BL O/179/04

23rd June 2004

PATENTS ACT 1977

APPLICANT F. Hoffmann – La Roche AG

ISSUE Whether patent application GB 0002665.8 complies with sub-sections 1(1)(a), 1(1)(b) and 14(5)(c)

HEARING OFFICER R J Walker

DECISION

Introduction

1 Patent application no. GB 0002665.8 ("the application") entitled "Human Intestinal Npt2B" was filed on 4 February 2000 by F. Hoffmann – La Roche AG ("the applicant") and was published on 11 October 2000 as GB 2348645 A.

2 The first examination report under section 18(3) was issued on 30 April 2003. In this report the examiner raised various objections, including objections to lack of novelty and inventive step on the basis of an earlier disclosure in European patent application no. EP 0875569 A1 (the "European application"). This European application was one of a number of publications which had been notified to the applicant earlier as the result of a search under section 17(5). In his first examination report the examiner informed the applicant that he had deferred consideration of the inventiveness of the claimed invention on the basis of the other publications found in the search. The first examination report also included an objection that certain claims of the so-called "Swiss type" lacked support. There followed a series of exchanges between the examiner and the applicant's agent, Forrester Ketley & Co. Although the applicant restricted the scope of the claimed invention, the examiner pursued an objection that the invention lacked an inventive step in view of the disclosure in the European application. In an examination report, dated 26 April 2004, the examiner bolstered his inventive step objection by introducing one of the other documents which had been found in the search. The applicant did not accept the examiner's view on this matter and requested a hearing in a letter dated 29 April 2004. The examiner then reviewed the application in preparation for the hearing and wrote to the applicant on 5 May 2004 setting out what he believed to be the outstanding issues. Regrettably this letter contained objections, which had not been put to the applicant previously, as well as objections, which although raised before, had not been pursued up until that point.

3 In accordance with rule 34(1)(a)(ii) of the Patents Rules 1995 the normal period allowed for complying fully with the requirements of the Act expired on 30 April 2004. On 27 April 2004 the applicant requested under rule 110(3) a one month extension of this period and a hearing was arranged for 18 May 2004. In the event the applicant sought to postpone the hearing because representatives of the applicant were unable to attend on that date. The applicant also requested the Comptroller to exercise his discretion under rule 110(4) to allow a further one month's extension of the rule 34 period in view of the significant new objections raised by the examiner. This request was allowed and the hearing was rearranged for 3 June 2004.

4 Prior to 3 June 2004 some of the outstanding issues identified by the examiner were dealt with by further amendment of the application but other objections could not be resolved. Therefore, these unresolved matters came before me at the planned hearing on 3 June 2004, at which Ms Kate Richardson of Forrester Ketley & Co. appeared for the applicant.

The application

5 I should outline briefly the content of the application before giving my decision. The application relates to ion transporters, particularly sodium phosphate co-transporters. As explained in the application, phosphorous plays an important role in membrane structure, transport and energy storage. The plasma level of inorganic phosphate ("Pi") in the body is maintained by control of Pi absorption in the small intestine under the influence of vitamin D, and by control of Pi excretion in the kidney under the influence of parathyroid hormone. The absorption of Pi requires transepithelial transport and Pi uptake is accomplished by sodium phosphate co-transporters present on the surface of appropriate epithelial cells, such as intestinal epithelial cells.

6 The application also lists a variety of disease conditions which are associated with disorders in the Pi metabolism. These disease conditions include those characterised by the presence of hypophosphatemia, for example, osteomalacia, hypocalciuria and rickets, and those characterised by the presence of hyperphosphatemia, for example, hyperparathyroidism, hypocalcemia, vitamin D deficiency, soft tissue or metastatic calcification.

