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PATENTS ACT 1977

APPLICANT F. Hoffmann – La Roche AG

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

HEARING OFFICER R J Walker

REASONS FOR 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 claimed priority from an earlier application filed in the USA on 9 February 1999. The application was published on 11 October 2000 as GB 2348645 A.

2 On 23 June 2004 I issued a decision refusing the application on the grounds that it did not comply with the requirements of sub-sections 1(1)(a), 1(1)(b) and 14(5)(c) of the Patents Act 1977. However, the decision did not contain my reasons and I undertook to provide them in writing later. I am now able to give the reasons for this decision.

3 My decision set out the background to the matters I had to decide and there is nothing to be gained by repeating it here. However, it would be helpful to outline once again the content of the application.

The application

4 The application relates to ion transporters, particularly sodium phosphate co-transporters. As explained, 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.

5 The application 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.

6 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 it is a co-transporter of sodium cation and phosphate anion in its native environment. 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 proteins of the invention may be obtained from naturally occurring sources or they may be produced synthetically. Moreover, they are present in a non-naturally occurring environment, for example they may be present in at least 99% pure form and so substantially free of other naturally occurring biological molecules.

7 It is stated that Npt2B and its corresponding nucleic acid find 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.

8 The claims of the application 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 matters to be decided

9 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 the description supports 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.

Novelty

Finding on novelty

10 In my decision I found that the nucleic acid claimed in claims 3 to 5 was anticipated because it was publicly available from a cDNA library before the priority date of the invention. I will give my reasons for this finding by first outlining the examiner's objection.

The examiner's objection

11 The basis for the examiner's objection was somewhat unusual because it was not based on any prior document known to him. Rather it was based on the disclosure in the application itself. 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 the 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 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. The examiner also understood that DNA clones held in Incyte's cDNA library were available individually to the public. Thus, in the

examiner's view the nucleic acid as claimed in claims 3 to 5 was not novel.

The applicant's response

12 This objection was addressed in a letter dated 28 May 2004 from the applicant's agent (Forrester Ketley & Co.). In this letter the agent made the point (again my emphasis):

> "With regard to the Examiner's novelty objection in paragraph 3 of the Examination Report of 5 May 2004**, it is of importance to note that the Incyte LifeSeq® database referred to on page 30 of the present Application contained only partial sequences for each clone (ie EST libraries)** and that the researchers/inventors involved had to obtain and isolate the clone and sequence it in its entirety before determining that the clone contained the full coding sequence of Npt2B. **Since the full-length sequence was <u>not</u> available in the Incyte database, it is respectfully submitted that Claims 4 to 6 (now renumbered as Claims 3 to 5) cannot be anticipated by the Incyte database**."

It seemed from this that the agent may have misunderstood the examiner's objection which was based on the availability of actual cDNA from Incyte's cDNA library and not, at least directly, on sequence information contained in the LifeSeq® database.

13 Moreover, at the hearing before me it became clear that the applicant's representative, Ms Richardson who is a patent attorney with the firm Forrester Ketley & Co., was not in a position to address certain fundamental assumptions made by the examiner when basing his novelty objection on the applicant's description of how the Npt2B nucleic acid of SEQ ID NO: 02 had been obtained. Although it had been clarified in the agent's letter dated 28 May 2004, particularly in the passage I have quoted above, that the Incyte LifeSeq® database contained partial sequences for each clone (i.e. EST libraries), Ms Richardson was unable to state if:

(a) the cDNA, obtained from Incyte and containing the full-length coding sequence, was available to the public before the priority date of the invention; and

(b) this cDNA was available from Incyte as an individual DNA clone; in other words not mixed with other clones.

14 It would have been wrong of me to rely solely on assumptions made by the examiner when reaching a decision on the novelty of the claimed nucleic acid but equally I considered it reasonable to seek clarification of these matters from the applicant. Bearing in mind that Ms Richardson could not provide any clarification at the time of the hearing, I gave her an opportunity to make a further submission, supported by evidence if she considered it appropriate, on the novelty of the nucleic acid of claims 3 to 5.

