BL O/171/05

23rd June 2005

PATENTS ACT 1977

APPLICANT Aeomica Inc

ISSUE Whether application number GB0201868.7 complies with sub-sections 1(1)(b)

HEARING OFFICER P M Back

DECISION

Introduction

1 Patent application No. GB 0201868.7 ("the application") entitled "Human testis expressed patched like protein" was filed on 28 January 2002 by Aeomica Inc ("the applicant") and claimed priority from an earlier application filed on 30 January 2001. The application was published on 13 November 2002 as GB 2375350 A.

2 The first examination report under section 18(3) was issued on 10 September 2002 as part of a combined search and examination. In this report the examiner raised an objection to lack of novelty on the basis of a disclosure in PCT application WO 00/36613 A2 (BAYER). The examiner also raised objections to lack of inventive step on the basis of disclosures of (i) a mouse Patched-like protein with NCBI Accession number AK015440 ("AK015440"), (ii) two patched genes identified in humans published in Proceedings of the National Academy of Science of the United States of America, Volume 95, 1998, Carpenter, D. *et al*., "Characterization of two patched receptors for the vertebrate hedgehog protein family", pp.13630-13634 ("PNAS") and (iii) Patched genes from a variety of species disclosed in US 6027882. 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 to support. In a second examination report, issued 10 July 2003, the examiner maintained the inventive step objection on the basis of the disclosure in AK015440 and also the industrial application objection; the other objections having been overcome by amendment or, in the case of the novelty objection, by the fact that WO00/36613 had been withdrawn before entering the national or regional phases. 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 January 2004. In a third examination report, issued 17 May 2004, the examiner maintained an objection that the invention lacked an inventive step in view of the disclosure in AK015440. The applicant did not accept the examiner's view

on this matter and requested a hearing in a letter dated 04 June 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 testis expressed patched like protein ("HTPL"), a protein which is stated to be involved in the Hedgehog signalling pathway.

5 The application provides isolated nucleic acids that encode HTPL, including two isoforms (HTPL-L and HTPL-S), variants having at least 65% sequence identity thereto, degenerate variants thereof, variants that encode HTPL proteins having conservative substitutions which retain the biological and functional activities of HTPL proteins, cross-hybridizing nucleic acids and fragments thereof. In particular the application relates to HTPL nucleic acids which comprise specific nucleotide sequences (HTPL-L:SEQ ID NO: 1, SEQ ID NO: 2; HTPL-S: SEQ ID NO:4 and SEQ ID NO:5) and HTPL polypeptides which comprise specific amino acid sequences (HTPL-L: SEQ ID NO: 3 and HTPL-S: SEQ ID NO:6). SEQ ID NO: 1 and SEQ ID NO:4 present the cDNA of HTPL-L and HTPL-S respectively and include the 5' and 3' untranslated (UT) regions. SEQ ID NO:2 and SEQ ID NO:5 present the genomic DNA. It is stated that the nucleic acid sequences SEQ ID NO: 1 and SEQ ID NO: 4 were identified using the applicant's own proprietary algorithm and that the deduced protein sequences contain several known domains shared with Patched, including a full or partial Patched domain and a Sterol-sensing domain, and show an overall structural organization with the Patched protein. The application explains that such similarities imply that HTPL plays a similar role to that of Patched in male germ cell development and is a potential tumor suppressor.

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

"1. An isolated nucleic acid that encodes a Patched like transmembrane protein, functioning in male germ cell development, and as a potential tumor suppressor consisting of:
(a) a nucleotide sequence selected from the group consisting of:
(i) SEQ ID NO:1, SEQ ID NO:4;
(ii) the complement of the sequences set forth in (i);
(iii) the nucleotide sequence of SEQ ID NO:2, SEQ ID NO:5;
(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, SEQ ID NO:6;

(ii) a nucleotide sequence that encodes a polypeptide having the sequence of SEQ ID NO:3, SEQ ID NO:6, with conservative amino acid substitutions; and
(iii) the complement of the sequences set forth in (i) and (ii).