7 The application relates in particular to an Npt2B polypeptide which comprises a specific amino acid sequence (SEQ ID NO: 01), and an Npt2B polypeptide which is encoded by a specific nucleotide sequence (SEQ ID NO: 02). It is stated that Npt2B is a membrane protein and that in its native environment it is a co-transporter of sodium cation and phosphate anion. The application explains that Npt2B is expressed, among other locations, on the surface of intestinal epithelial cells and provides for the transport of sodium and phosphate ions from the intestinal lumen into the intestinal epithelial cells. It is further stated that the proteins of the invention may be obtained from naturally occurring sources or they may be produced synthetically, and that they are present in a non-naturally occurring environment, for example they may be present in a 99% pure form and so substantially free of other naturally occurring biological molecules.

8 Npt2B and its corresponding nucleic acid are stated as finding use in a variety of applications, including research, diagnostic, and therapeutic agent screening applications, as

well as in treatment therapies. The description provides details of such uses.

9 I can now turn to the claims of the application, which relate to various aspects of the invention as follows:

"1. An Npt2B polypeptide comprising the amino acid sequence of SEQ ID NO: 01.

2. An Npt2B polypeptide encoded by the nucleotide sequence of SEQ ID NO: 02.

3. An isolated nucleic acid encoding a polypeptide according to any one of Claims 1 to 2.

4. A nucleic acid according to Claim 3, wherein said nucleic acid has a nucleic acid sequence that is substantially identical to the nucleotide sequence of SEQ ID NO: 02.

5. A nucleic acid encoding an Npt2B protein or polypeptide, where the nucleic acid comprises the nucleotide sequence of SEQ ID NO: 02.

6. An expression cassette comprising a transcriptional initiation region functional in an expression host, a nucleic acid according to any one of Claims 3 to 5 under the transcriptional regulation of said transcriptional initiation region, and a transcriptional termination region functional in said expression host.

7. A host cell comprising an expression cassette according to Claim 6 as part of an extrachromosomal element or integrated into the genome of a host cell as a result of introduction of said expression cassette into said host cell.

8. The cellular progeny of the host cell according to Claim 7, wherein the cellular progeny comprises the expression cassette of Claim 6.

9. A method of producing Npt2B, said method comprising growing a cell according to Claim 7 or 8, whereby said Npt2B is expressed: and isolating said Npt2B substantially free of other proteins.

10. A non-human transgenic animal model capable of expressing Npt2B according to any one of Claims 1 or 2.

11. A method of screening to identify Npt2B modulatory agents, said method comprising contacting a cell expressing functional Npt2B according to any one of Claims 1 or 2 on its surface with a candidate agent in the presence of phosphorous anion; and determining the amount of phosphorous anion uptake by said cell.

12. The method according to Claim 11, wherein said phosphorous anion is labeled with a detectable label.

13. The method according to Claim 11 or 12, wherein said label is isotopic.

14. The use of a polypeptide as defined in any one of Claims 1 or 2 for the screening of Npt2B modulating agents.

15. A pharmaceutical composition comprising an Npt2B polypeptide according to any one of Claims 1 or 2, or a nucleic acid encoding an Npt2B protein or polypeptide according to any one of Claims 3 to 5, and a pharmaceutically acceptable adjuvant, diluent or carrier.

16. An Npt2B polypeptide according to any one of Claims 1 or 2, or a nucleic acid encoding an Npt2B protein or polypeptide according to any one of Claims 3 to 5, for use in therapy.

17. Use of an Npt2B polypeptide according to any one of Claims 1 or 2, or a nucleic acid encoding an Npt2B protein or polypeptide according to any one of Claims 3 to 5, for the production of a medicament for the treatment of a host suffering from a disease condition associated with Npt2B activity, said disease condition being selected from hypophosphatemia, osteomalacia, hypocalciurea, rickets, hyperphosphatemia, including hyperphosphatemia resulting from renal insufficiency, hyperparathyroidism, hypocalcemia, vitamin D deficiency, or soft tissue or metastatic calcification.

18. An Npt2B polypeptide according to any one of Claims 1 or 2 or 16, a nucleic acid according to any one of Claims 3 to 5, an expression cassette according to Claim 6, a cell according to Claim 7 or 8, a method according to any one of Claims 9 or 11 to 13, a non-human transgenic animal model according to Claim 10, a use according to any one of Claims 14 or 17, or a pharmaceutical composition according to Claim 15, as hereinbefore described."

