by the applicant that most genes have conserved regions within their functional domains and, in Dr Bentley's declaration, it is stated that gene identification can be carried out using protein sequences, searches using the protein sequence of the full-length POSH and of its specific functional domains would be envisaged to provide more robust results. The skilled addressee would therefore have searched the *Homo sapiens* database with both the full-length protein sequence of AF030131 and the individual functional regions identified in the Tapon paper, *i.e.* the zinc-finger domain, the SH3 binding domains and the minimal Rac-binding site. I would also consider that the skilled person, once provided with results obtained from BLASTing the mouse sequences, would have used the human sequences generated to re-BLAST the *Homo sapiens* database, and thereby identify all related genes using human starting sequences. Such work would, in my view, have identified the sequences contained on chromosome 5 and hence the sequences of POSHL1.

47 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”.

48 In the present case the material, the sequence of the human genome containing POSHL1 (specifically the BAC clones of chromosome 5), was indeed “lying in the road” for the skilled man to use. That the “top” BLAST answer was not the sequence claimed seems to me to be immaterial: related sequences had been identified by BLASTing the POSH nucleotide sequence and, from his common general knowledge, the skilled addressee would have known to develop these searches using protein sequences in order to identify genes with a similarity to POSH. It should be noted that nowhere in his declaration does Dr Bentley state that POSHL1 would not have been found using standard BLAST processes using the mouse POSH sequences as a starting point. The relevant sequences were available in the databases at the priority date and Dr Bentley himself demonstrated that using an obvious, standard method starting with the mouse POSH sequence, the related human POSHL1 sequence is obtained. Acknowledging that the skilled person would have carried out supplementary searching it is sufficient for me to accept that the skilled addressee would have found the sequences of SEQ\_ID\_NOs 1-3 of POSHL1 using mouse POSH gene and protein sequences as a springboard, without the need for inventive ingenuity.

49 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 appreciated this difficulty and adopted a different approach to identifying the polynucleotides and polypeptides of the invention than had hitherto been used; this approach is described on pages 127-135 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 these genes.

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, such as the POSH protein from mouse (described in NCBI Accession No. AF030131) and conducting a homology search of the human genome to identify an equivalent human gene.”

50 That the applicants have used a different, “proprietary” method to identify the human POSHL1 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. Rather than carry out the applicants proprietary method to isolate POSHL1 and infer a function based on conserved regions described in the prior art (the Tapon paper), the

skilled person would have concentrated on the mouse protein sequence, and particularly the conserved regions identified in the POSH protein, and used those in BLAST searches to identify related genes in humans. Moreover, given the task of identifying POSH orthologs, the skilled person would not just have picked the “top” hit following an isolated BLAST search using only the nucleotide sequence of AF030131, but would have identified all hits that appeared relevant after rigorous BLAST searching in order that all related genes were identified.

- 51 Mr Bassett submitted that the claimed sequences were not attained simply by the application of computer programs but that human effort and ingenuity were involved. He considered that the detection of expression of the genes, and in some cases the differential expression between different human tissues, took the claimed invention beyond mere data-mining. He stressed that Dr Bentley had emphasised that gene expression had been demonstrated and that detection of such expression rules out the possibility of the sequence being a false positive, and furthermore that the evidence of expression takes the work beyond any routine application of computer data-mining techniques. At page three of his declaration Dr Bentley stresses the importance of expression analysis in taking the work beyond any routine application of such techniques. I agree that such experimentation goes further than mere data-mining but it does not provide an inventive step since such analysis is a course of action which any worker skilled in the art would follow when provided with a new gene sequence. In my opinion Dr Bentley is simply asserting that expression analysis provides information on the identified gene that data-mining alone can not - a view with which I agree. However, I do not consider that such analysis goes beyond what is normally practiced in the art and therefore I consider that such activity is an obvious step to take.
- 52 Mr Bassett also claimed that the effort and ingenuity represented by the application represents at least as much effort and ingenuity as the sort of inventions in other arts where a relatively small alteration can be made to a mechanical device and that can be considered worthy of a patent. However, in the case of a non-obvious modification to a mechanical device it can be assumed that there was nothing pointing in the direction of that modification otherwise it would lack an inventive step. In the present application there was such a pointer, the mouse POSH sequence, and the identification of a human ortholog, given this pointer, would have been obvious.
- 53 At the hearing Mr Bassett suggested that the figures and terms relating to similarity/identity of the sequences given at page 133 of the application were incorrect. He provided revised figures and submitted that they represented % identities that would be too low for the sequence that is claimed to be regarded as a homologue of the prior art sequence. I am not convinced that this is so, nor that it actually bears any relevance to this decision. That Mr Bassett had re-aligned the mouse AF030131 sequence with the claimed human sequence and arrived at slightly different values for the amino acid identity would not appear to have any consequence. As has been verified by Dr Bentley’s declaration, the relatively low similarity did not prevent the mouse POSH sequence from being used to identify related human sequences, even at the nucleotide level. Furthermore, the low identity (29%) did not prevent the applicants from using the Tapon paper to infer a function for POSHL1: the mouse and human proteins must have been considered to be sufficiently similar for the applicants to consider them orthologs in order to make this inference. Whichever figures are used



to denote the percent identity of the orthologs it doesn't change the fact that the mouse sequence can be used to isolate the human POSHL1 sequences and therefore whether the quoted figures in the application are right or not is of no importance.

- 54 In quoting Judge G.S. Rich (CIPA Guide to the Patents Act at page 83) Mr Bassett implies that what the applicants have done is to give the world something that it did not truly have before, *i.e.* the POSHL1 gene and polypeptide sequences. I would disagree with Mr Bassett but concur with Judge Rich's definition of a bad patent. To my mind, what the applicants have made as a contribution to the world is the human POSHL1 gene and protein sequences; sequences which were present in the human genome databases at the priority date and lying in the road for the skilled addressee to identify.

*Finding on inventive step*

- 55 Thus I have found, for the above reasons, that the human POSHL1 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 13 do not have an inventive step having regard to the prior disclosure in the Tapon paper 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 appreciate exactly what the possible variations could be, and 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 2-12 and 14-30 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.
- 56 Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days

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Divisional Director acting for the Comptroller