15 As a result the applicant's agent wrote on 11 June 2004 enclosing a witness statement, dated 10 June 2004, by Suryanarayana Sankuratri who is named in the application as one of the inventors. In this statement Mr Sankuratri states:

"at the priority date of GB 0002665.8 (9 February 1999) the Incyte LifeSeq® DNA library referred to on page 30 of GB 0002665.8 was a random collection of individualised clones which had not been indexed, and the DNA clone referred to on page 30, lines 15 to 16 of GB 0002665.8 had not been indexed in any way within this library";

"the DNA clone referred to on page 30, lines 15 to 16 of GB 0002665.8 could not have been

identified without working through a vast number of samples and that proper identification of the DNA clone was possible only after the inventors performed bioinformatics analyses and sequenced the clone in its entirety, as mentioned in the letter filed at the Patent Office by the agent for this Application on 28 May 2004"; and

"to the best of my knowledge, the presence of the DNA clone referred to at page 30, line 15 to 16 of GB 00026665.8 in the Incyte LifeSeq DNA library had not previously been recognised before the priority date of GB 0002665.8".

16 At the hearing Ms Richardson stated that the applicant was seeking protection based on very narrow claims. Thus, the invention was restricted to essentially a polypeptide comprising the amino acid sequence of SEQ ID NO: 01 and a nucleic acid encoding this polypeptide. According to Ms Richardson the applicant no longer sought to protect related polypeptides, such as variants, which are homologous or similar to the polypeptide of SEQ ID NO: 01, or fragments of this polypeptide. I pointed out to Ms Richardson that whatever the applicant's intention might be, I would need to determine the extent of the invention by interpreting the claims with reference to the description in the normal way. I also noted that the description, as it stood at the time of the hearing, included various statements casting doubt on the applicant's view of the scope of the claimed invention. Ms Richardson took this point on board and asked for an opportunity to reconsider the description and to amend it where it was inconsistent with the claims. I agreed to this request and Ms Richardson filed an amended specification on 11 June 2004. Therefore, it was this amended specification, and not the specification as it existed at the time of the hearing, which formed the basis for my decision.

The law

17 Section 1(1)(a) states that that a patent may only be granted for an invention if it is new and section 2(1) states that an invention shall be taken to be new if it does not form part of the state of the art. The state of the art for the purposes of this decision is defined in section 2(2) (my emphasis):

> "(2) The state of the art in the case of an invention shall be taken to comprise **all matter** (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use **or in any other way**."

Thus, the novelty of an invention can be impugned not only by a written or oral description or by use, but also by the invention being made available to the public "in any other way". Thus, for example, the novelty of an invention could be destroyed if the public were able to buy or otherwise obtain the invention before the priority date of the invention.

18 At the hearing before me Ms Richardson opened by setting out basic principles which she considered particularly relevant to the question of novelty. Her first basic principle was that a generic disclosure does not destroy the novelty of a more specific claim. A further basic principle identified by Ms Richardson was that to anticipate a claim the prior disclosure must contain clear and unmistakable directions to do what the patentee claims to have invented. Thus, a signpost upon the road to the patentee's invention will not suffice. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee. Ms Richardson's next basic principle was that the prior disclosure must be enabling and she referred me to the House of Lords judgment in *Asahi Kasei Kogyo KK* [1991] RPC 485 in which it was stated with regard to section 2(2) that an invention cannot be said to have been

made available to the public merely by a published statement of its existence (unless the method of working is so self-evident as to require no explanation); an enabling disclosure is necessary. I accept fully these basic principles put forward by Ms Richardson.

19 Ms Richardson then referred me to two decisions of the European Patent Office's Enlarged Board of Appeal, namely G 2/88 (Mobil Oil) and G 6/88 (Bayer). In paragraph 10 of its decision in G 2/88 the Enlarged Board considered the definition of the state of the art in Article 54(2) EPC, which is "everything made available to the public by means of a written or oral description, by use, or in any other way". In doing so it commented:

> "The word "available" carries with it the idea that, for lack of novelty to be found, all the technical features of the claimed invention in combination must have been communicated to the public, or laid open for inspection."

Ms Richardson drew my attention to particular statements made by the Enlarged Board in paragraphs 10 and 10.1 of its decision in G 2/88:

> " ……, a line must be drawn between what is in fact made available, and what remains hidden or otherwise has not been made available."; and
>
> "……. under Article 54(2) EPC the question to be decided is what has been "made available" to the public: the question is not what may have been "inherent" in what was made available (by a prior written description, or in what has previously been used (prior use), for example)".

