BL O/197/05

13th July 2005

PATENTS ACT 1977

APPLICANT Aeomica Inc.

ISSUE Whether application number GB0201681.4 complies with sub-sections 1(1)(b)

HEARING OFFICER P M Back

DECISION

Introduction

1 Patent application No. GB 0201681.4 ("the application") entitled "Human RALGDS-like protein 3" was filed on 25 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 9 April 2003 as GB 2380478 A.

2 The first examination report under section 18(3) was issued on 23 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 Oncogene, Volume 20, 11 January 2001, Ehrhardt, G.R. *et al.* "A novel potential effector of M-Ras and p21 Ras negatively regulates p21 Ras-mediated gene induction and cell growth", pp 188-197 ("The Ehrhardt paper"), and a paper published in The Journal of Biological Chemistry, Volume 275, 2000, Shao and Andres "A novel RalGEF-like protein, RGL3, as a candidate effector for Rit and Ras", pp 26914-26924 ("The Shao paper"). Also raised in the first examination report was an objection concerning industrial application and objections relating to paragraph 3 of schedule A2 to the Patents Act and support. In a second examination report, issued 10 June 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 (the agent for the applicant), 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 07 April 2004, the examiner maintained an objection that the invention lacked an inventive step in view of the disclosures in the Ehrhardt paper and the Shao paper. The examiner also cited seven additional documents ("the seven documents") that disclosed the isolation of human genes based upon the sequence of their murine equivalents. 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 RALGDS-like protein 3 ("RGL3"), a protein which is a guanine nucleotide exchange factor for the small GTPase Ral and a downstream effector for both Rit and Ras, and is thought to be a regulator of cellular proliferation and transformation. The application provides isolated nucleic acids that encode RGL3, variants having at least 65% sequence identity thereto, degenerate variants thereof, variants that encode human RGL3 proteins having conservative substitutions which retain the biological and functional activities of human RGL3 proteins, cross-hybridizing nucleic acids, and fragments thereof. In particular the application relates to a RGL3 nucleic acid which comprises a specific nucleotide sequence (SEQ_ID_NO: 1 or SEQ_ID_NO: 2) and a RGL3 polypeptide which comprises a specific amino acid sequence (SEQ_ID_NO: 3). SEQ_ID_NO: 1 presents the cDNA of human RGL3 and includes the 5' and 3' untranslated (UT) regions and SEQ_ID_NO:2 presents the open reading frame (ORF) from SEQ _ID_NO: 1).

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 RGL3 protein. The application explains that such similarities imply that human RGL3 plays a similar role to that of mouse RGL3 protein and therefore has a potential role as a downstream effector for both Rit and Ras and as a regulator of cellular proliferation and transformation.

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

"1. An isolated nucleic acid that encodes a guanine nucleotide exchange factor for the small GTPase Ral and a downstream effector for both Rit and Ras, or a protein with RasGEFN domain, and/or RA domain, 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, is expressed in adrenal, adult liver, bone marrow, brain fetal liver, heart, kidney, lung, placenta, colon, skeletal muscle and prostate, and/or a cell line, 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, wherein said probe according to (b) hybridizes with a target nucleic acid under high stringency hybridization conditions.

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 5.

7. The isolated nucleic acid molecule of any of claims 1-2, 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 1-2 or 7.

9. A non-human host cell transformed to contain the nucleic acid molecule of any of claims 1-2 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 of SEQ_ID_NO_3;
(b) an amino acid sequence having at least 65% amino acid sequence identity and displaying the same biological and functional activities to that of (a);
(c) an amino acid sequence according to (a) in which at least 95% of deviations from the sequence of (a) are conservative substitutions; or
(d) a fragment of at least 8 contiguous amino acids of any of (a)-(c).

13. A fusion protein, said fusion protein comprising a polypeptide of claim 12 fused to a heterologous amino acid sequence.