The outstanding objections

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

(a) whether the nucleic acid, as claimed in claims 3 to 5 and 18 (in part), is novel;

(b) whether the subject matter of claims 1 to 18 involves an inventive step; and

(c) whether claims 16, 17 and 18 (in part) to first and second medical uses of an Npt2B polypeptide according to any one of claims 1 or 2, or of a nucleic acid encoding an Npt2B protein or polypeptide according to any one of claims 3 to 5, are supported by the description.

Assessment

11 It is the Comptroller's normal practice to issue reasoned decisions but in this case I am conscious that the extended period for complying with the requirements of the Act expires on 30 June 2004. If I delay issuing my decision until such time that I am able to issue a reasoned decision, it would leave the applicant very little opportunity to consider amending the application in the light of the decision. Therefore, in this case I consider it appropriate to issue a decision without delay and to provide my reasons in writing later.

12 When deciding the outstanding matters before me, I gave full and careful consideration to the submissions made by Ms Richardson at the hearing as well as to the various authorities she

drew to my attention. I have also taken full account of submissions made following the hearing in a faxed letter, dated 11 June 2004, from the applicant's agent, and of evidence originally faxed with that letter and in the form of a witness statement by Suryanarayana Sankuratri, who is named in the application as one of the inventors. I note that Ms Richardson stated in a telephone call on 15 June 2004 that she did not wish to have a further hearing to supplement these latest submissions before I issued my decision. I shall now deal with each of the outstanding matters in turn.

Novelty

13 The examiner's objection that the nucleic acid of claims 3 to 5 lacks novelty, was developed from the disclosure in the application detailing how the invention was obtained. The relevant passage appears towards the end of the description under the heading "EXPERIMENTAL" where the process that led to the identification of the Npt2B sequence is described. According to this passage (my emphasis):

> "A. Identification of the Npt2B Sequence
>
> Comparison of type II sodium-phosphate cotransporter protein sequences from different species available from public databases revealed that whilst most were very closely related, the bovine and flounder sequences appeared to form a distinct sub-family. The Incyte LifeSeq® database was thus searched for Npt2-like clones that more closely resembled the bovine sequence than they did the human. A number of clones were identified and three of them were obtained and the DNA sequence of the entire inserts determined. DNA sequencing was performed on an automated sequencer (PE/Applied Biosystems Model 373A, Foster City, CA) using vendor's dye dideoxy termination sequencing kit. Comparison of the sequences revealed that they represented the same cDNA and that the longest was only a partial clone missing approximately 150 amino acids from the N-terminus, based on homology to the bovine protein. **The consensus sequence was used to further screen the LifeSeq® database and a large number of clones were identified, including one which appeared to contain the full-length coding sequence. The latter was obtained from Incyte and sequenced. This revealed the presence of a 689 amino acid open reading frame which appeared to be a human member of the bovine / flounder type II cotransporter subfamily.** The majority of the clones identified in the LifeSeq® database were from libraries derived from lung-related tissue samples, however some of the clones were from libraries of small intestine and ovarian origin. This suggested that this cDNA might be a candidate for human intestinal sodium-phosphate cotransporter. Experiments using RT-PCR confirmed the expression of this gene in cDNA derived from human small intestine samples (obtained from Clontech Corporation, Palo Alto, CA). Subsequently, assignment of this sequence as the human intestinal transporter was strengthened by a high degree of homology to published sequences for Xenopus (A. Ishizuya-Oka et al. (1997) Temporal and Spatial Expression of an Intestinal Na^+/PO_4^{3-} Cotransporter Correlates With Epithelial Transformation During Thyroid Hormone-Dependent Frog

Metamorphosis. Development Genetics 20:53-66) and mouse (H. Hilfiker et al., Characterization of a murine type II sodium-phosphate cotransporter expressed in mammalian small intestine. PNAS 1998 95: 14564-14569) intestinal transporters."