This last statement was repeated by the Enlarged Board in G 6/88. Both G 2/88 and G 6/88 were concerned with the novelty of a second non-medical use where the second use was dependent on something which was inherent in the prior use. However, I did not understand Ms Richardson to be relying on these decisions for this purpose. Indeed, it was my understanding that her reason for referring to them was to confirm the need for an enabling disclosure, which is something I have already accepted.

20 Ms Richardson also referred to two decisions of the Technical Boards of Appeal of the European Patent Office, in which novelty was considered in the light of genetic material contained in a gene bank. These decisions are T 301/87 (Biogen) and T412/93 (Kirin-Amgen Inc.). In decision T 301/87 the Board had to consider whether the unconfirmed presence of a particular nucleotide sequence in Lawn's gene bank could be regarded as the state of the art for the purposes of Article 54 EPC. On the facts of that case, the Board decided (my emphasis):

> "Accordingly, the mere existence of a DNA sequence coding for a polypeptide of the IFN-alpha type, within the multitude of clones of "Lawn's gene bank" cannot automatically mean that the chemical compound (polynucleotide) concerned does become part of the state of the art. **The latter would only then be the case if the existence of the compound concerned had recognisably been made publicly available.**"

In the same decision the Board commented (again my emphasis):

> "5.6 As a matter of general interest, it can be stated that even if some fragments of the collection were to have all the required properties, **the availability of such material without undue burden has not been established**. The fact that such phages are

hidden in a random collection of 240 000 unidentified individual samples is not irrelevant to the issue. Whilst there was undoubtedly reference in the patent to positive hybridisation results with the probe "Hif-2h", this does not yet imply that the independent criteria for IFN-alpha type activity after expression would have also been complied with as far as some materials in the gene bank were concerned. No relevant tests in this respect were reported.

5.7 The assumed presence of some fragments satisfying the criteria of the claim is not like the incidental availability of an unindexed book in a library. The interrogation of a library material is, at least for some members of the public, a direct mental procedure. **The collection in the present case must be interrogated by physical interactions, and a consequent biochemical process in each case. Although any vial containing the relevant phage is a separate entity here, it is impossible to get to the vial without working through tens of thousands of samples.** The circumstances are such as if the material were under lock and where the key has to be first manufactured and applied.

5.8 If anything, the situation resembles that prevailing with natural substances, since the availability of phages is not direct, and is rather like the isolation of a component or bacterium from the soil where the same exists in admixture with other useless materials. **Thus, the idea that the gene bank itself would once for all anticipate an invention relating to a nucleotide sequence which may be contained therein somewhere, cannot be sustained**."

In its other decision (T 412/93), which concerned the gene for erythropoietin ("Epo"), the Board noted that no probe was known for identifying the relevant gene and found that the nucleotide sequence of the Epo gene was not part of the state of the art merely because the nucleotide sequence would have been present in the Lawn gene bank or possibly others.

21 Another authority mentioned by Ms Richardson was V 8/94 (Howard Florey Institute), which was a decision by the European Patent Office's Opposition Division. As recognised by Ms Richardson, this decision deals with the question of "discovery" but the point she wanted to draw from it was that the general disclosure of the human genome, for example, does not disclose each and every individual element within it.

22 I should add that Ms Richardson also referred very briefly at the hearing to *Colley's Application* [1999] RPC 97 thinking that the examiner's objection might have been based on prior use of a nucleic acid comprising the nucleotide sequence SEQ ID NO: 02. However, it was and remains my understanding that the examiner's objection was based on the availability of this nucleic acid from Incyte's cDNA library and not on any prior use of this nucleic acid. Therefore, I do not believe I need consider this authority further.