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

15. A method of identifying agents that modulate the expression of human RGL3 according to the nucleic acids as defined in claim 1, the method comprising:
contacting a cell or tissue sample believed to express human RGL3 with a chemical or biological agent, and then comparing the amount of human RGL3 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 RGL3.

16. A method of identifying agonists and antagonists of human RGL3 according to the nucleic acids as defined in claim 1, the method comprising:
contacting a cell or tissue sample believed to express RGL3 with a chemical or biological agent, and then comparing the activity of RGL3 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 12, 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 1-2 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, and optionally the amount, of said binding.

20. A method of diagnosing or monitoring a disease caused by altered expression of human RGL3, comprising:
determining the level of expression of RGL3 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 1-2, 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 12, 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 1-2 or 7 or 8 and a pharmaceutically acceptable excipient.

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

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

28. Polypeptide of claim 12 for use in therapy.

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

30. 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

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 Oncogene, Volume 20, 2001, Ehrhardt, G.R. *et al.* "A novel potential effector of M-Ras and p21 Ras negatively regulates p21 Ras-mediated gene induction and cell growth", pp 188-197 ("The Ehrhardt paper"), and a paper published in The Journal of Biological Chemistry, Volume 275, 2000, Shao and Andres "A novel RalGEF-like protein, RGL3, as a candidate effector for Rit and Ras", pp 26914-26924 ("The Shao paper"). These papers were published 11th January 2001 and September 2000 respectively, and describe the RGL3 protein from mouse. RGL3 (Ral GDS-like 3) is a *Ral* exchange factor whose *in vivo* guanine nucleotide exchange factor activity is stimulated by GTP-bound Rit and Ras. Its function in the regulation of cell growth suggests a potential role in oncogenesis.

9 In her first report of 23 August 2002, the examiner stated that the invention was obvious given the murine RGL3 sequences disclosed in the Ehrhardt and Shao papers. It was obvious, in her opinion, to look for an RGL3 ortholog in a species other than mouse and therefore the identification of the human RGL3 gene did not involve any inventive step. The examiner maintained this inventive step objection in both her

second and third examination reports of 10 June 2003 and 7 April 2004. She argued that since the goal was known (the human RGL3 ortholog) and that the relevant materials were available (the mouse RGL3 sequence and the human genome sequence) there would be no inventive step in isolating human RGL3. Additionally, in her third examination report of 7 April 2004, the examiner cited seven documents that disclosed the isolation of human genes based upon the sequence of their murine equivalents, and she argued that these documents demonstrated that such a process was common practice at the priority date of the application. The examiner also stressed that the method the applicants used to identify RGL3, their proprietory 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 commenting upon the seven prior art documents cited by the examiner in her third examination report that demonstrated the isolation of a human ortholog of a known mouse gene. He stated that simply because on other occasions people have gone from mouse sequence and have found a human sequence, and have then published the results of it, this does not mean that in every situation it is going to be obvious to do so. Mr Bassett asserted that the present situation was different, and was not the same as the situation in other areas when assessing inventive step. On this point, Mr Bassett referred to the analogy that there may be a piece of kit that deadens the sound of noisy machinery, and that there are published examples of it being applied to a noisy machine, and the invention in question is another noisy machine with the sound deadening kit bolted onto it. As the kit had been bolted onto noisy machines in the past it would be possible to state that such an invention would merely be a repetition of the prior art but in a slightly different context. However, Mr Bassett asserted that the present situation was different to this, as the seven papers cited were dealing with completely different sequences, completely different genes. This situation was not simply winding the handle and applying a known prior art approach and a known prior art compound or sequence to a new bit of prior art to achieve the same effect. In the present situation the starting point was completely different.