2. The isolated nucleic acid of claim 1, wherein said nucleic acid, or the complement of said nucleic acid, is expressed in testis, as well as in adrenal, adult and fetal liver, bone marrow, brain, kidney, lung, placenta, prostate, skeletal muscle and/or colon.

3. A nucleic acid probe, comprising: (a) a nucleic acid of claim 1; or
(b) at least 17 contiguous nucleotides of SEQ ID NO:7, SEQ ID NO:11, SEQ ID NO:4796, SEQ ID NO:4800.

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

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

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

7. The isolated nucleic acid molecule of any of claims 1-2, 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 one 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, SEQ ID NO:6; (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.

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

14. A method of identifying agents that modulate the expression of HTPL, the method comprising: contacting a cell or tissue sample believed to express HTPL with a chemical or biological agent, and then comparing the

amount of HTPL 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 HTPL.

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

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

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

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

19. A method of diagnosing or monitoring a disease caused by altered expression of HTPL, comprising: determining the level of expression of HTPL in a sample of nucleic acids or proteins that derives from a subject suspected to have said disease, alterations from a normal level of expression providing diagnostic and/or monitoring information.

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

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

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

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

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

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

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

27. Polypeptide of claim 12 for use in therapy.

28. A method of modulating the expression of a nucleic acid according to any of claims 1-2 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.

29. A method of modulating at least one activity of a polypeptide according to claim 12, the method comprising: administering an effective amount of an agent which modulates at least one activity of a polypeptide acording 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 1-29 involves an inventive step.

Inventive step

The examiner's objection

8 The examiner's objection was based on the disclosure of nucleotide and amino acid sequences submitted to the NCBI database on 10 July 2000 and "first seen" by NCBI on 16 February 2001 and given the Accession Number AK015440. The NCBI accession document contained references to three journal documents having publication dates earlier than the priority date of the present application.

9 In his first report of 10 September 2002 the examiner stated that the invention was obvious given the protein sequence of AK015440 which showed a 65% identity to HTPL and was described as a Patched-like protein expressed in the testes of mice. Two further documents were cited at the first examination stage in relation to lack of inventive step: US 6027882 (UNIV. CALIFORNIA) and Proceedings of the National Academy of Sciences USA, Vol.95, 1998, Carpenter, D. et al., "Characterization of two patched receptors for the vertebrate hedgehog protein family", pp.13630-13634, but these documents were not relied upon in further examination reports.

10 The examiner considered that it was obvious to look for Patched-like orthologs in organisms other than mouse and therefore the identification of the HTPL sequences did not involve any inventive step. The examiner maintained this inventive step objection in both his second and third examination reports of 10 July 2003 and 17 May 2004. He argued that since the goal was known and that the relevant materials were readily available (the mouse Patched-like sequences and the human genome sequence) there would be no inventive step in isolating HTPL. The examiner also stressed that the method the applicants had used to identify HTPL, 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

11 Mr Bassett began by stating that there was a prior art mouse sequence which the examiner had explicitly said he regarded as being a suitable starting point for identifying the human sequence. He commented that simply because on other occasions people have used a mouse sequence to identify a human sequence, and have published the results of it, does not mean that in every situation it is going to be obvious to do so. He suggested, for example, that there might be a bit of kit that deadens the sound of noisy machinery and there are published examples of it being applied to a noisy machine and the invention in front of us is another noisy machine with this sound deadening kit bolted on. In that case it would be possible to say, "Well, it has been done before. People have bolted this kit onto noisy machines, so this is just the mere repetition of the prior art but in a slightly different context". In the present case Mr Bassett considered this was not the situation, because the papers that were cited were dealing with completely different sequences, completely different genes. It was not simply a case of 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: there is a totally different starting point. Mr Bassett also pointed out that he believed that there was something meritorous and significant about going from a mouse to a human gene, particularly when the sequence is published in a journal such as PNAS. He did not consider that there would have been any justification in publishing such a paper if all that was being done was pushing a mouse sequence into a computer and obtaining a corresponding human sequence. The fact that the sequences were published indicated that the work was significant.

12 Mr Bassett considered that work that led to such publications was meritorious, ingenious and with an amount of effort required that deserves a patent; but also that the whole thing is in the nature of an open-ended research program. He considered that even starting with a prior art sequence you don't know that there is going to be a human homologue; you may have a hope that there will be something there, but you have no reason to suppose that it necessarily will be there.