The sequence, disclosed as SEQ ID NO: 01 in the application, is also a 689 amino acid sequence. This led the examiner to conclude that the full length cDNA, which the applicant obtained from the Incyte Corporation ("Incyte") and then sequenced, was the nucleic acid having the sequence SEQ ID NO: 02 claimed in the application.

14 I am satisfied that the DNA clone, obtained by the applicant from Incyte, is the clone described in the application as having the nucleotide sequence SEQ ID NO: 02. I am also satisfied that this clone in Incyte's DNA library was made available to the public, as an individual clone, before the priority date of the invention. Thus, in my opinion the Incyte clone with its 689 amino acid open reading frame was a part of the state of the art in the case of the present invention and as such it anticipates the nucleic acid of claims 3, 4, 5 and 18.

Inventive step

15 In the examiner's view the subject matter of claims 1 to 18 did not involve an inventive step in view of the disclosure in:

(i) the European application which was in the name of SmithKline Beecham Corporation; and

(ii) the Proceedings of the National Academy of Sciences of the United States of America, Volume 95, pages 14564 to 14569, November 1998, H. Hilfiker et al, "Characterization of a murine type II sodium-phosphate cotransporter expressed in mammalian small intestine" ("the Hilfiker paper").

16 The European application was published on 4 November 1998 with the title "A human sodium dependent phosphate transporter (IPT-1)". It discloses polynucleotides and polypeptides relating to the sodium dependent phosphate transporters family. By way of background this European application states that blockade of phosphate absorption with a specific inhibitor of the intestinal phosphate transporter would provide a major advance in the treatment of patients with end stage renal disease who develop hyperphosphatemia. One of the polypeptides, designated as "IPT-1" and characterised by SEQ ID NO: 2, has a length of 690 amino acids and is identical to the Npt2B polypeptide of the application, except that at positions 38 and 39 the amino acids threonine and aspartic acid of the IPT-1 polypeptide are replaced in the Npt2B polypeptide by the single amino acid asparagine and at position 620 the amino acid tyrosine of the IPT-1 polypeptide is replaced by the amino acid cysteine in the Npt2B polypeptide. The European application also discloses a nucleotide sequence, SEQ ID NO: 1 which is a very close match to the nucleotide sequence SEQ ID NO: 02 of the application. By comparing SEQ ID NO: 2 with known sodium dependent phosphate transporters it is deduced in the European application that the IPT-1 polypeptide and polynucleotide are expected to have similar biological properties to their homologous polypeptides and polynucleotides. It is also stated that a polynucleotide encoding IPT-1 may

be obtained using standard cloning and screening from a cDNA library derived from mRNA in cells of human small intestine and lung.

17 The Hilfiker paper acknowledges that the kidney and the small intestine are important control sites to maintain and balance the extracellular concentration of Pi. It also states that two dissimilar sodium phosphate co-transporters, named type I and type II, have been identified and that the type II sodium phosphate co-transporter represents the major pathway by which Pi is reabsorbed. The paper describes how a functional full length clone, containing an open reading frame coding for a protein of 697 amino acids, was obtained and that amino acid comparisons revealed that this protein was 57% – 75% homologous to the sodium phosphate co-transporters identified in bovine NBL cells, flounder kidney and intestine, and intestine and lung of *X. laevis* and to the renal type II sodium phosphate co-transporter. However, the authors noted a striking difference between their newly identified protein and mouse renal type II sodium phosphate co-transporter and proposed to subdivide type II sodium phosphate co-transporters into a subfamily type IIa (represented by the renal isoforms of mouse, rat, rabbit, opossum kidney cells, and human) and type IIb (represented by the isoforms of bovine, flounder and *Xenopus* as well as their protein). Based on various observations the authors favoured the notion that the protein they had identified was a candidate for a sodium phosphate transporter involved in intestinal Pi reabsorption.