23 Prior to the hearing the examiner had identified and notified the applicant's agent of some authorities, which he considered relevant to the matters I had to decide. One of these authorities was *Evans Medical Ltd's Patent* [1998] RPC 517. This case concerned a vaccine containing pertactin, which is a surface antigen of the whooping cough bacterium *Bordetella pertussis*, and Laddie J found that the patent was invalidated on the basis of anticipation by a vaccine despite no one knowing at the relevant time that it contained pertactin. The prior art vaccine was a product within the claims and it was open to anyone to analyse it. Another authority noted by the examiner was *PCME Ltd v Goyen Controls Co. U.K. Ltd* [1999] FSR 801. This case concerned the prior use of a "black box" which was supplied on a sale or return basis and which had its circuit components sealed. In his judgment Laddie J found that it

was appropriate to consider what an expert could deduce about the circuitry by submitting the device to non-destructive analysis.

Assessment and conclusion on novelty

24 Before I could reach any conclusion on this matter I had first to construe claims 3 to 5 in the light of the entire specification. After giving careful consideration to the amended specification, which was filed on 11 June 2004, I am satisfied that I should construe claims 3 to 5 narrowly, as intended by the applicant. However, it was clear to me that claims 3 to 5 would be anticipated, despite this narrow construction, if I found that an isolated cDNA of SEQ ID NO: 02 had been made available to the public before the priority date of the invention.

25 I should also make it clear that I was looking to decide whether the cDNA itself was publicly available. Although information about the nucleotide sequence of this cDNA is important for confirming the relationship between the cDNA obtained from Incyte and the nucleic acid claimed in the application, I do not consider it necessary for the cDNA to have been sequenced before the priority date of the invention in order to impugn the novelty of the claimed nucleic acid. It is clear to me from *Evans Medical Ltd's Patent* and *PCME Ltd v Goyen Controls Co. U.K. Ltd.* that a substance or an article can anticipate even if no one knew the make up or the constitution of the substance or article prior to the relevant date. In the present case the unknown feature was the nucleotide sequence of a DNA clone and this sequence could have been readily determined using an automated sequencer.

26 I should now address the assumptions which were made by the examiner and which had a bearing on the question of novelty of the nucleic acid of SEQ ID NO: 02. Neither at the hearing nor afterwards did the applicant contradict the examiner's view that the cDNA of SEQ ID NO: 02 is in fact the clone containing the full-length coding sequence obtained from Incyte. Indeed, it seems to me that there is a clear inference in Mr Sankuratri's witness statement that this clone was present in Incyte's DNA library, when he states that it had not been indexed in any way within that library. I am therefore satisfied that I am dealing with one and the same clone. Furthermore, I gave Ms Richardson an opportunity, following the hearing, to address the examiner's assumption that clones in Incyte's cDNA library, and in particular the cDNA of SEQ ID NO: 02, were available to the public before the priority date of the invention. The agent's letter, dated 11 June 2004, which was filed with the witness statement of Suryanarayana Sankuratri, does not address this point and in the absence of any indication to the contrary I am satisfied that the examiner's assumption on this matter is also well founded. Finally, there is the question of whether the full length cDNA, obtained from Incyte, was present as an individual clone or mixed with other clones. The answer to this question is provided by the witness statement of Mr Sankuratri in which he states (my emphasis) that Incyte's DNA library was "a random collection of **individualised** clones".

27 I have already stated that I accept the basic legal principles identified by Ms Richardson. Applying these principles to the present case, if the cDNA of SEQ ID NO: 02 was available from Incyte, this could not be more specific in my view. The flag would have been planted precisely on the DNA of the present invention. Moreover, it seems to me that a sample of cDNA is enabling in itself. Here I would draw a comparison with the possibility of depositing biological material for patent purposes under section 125A of the Patents Act 1977 so that a specification is treated as disclosing the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art.

28 Ms Richardson's main submission to me on the question of novelty was that a publicly available DNA library does not disclose each and every as yet unidentified element of that library in the

same way that a generic disclosure does not disclose the specific. She argued that this principle had already been confirmed by decisions T 301/87 and T 412/93 of the Technical Boards of Appeal. Although I am not bound to follow such decisions, it is obviously desirable that the practice in the UK Patent Office should be consistent with that of the European Patent Office. Therefore I should consider them.