11 Mr Bassett suggested that as these seven papers cited by the examiner <u>were</u> published and were published in reputable journals like PNAS, it indicated that there is something significant and meritorious about going from the mouse to the human gene. He considered that the authors of these papers set out details of the techniques used and effort that went into it to achieve success, and that if it was simply a question of winding a handle, putting a mouse sequence into a computer program and retrieving the human gene, there wouldn't have been any justification for publishing the scientific papers. According to Mr Bassett, the publishing of those papers disclosing what had been done demonstrates that the work was significant.

12 Mr Bassett considered that any exercise of this kind would be regarded as meritorious, ingenious, and with an amount of effort required that deserves a patent, and that the whole thing is in the nature of an open-ended research programme. He stated that even starting with a prior art sequence, one does not know that there is going to be a human homologue of that sequence, however homologue is defined. Whether homologue is defined in an evolutionary context or a sequence identity context, one wouldn't know that it will exist, how many candidate sequences might be found, or

whether they are going to be expressed. Mr Bassett suggested that during such an exercise you might find chunks of genes due to evolutionary rearrangement, and that whilst you can find similarities and connections between parts of sequences, you won't know that there will be an intact gene there that corresponds to the mouse gene. He referred to the official letter of 7 April 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"

13 Mr Bassett submitted that you may have a hope that there will be something there, but you have no reason to suppose that it will necessarily be there, and that this applies to the present case.

14 Mr Bassett asserted that an inventive step is present when one goes beyond something that is routine, and that if something is merely routine, an immediate next step that the perfectly unimaginative person skilled in the art would take should be regarded as obvious. He referred to the declaration by Dr David Bentley which indicated that the work reflected in the application goes beyond the routine, and that it is significant and adds significantly to the sum of human knowledge.

The Law

15 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)."

16 The test for obviousness should be an objective one as was made very clear by the Court of Appeal in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd,* [1985] RPC59 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.

Assessment and conclusion on inventive step

17 It has been accepted by the applicants that the Shao paper and the Ehrhardt paper show a mouse ortholog of human RGL3 since this prior art was used to infer a function for the human protein (application page 6 lines 22-29):

> "…the newly isolated gene product shares certain protein domains and an overall structural organization with mouse RGL3 and other RasGEF molecules. The shared structural features strongly imply that RGL3 plays a role similar to that of mouse RGL3…".

It has also been acknowledged by Mr Bassett that the skilled person could have located the claimed sequence by using the prior art sequences in the Shao and Ehrhardt papers. However, it is for me to decide whether the skilled addressee would have located the claimed human RGL3 sequence given the sequence of the mouse RGL3 protein in the prior art.

18 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.

19 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.

20 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 Shao and Ehrhardt papers, must be identified. The Shao paper discloses work done to identify murine Rit-binding proteins using the yeast two-hybrid system. This screening method identified a new member of the RalGEF family of proteins, termed RGL3. By June 2000 the nucleic acid and polypeptide sequences of mouse RGL3 identified in this paper were accessible *via* the NCBI database with accession number AF237669. The Ehrhardt paper discloses work to identify proteins that associated with M-Ras G22V, an activated mutant of M-Ras, also using the yeast two-hybrid system. A protein termed RPM (Ras pathway modulator) was identified by this method, and analysis of this protein demonstrated that it was identical to that identified in the Shao paper and termed RGL3. Thus, the Shao paper and the Ehrhardt paper and the alleged invention all concern RGL3 proteins but they have their origins in different species, namely mice and humans. Not surprisingly, the nucleotide and amino acid sequences of RGL3, which are the subjects of the Shao and Ehrhardt papers, are different from the nucleotide and amino acid sequences of the present inventive concept.

21 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?

22 The question of whether it would have been obvious to the addressee to obtain a human ortholog of the mouse RGL3 must first be considered. In the agent's letter of 6 May 2003 it was stated that (emphasis added):

> "…the [Shao and Ehrdardt papers] do not teach the use of murine gene sequences to identify RGL3 genes and proteins in other species, let alone in humans, as employed in the claimed invention. Furthermore, none of the prior art documents teach or suggest modification in general of known gene sequences to arrive at novel RGL3 encoding genes, or of specific modifications 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.
>
> Furthermore, there is no disclosure in the prior art of the specific gene or proteins of the claimed invention. Thus, it is submitted**, the cited art offers no guidance** to the solution provided by the claimed invention."