13 Mr Bassett then referred to the declaration in which Dr Bentley stated that an inventive step is present when one goes beyond something that is routine. Dr Bentley considered that the work that was reflected in the present application went beyond such routine and that it was significant and added significantly to the sum of human knowledge. On the basis of this declaration, Mr Bassett considered there to be an inventive step in the application.

Assessment and conclusion on inventive step

14 AK015440 discloses an amino acid sequence having a 65% identity to HTPL and described as a Patched-like protein expressed in the testes of mice. The sequences contained within this document were submitted to the NCBI on 10 July 2000 but "first seen" on 16 February 2001, some 17 days after the priority date of the application. Prior to this "first seen" date (the intervening time following submission) it is assumed that the sequences were put on hold: a process whereby release of new submissions is delayed for a specified period of time. The priority documents have been investigated and the application is considered to be entitled to its priority date of 30 January 2001. The usefulness of the AK015440 document as an inventive step citation therefore lies in the three other references contained in this document which have publication dates earlier than 30 January 2001.

15 The first reference, Methods in Enzymology, Volume 303, 1999, Carninci, P and Hayashizaki, Y., "High-efficiency full-length cDNA cloning", pp.19-44 describes the methodology for the production of full-length cDNA libraries from mouse RNA. The document states at pages 42-43 that:

> "The sequences of several clones will be present in GenBank and can be checked if they are full-length; more than 90-95% of identifed clones should be full-length."

16 There is, however, no reference to the specific sequence with accession number AK015440 nor to any other accession numbers within the GenBank database.

17 The second reference, Genome Research, Volume 10, 2000, Carninci, P. *et al*., "Normalization and subtraction of cap-trapper-selected cDNAs to prepare full-length cDNA libraries for rapid discovery of new genes", pp.1617-1630 describes improvements to the methods for producing full-length cDNA libraries detailed in the reference above. The document explains that approximatley 30 000 cDNA clones for preparing cDNA libraries for the mouse cDNA encyclopedia project have been arrayed (http://genome.rtc.riken.go.jp/). This web site provides a link to the DNA Data Bank of Japan (DDBJ) where the AK015440 accession is available. The oldest version of the sequence was known at 8 February 2001, the date at which a Nature paper detailing the annotation of the mouse cDNA database was published (Nature, Vol.409, 8 February 2001, The RIKEN Genome Exploration Research GroupPhase II Team and the FANTOM Consortium, "Functional annotation of a full-length mouse cDNA collection", pp.685-690). Following the publication of this document it is presumed that the sequences were released into the public domain and "first seen" at NCBI eight days later (16 February 2001).

18 The third reference, Genome Research, Volume 10, 2000, Shibata, K. *et al*., "RIKEN integrated sequence analysis (RISA) system-384-format sequencing pipeline with 384 multicapillary sequencer", pp.1757-1771, describes a high-throughput sequencing system developed for the RIKEN mouse encyclopedia project. There is nothing in the document relating to the sequence given in AK015440.

19 There is therefore no disclosure and no evidence that the AK015440 sequence was disclosed prior to the priority date of the application and it is perhaps unfortunate that neither the Office or the applicant or his agent noticed this date issue earlier. However, in light of this it is considered that the AK015440 citation, and references contained therein, can not be used to make an inventive step objection against the claimed invention of the application. Consequently, since there are no other citations to consider, the documents US6027882 and PNAS having been dropped following the response to the first examination report, the application is deemed to possess an inventive step.

Finding on inventive step

20 For the above reasons the HTPL nucleotide sequences of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:5 and complements thereof, and HTPL polypeptide sequences SEQ ID NO:3 and SEQ ID NO:6, as claimed in claims 1 and 12, are considered to posess an inventive step. 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 1-6, also show an inventive step. The remaining claims 2-11 and 13-29 all relate to standard features or applications of polypeptides and polynucleotides which would be considered when any gene and/or protein is identified and, given the inventiveness of the above sequences, are themselves also considered to be inventive.

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Divisional Director acting for the Comptroller