29 Both of these decisions addressed a situation where it was assumed that the relevant nucleotide sequence was present in Lawn's gene bank but it would have been necessary to interrogate the collection by physical interactions to confirm this. In the present case, I am satisfied that Incyte's DNA library contained a DNA clone of SEQ ID NO: 02. Thus, unlike the cases considered by the Technical Boards of Appeal, the existence of the DNA clone in a gene bank or cDNA library is not based on a mere assumption. Nevertheless, I was left to consider whether this clone was available without undue burden and Ms Richardson sought to persuade me that the burden was considerable.

30 In the application it is stated that the LifeSeq® database was screened using a consensus sequence and that a large number of clones were identified, including one which appeared to contain a full-length coding sequence. Mr Sankuratri states in his witness statement that identification of the DNA clone containing the full-length coding sequence was possible only after working through a vast number of samples and the use of bioinformatics. The Agent's letter of 28 May 2004 explains that the LifeSeq® database contained sequences, commonly referred to as Expressed Sequence Tags ("ESTs"). ESTs are small pieces of DNA which are representative of genes expressed in certain cells, tissues, or organs and when included in a searchable database can provide access to other genomic data using standard bioinformatics techniques. Thus, unlike the situations considered by the Technical Boards of Appeal in T 301/87 and T 412/93 where it would have been necessary to physically probe tens of thousands of samples in Lawn's gene bank, the applicant was able to select DNA clones in Incyte's cDNA library by screening the associated LifeSeq® database. Moreover, although a large number of clones were identified as the result of screening the LifeSeq® database using the consensus sequence, the application states that the applicant was able to select one, apparently containing a full-length coding sequence, from the database. There is nothing in the application or Mr Sankuratri's evidence to suggest that a vast number of clones had to be obtained from Incyte for physical testing. Indeed, the description only refers to four clones, including the clone of the invention, being obtained for sequencing. Therefore, I am not persuaded that there was an undue burden associated with making the cDNA of sequence ID NO: 02 available in Incyte's DNA library. Even though this cDNA was not individually indexed in the library, as stated by Mr Sankuratri in his evidence, it was possible to pin point it using the LifeSeq® database. Thus, my conclusion was that an individual nucleic acid of SEQ ID NO: 02 was publicly available in Incyte's cDNA library before the priority date of the invention and that it anticipated the nucleic acid of claims 3 to 5.

Inventive step

Finding on inventive step

31 In addition to my finding on novelty, I found that the subject matter of claims 1 to 18 did not involve an inventive step because it would have been obvious to a person skilled in the art having regard to the disclosure in two documents which had been cited by the examiner. Once again I will explain my reasons by first outlining the examiner's objection.

The examiner's objection

32 The documents, cited by the examiner, were European patent application no. EP 875569 A1 (the "European application") and a paper published in 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").

33 The European application was filed by SmithKline Beecham and 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 one 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.

34 The Hilfiker paper, which was also published in November 1998, 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, 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 the protein they had found). 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.

The applicant's position

35 In the agent's letter, dated 28 May 2004, it was suggested that the question of inventive step should be determined by applying the "problem-solution" approach adopted by the European Patent Office. The examiner responded to this letter by reminding the agent that inventive step was normally assessed by the courts in the UK using the structured approach formulated by the Court of Appeal in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59. At the hearing Ms Richardson sought to persuade me that whatever approach was taken, it could be shown that the invention of the application was inventive.

36 Ms Richardson explained that the "problem-solution" approach, involved three main stages, as follows:

(i) determining the closest prior art;

(ii) establishing the "objective technical problem" to be solved; and

(iii) considering whether or not the claimed invention, starting for the closest prior art and the objective technical problem, would have been obvious to the skilled person.

37 According to Ms Richardson the closest prior art or, as she described it, the most promising springboard towards the invention was the European application. Turning then to the second stage, Ms Richardson submitted that the technical problem to be solved was the identification of an alternative human intestinal sodium phosphate co-transporter. Finally, in Ms Richardson's view the third stage required an answer to the question whether a person skilled in the art would have arrived at the invention by adapting or modifying the closest prior art. Ms Richardson stressed that the question was not whether a person skilled in the art could have arrived at the invention but whether he would have done so. In her submission to me Ms Richardson was firmly of the view that the skilled person would not have arrived at the invention from the European application. In reaching this view she acknowledged that the European application envisages the possibility of variants which retain the essential properties of the specific sequence disclosed in that application. Against this background, she suggested that when a skilled person was looking to find an alternative functional protein to the one specifically disclosed, he would consider what changes he could make to the sequence while retaining its essential properties. In doing so he would use his common general knowledge that protein function is dependent on the three dimensional structure of the protein and that this three dimensional structure is dependent on its underlying amino acid sequence.