23 I believe that there was such an incentive, and I shall now expand my reasons for such a belief. The Shao paper states that an effector molecule for Rit and Ras has been identified in mice, and expression of this protein leads to modulation of the Rit and Ras signaling cascades. The skilled person, on reading the Shao paper and references contained therein, would be aware that the modulation of the Ras pathway in particular, is associated with a wide variety of responses, including proliferation, differentiation, nuclear transport, cytoskeletal organization and vesicular transport, and that this pathway has been implicated in the pathogenesis of human malignancies. Identification of components that control these pathways would therefore allow the determination of the role of Ras in various cellular events such as cancer. This document also states that a large number of effectors of Ras have been identified. The Ehrhardt paper also demonstrates the identification of a Ras effector molecule, and establishes that this molecule has an inhibitory action upon the downstream actions of p21 Ras. The Ehrhardt paper, including cited references, illustrates the role that p21 Ras plays in oncogenesis and thus provides an important insight into the mechanisms of tumourigenesis. The knowledge that RGL3 is involved in cellular pathways associated with malignancy would provide more than enough incentive to identify related human proteins that would be expected to function in a similar manner.

24 In her examination report of 7 April 2004, the examiner cited seven documents that demonstrated the isolation of a human gene based upon the sequence of the murine equivalent. It is my belief that these papers, which the examiner pointed out are merely examples of such documents, demonstrate the routine nature of identifying a human sequence based upon its murine equivalent. The fact that these papers relate to seven completely different genes supports this belief, because such a process is clearly not limited to a specific family or class of genes. These seven documents would therefore, in my opinion, provide a further incentive for the skilled man to identify the human equivalent of the mouse RGL3 gene identified in the Shao and Ehrhardt papers.

25 In coming to a judgement on inventive step in *Genentech Inc.'s Patent [1989]* RPC 147-287, 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."

26 Consistent with Dillon's judgement I consider that, given the above evidence, the person skilled in the art would have assessed there to be a reasonable expectation of success in identifying human RGL3 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.

27 Now I am confident that the disclosures in both the Shao and Ehrhardt papers would have led the skilled person to look for a human ortholog of RGL3 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.

28 It has been common practice for many years to use the BLAST bioinformatics 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."

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

30 At page 7 lines 29-31, and in Figure 2 of the present application, reference is made to two bacterial artificial chromosomes (BACs) that span the human RGL3 locus. The first BAC, with Genbank accession number AC008481, was available *via* the NCBI database by August 1999, and the second BAC, with Genbank accession number AC024575, was available by February 2000. BACs are artificially constructed chromosomes in which DNA from one species are cloned into bacteria. They are commonly used to produce genetic maps of large regions of DNA and for the isolation of genes.

31 At the hearing, Mr Bassett stated that:

> "…simply because on other occasions people have gone from a mouse sequence and have found a human sequence, and have then published the results of it, does not mean to say that in every situation it is going to be obvious to do so. They have done it; but we are talking about a different situation here, and it is not the kind of situation that you are in in other areas when assessing inventive step.

32 Whilst I agree that in some circumstances there may not be a human equivalent of a murine gene, it is clear to me that at the priority date of the present application the skilled man would have considered it likely that a human equivalent of the mouse RGL3 existed. A simple BLAST search using the mouse RGL3 sequence as a starting point identified the two BACs referred to above and thus the sequences claimed in the present application - those contained on chromosome 19 - **would** have been identified following a nucleotide BLAST of the AF237669 sequence. Furthermore, methods for obtaining a human gene, given a mouse sequence, were known at the priority date of the application and are exemplifed in the seven documents cited by the examiner in her examination report of 7 April 2004. It is unclear to me why Mr Bassett considers that the sequences in the present application represent "…a different situation…". It has been clearly shown that it is possible to identify a human sequence given a murine equivalent and it is not apparent why this should not be the case with the sequences in the present application.