18 In my view these documents, taken separately or together, would lead a person skilled in the art, without the need for any inventive ingenuity, to a nucleic acid which has the nucleotide sequence of SEQ ID NO: 02 described and claimed in the application. This skilled person then would go on to obtain the polypeptide of claims 1 to 3, again without requiring any inventive ingenuity. At the hearing Ms Richardson accepted that claims 6 to 10, which relate to an expression cassette, a host cell comprising the expression cassette, a method of expressing Npt2B in the host cell and a non-human transgenic animal model, had no independent inventiveness over the polypeptide and nucleic acid of claims 1 to 5. However, Ms Richardson did argue that the remaining claims were independently inventive based on the function of the polypeptide as a type IIB sodium phosphate human intestinal co-transporter. In my view this conclusion would be obvious to the skilled person from the disclosure in the cited documents. Moreover, the various applications of the polypeptide and nucleic acid, claimed in claims 11 to 17, would be equally obvious to him. Claim 18 is an omnibus claim but there seems nothing in the description that could provide the necessary inventive step. Thus, I conclude that the subject matter of claims 1 to 18 does not involve an inventive step.

Support

19 The examiner's objection to lack of support was directed against claims 16 and 17 for first and second medical uses of the polypeptide and the nucleic acid of the invention. In the examiner's view the application did not contain any evidence that the polypeptide and the nucleic acid had any therapeutic potential. In other words, the claimed therapeutic uses of the polypeptide and of the nucleic acid were no more than speculation. Ms Richardson, on the other hand, argued that the polypeptide of the invention is identified in the application as a sodium phosphate co-transporter and that this was a sufficient indication of potential therapeutic use. Thus, in her view there should be no requirement for experimental evidence

to substantiate a therapeutic effect for the polypeptide.

20 I have no reason to doubt on the basis of what is contained in the application that the nucleic acid of the invention encodes a polypeptide which in its native environment, as a membrane protein, is a co-transporter of sodium cation and phosphate anion. However, it is clearly stated in the application that the protein of the invention is present in a non-naturally occurring environment, for example, it may be in 99% pure form. Moreover, although the specification of the application envisages the use of the polypeptide and nucleic acid to treat disease conditions resulting from abnormally low sodium phosphate co-transporting activity, there is no indication that the polypeptide and nucleic acid could be used to treat disease conditions characterised by abnormally high sodium phosphate co-transporter activity. Against this background I find that there is no support in the description for:

(a) extra-cellular polypeptide according to the invention for use in therapy or for use for the production of a medicament for the treatment of diseases selected from hypophosphatemia, osteomalacia, hypocalciurea, rickets, hyperphosphatemia, including hyperphosphatemia resulting from renal insufficiency, hyperparathyroidism, hypocalcemia, vitamin D deficiency, or soft tissue or metastatic calcification; and

(b) the use of the polypeptide and the nucleic acid of the invention for the production of a medicament for the treatment of a host suffering from hyperphosphatemia, including hyperphosphatemia resulting from renal insufficiency, hyperparathyroidism, hypocalcemia, vitamin D deficiency, or soft tissue or metastatic calcification.

Summary and conclusion

21 I have found that:

(a) the nucleic acid of claims 3 to 5 and 18 is not new;

(b) the subject matter of claims 1 to 18 does not involve an inventive step; and

(c) the description does not wholly support the subject matter of claims 16, 17 and 18 relating to therapeutic use of the polypeptide and nucleic acid of the invention.

Therefore, I refuse the application on the grounds that it does not comply with the requirements of sub-sections 1(1)(a), 1(1)(b) and 14(5)(c).

Amendment

22 The extended period for complying with the requirements of the Act does not expire until 30 June 2004. Therefore, there remains an opportunity to amend the application so that it complies with the requirements of the Act. If the applicant chooses to take this opportunity, the application would be remitted to the examiner for further examination.

Appeal

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

Reasons for this decision

24 I will issue my reasons for this decision in writing as soon as possible.

R J WALKER
Deputy Director acting for the Comptroller