38 On this point Ms Richardson referred me to the agent's letter, dated 28 May 2004, which explains that the molecular structure of a protein is generally considered to consist of four levels of structural organisation. The primary structure consists of a sequence of amino acids in a polypeptide chain. The secondary structure refers to the spatial arrangement of amino acid residues which are near one another in the linear sequence, some of which give rise to a periodic structure, such as a-helices and ß-strands stabilised by hydrogen bonds. The tertiary structure involves the specific folding of the polypeptide chain, which is maintained by the interaction of ionic, hydrogen and di-sulphide bonds, as well as hydrophobic interactions. Finally, where a protein consists of more than one polypeptide chain, the quaternary structure refers to the specific aggregate of those polypeptide chains. The primary amino acid sequence of a protein determines its secondary, tertiary and quaternary structure and hence the protein's functional state. The agent's letter of 28 May 2004 continues by explaining that naturally occurring amino acid residues may be divided into different classes based on their side chain properties. Changing amino acid residues within the same class, so called "conservative" modifications, will normally produce proteins having functional and chemical characteristics similar to those of the wild type protein. In contrast, changing one class of amino acid for another at a particular position can have a significant effect.

39 Ms Richardson argued that from the vast number of different possibilities for modifying the sequence disclosed in the European application, the solution provided by the applicant is the specific substitution of a cysteine residue for a tyrosine residue at position 619 of the amino acid sequence, disclosed in the present application as SEQ ID NO: 01. In Ms Richardson's view this is an extremely unlikely change for a skilled person, who was aware of the problem, to consider making. Firstly, cysteine is a neutral hydrophilic residue which has completely

different properties from the less hydrophilic aromatic residue, tyrosine. Even more important in Ms Richardson's submission was that position 619 is in a cluster of cysteine residues and that the skilled person would be very much aware, as part of his common general knowledge, that cysteine residues are extremely important to the structure and hence the function of the polypeptide. Thus, in Ms Richardson's submission, this is a very unlikely area for the skilled person to consider a change of amino acid residue when faced with the problem of finding an alternative protein which has sodium phosphate co-transporting activity. On this basis Ms Richardson concluded that the change of amino acid residue at position 619 was not an obvious modification. Indeed, in her view it was a very fundamental change which moved away from the prior art and to the claimed invention in a non-obvious way.

40 Ms Richardson then moved on to explain that when the question of inventive step was analyzed using the alternative *Windsurfing* approach, the conclusion was the same. The four step approach formulated by the court in *Windsurfing* is well known but nevertheless I will set out the steps here. The first step is to identify the inventive concept embodied in the application in suit. The second step is to assume the mantle of the normally skilled but unimaginative addressee in the art at the priority date and to impute to him what was, at that date, common general knowledge in the art in question. The third step is to identify the differences, if any, between the matter cited as being "known or used" and the alleged invention. The final step is then to decide "whether, viewed without any knowledge of the alleged invention, those differences constitute steps which would have been obvious to the skilled man or whether they require any degree of invention".

41 Ms Richardson initially identified the inventive concept as an alternative human intestinal sodium phosphate co-transporter. However, upon reflection and in line with claim1, for example, she identified the inventive concept as a polypeptide comprising the amino acid sequence of SEQ ID NO: 01. Addressing the second *Windsurfing* step, Ms Richardson imputed to the normally skilled but unimaginative addressee knowledge of protein structure and the fact that function is critically dependent on structure. As before she identified the difference between what was known and the claimed invention as the substitution by a cysteine residue at position 619 and she argued that this change of amino acid residue would not have been obvious to the skilled man.