33 Mr Bassett continued by describing a "bit of kit" that deadens the sound of noisy machinery and how applying it to one piece of machinery would make it obvious to attach it to another noisy piece of apparatus. Since it had been done before it is just the mere repetition of the prior art but in a slightly different context. He explained that this was not the situation with the present case: because the seven cited papers deal with completely different sequences and completely different genes it is not merely a case of winding the handle and applying a known prior art approach to achieve the same effect; there is a totally different starting point. I would disagree with Mr Bassetts interpretation of the present situation. There may indeed be a totally different starting point, the murine RGL3 sequences, but the skilled man, using his common general knowledge together with the information contained within the seven documents and the Ehrhardt and Shao papers, would know how to go about identifying the human equivalent of mouse RGL3. That the seven papers deal with different genes is irrelevant; the approach described within these papers may be applied to achieve the same effect, albeit with a different gene.

34 Regarding the seven papers, Mr Bassett asserted that since they had been published in reputable journals like PNAS, it demonstrated that there was something meritorious and significant about going from the mouse to the human gene. Whilst I agree with Mr Bassett that the information contained within these papers is important, it is in terms of the advancement of science and the expansion of scientific knowledge, and not all advancements in science are worthy of patent protection. Consequently, what needs to be decided is whether the disclosure in the present application is inventive, and not whether it is meritorious or successful. Mr Bassett also tried to persuade me that the exercise described in the present application was ingenious and had an amount of effort that deserved a patent. I am not swayed by this argument since 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:

> "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."

35 In my view, the skilled addressee would have had some expectation of success of finding the human RGL3 gene given that the mouse homologue had already been isolated and characterised, and the locus of the human gene had been identified by the two BACs. The skilled addressee would have therefore searched the *Homo sapiens* database with the full length nucleotide sequence of the AF237669 sequence, and would have identified BACs AC008481 and AC024575. Such work would, in my view, have identified the sequences on chromosome 19 from which the human RGL3 gene was expressed.

36 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."

37 In the present case the material, the sequence of the human genome containing RGL3 (specifically the BAC clones of chromosome 19), was indeed "lying in the road" for the skilled man to use. Moreover, the mouse sequence had been identified, thus giving the skilled man a starting point for the identification of this human gene. These facts, together with the common general knowledge, are sufficient for me to accept that the skilled addressee would have found the sequences of SEQ_ID_NOs 1-3 of the human RGL3 using the mouse RGL3 gene and protein sequences as a springboard and without the need for any inventive ingenuity.

38 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 gene of interest, such as the mouse RGL3 gene described in *J Biol Chem 2000, 275, 26914-24*, and conducting a homology search of the human genome to identify an equivalent human gene."

39 That the applicants have used a different, "proprietary" method to identify the human RGL3 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 RGL3 and infer a function based on conserved regions described in the prior art (the Shao and the Ehrhardt papers), the skilled person would have concentrated on the mouse sequences and used those in BLAST searches to identify related genes in humans.

40 At the hearing, Mr Bassett submitted that an inventive step is present when one goes beyond something that is routine, and that conversely, if something is merely routine, an immediate next step that the perfectly unimaginative person skilled in the art would take should be regarded as obvious. 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 identifed 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. Once a gene has been identified using data mining techniques, the immediate next step to a person skilled in the art would be to see if, and where, the gene is expressed. As Mr Bassett himself stated, such a next step should be regarded as obvious.

Finding on inventive step

41 Thus I have found, for the above reasons, that the human RGL3 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 inventive step having regard to the prior disclosure in the Shao and Ehrhadt papers 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 2-11 and 13-30 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.

42 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