42 Up until that point at the hearing Ms Richardson's submission on inventive step had been based on the differences between the claimed invention and the polypeptide sequence disclosed in the European application. Therefore, I asked her how she would apply the *Windsurfing* approach on the basis of the prior disclosure in the Hilfiker paper. In Ms Richardson's view the skilled person would look at the prior art as a whole and in so doing he would find no motivation to use as a starting point the disclosure in the Hilfiker paper, which relates to mouse type IIb sodium phosphate co- transporter expressed in the small intestine, when he has the closer prior art disclosed in the European application. Ms Richardson's submission was that although the *Windsurfing* approach does not require identification of the closest prior art, it was only fair to put the applicant into the position of having a fair starting point.

43 At the hearing I also asked Ms Richardson whether in her view any of the claims were independently inventive of the claimed polypeptide and nucleic acid. She accepted that if claims 1 to 5 fell, claims 6 to 10 would fall with them because they did not provide any independent inventive step. However, in her opinion claims 11 to 17 were independently inventive of claims 1 to 5 and she stated that the applicant would want to maintain them on the basis that the prior art does not demonstrate a human Type IIb sodium phosphate intestinal co-transporter. Therefore, after I have given the reasons for my finding that the invention claimed in claims 1 to 5 does not have an inventive step, I will also need to explain why I found the

subject matter claims 11 to 17 obvious.

The law

44 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)."

45 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 I have already referred to.

46 It is also well established that even if the skilled person "could" have done what is claimed as the invention, the invention is not obvious unless it can be found on the balance of probabilities that the skilled person "would" have done that thing. The agent's letter of 28 May 2004 noted decision T 2/83 (Rider) of the Technical Boards of Appeal of the European Patent Office, in which the Board held that the proper question to be asked is not whether the skilled person could have done what was claimed but whether he would have done so in expectation of some improvement or advantage.

47 The question of "obvious to try" was also raised at the hearing in the context of *Pfizer Ltd's Patent* [2001] FSR 16 in which Laddie J stated in his judgment at paragraph 106:

> "Whether something is obvious to try depends to a large extent on balancing the expected rewards if there is success against the size of the risk of failure."

Laddie J also stated at paragraph 66 of his judgment in *Pfizer*:

> "When any piece of prior art is considered for the purposes of an obviousness attack, the question asked is 'what would the skilled addressee think and do on the basis of this disclosure?'"

48 At the hearing Ms Richardson drew my attention to two further decisions of the Technical Boards of Appeal, which illustrate an approach of the European Patent Office that an invention cannot be considered obvious if there is no reasonable expectation of success. These decisions are T 296/93 (Biogen Inc.) and T 207/94 (Biogen Inc.). In decision T 296/93 the Board stated:

> "The fact that other persons (or teams) were also working on the same project might suggest that is *(sic)* was "obvious to try" or that it was "an interesting area to explore", but it does not necessarily imply that there was "a reasonable expectation of success". "A reasonable expectation of success", which should not be confused with the

> understandable "hope to succeed", implies the ability of the skilled person to reasonably predict, on the basis of the existing knowledge before the starting of a research project, a successful conclusion to the said project within acceptable time limits. The more unexplored a technical filed of research is, the more difficult is the making of predictions about its successful conclusion and, consequently, the lower the expectation of success."

Decision T 207/94 acknowledges the Board's earlier decision in T 296/93 when it stated:

> "31. ……., it has to be borne in mind that "the hope to succeed" should not be misconstrued as a "reasonable expectation of success" (see T 296/93, OJEPO 1995, 627). In the board's judgement, the former is the mere expression of a wish whereas the latter requires a scientific evaluation of the facts at hand. In the case of gene expression, this evaluation necessitates that the properties of the "expression partners" (the gene to be expressed and its protein product on the one hand, and the recombinant host on the other) be compared.
>
> 32. If any one of them has properties which common general knowledge at the priority date would have suggested might be unfavourable to their relationship, it is justified to conclude that the person skilled in the art would have had no reasonable expectation of success."

Assessment and conclusions on inventive step

49 In my decision I found that the subject matter of claims 1 to 18 does not involve an inventive step because it would have been obvious to a person skilled in the art having regard to the disclosure in the two documents cited by the examiner.

50 An assessment on inventive step requires a structured approach and my preference is to follow that established by the Court of Appeal in *Windsurfing*. Thus, while I am grateful to Ms Richardson for her submissions based not only on the European Patent Office's "problem-solution" approach but also on the *Windsurfing* approach, I will base my reasons solely on the latter approach which is more commonly adopted in the United Kingdom.

51 I should start by considering Ms Richardson's submissions to me at the hearing. Applying the first step of the *Windsurfing* approach, Ms Richardson identified the inventive concept as a polypeptide comprising the amino acid sequence of SEQ ID NO: 01. I agree with Ms Richardson on this matter in that it fairly represents the inventive concept of at least claims 1 to 5.

52 Ms Richardson did not suggest to me who the notional skilled person or addressee might be in this case but when considering the second *Windsurfing* step she did argue that he would know about protein structure and that function is critically dependent on structure. It is often difficult to assess the common general knowledge of the skilled but unimaginative addressee in the art at the priority date of the invention. However, this is what I must do and in the present case I would identify the addressee as a molecular biologist. I agree with Ms Richardson that he would know about protein structure and its relationship to function but in my view his common general knowledge would go wider than this and this is something I will consider later. For the moment I will stick with Ms Richardson's submission on the common general knowledge possessed by the skilled person.

53 Ms Richardson addressed the third *Windsurfing* step by highlighting the amino acid substitution at position 619 of SEQ ID NO: 01 as the critical difference between the invention in suit and

what was known from the cited European application. Finally, she concluded that this difference was not an obvious one for reasons I have already referred to above. Ms Richardson did not address me in any detail on the differences between the invention in suit and the prior art as described in the Hilfiker paper, and whether the differences would have been obvious to the addressee.

54 At the hearing I asked Ms Richardson whether she considered that her assessment based on the *Windsurfing* approach took adequate account of the common general knowledge of the normally skilled but unimaginative addressee. In particular, I sought her views on whether the addressee could be imputed to have common general knowledge which would have enabled him to approach the invention in suit in a different way from the one she suggested. Ms Richardson acknowledged that her approach was a very theoretical, artificial one but in her view the test for inventive step was not based on real life situations. I would accept this point so far as it is generally recognised that the skilled but unimaginative addressee is a notional character who differs from a real worker in a number of ways. Nevertheless, as stated by Laddie J in *Pfizer*, I should consider what the addressee would **think and do** on the basis of the disclosure in the prior art. I believe this includes considering what route the addressee would take in the light of the prior art. Thus, in my view I am not constrained to consider simply what direct changes the addressee would make to a published polynucleotide or polypeptide sequence in the way suggested by Ms Richardson. Moreover, by basing my assessment on what the addressee would think and do, I am not constrained to consider whether the way the applicant came to the invention was obvious. However, before I can form a view about what the skilled but unimaginative addressee would have thought and done, I must consider what common general knowledge I can impute to him.

55 The application, as originally filed, stated:

> "Between mammalian species, *eg*., human and mouse, homologs have substantial sequence similarity, *e.g.* at least 75% sequence identity, usually at least 90%, more usually at least 95% between nucleotide sequences."

This reflects what I consider would have been common general knowledge to the skilled but unimaginative addressee at the priority date of the invention in suit. Moreover, not only would he have known that the similarities between mouse and human genes were high, he would have recognised also that gene for gene humans are very similar to mice in that only a small number of human genes do not have a mouse counterpart. When I questioned Ms Richardson on this point at the hearing she accepted that homologs for genes in one species may exist in another and agreed that this would have been common general knowledge. I think it is only fair that I should also refer to the agent's letter, dated 28 May 2004, which addressed the question of protein families (my emphasis):

> "It should, however, be noted that it is not a forgone conclusion that a member of a protein family found in one species will also be found in another. In this regard, gene families are created by gene duplication which is a random evolutionary event. Because the size of a gene family is dependent on random evolutionary events, the number of members in a gene family is also **totally** unforeseeable and again it cannot **reasonably** be predicted whether a family of genes or proteins has more members until after they have been found."

I accept that the addressee would not know with absolute certainty that a human counterpart could be found for a particular mouse gene but I disagree with the applicant about the likelihood of this occurring. As I have already stated the addressee would know that for the most part

there is a one-to-one correspondence between the human and mouse genes. Thus, in my view the chances of finding a counterpart are high.

56 The above extract from the agent's letter touches on another point which I believe would have been common general knowledge to the addressee at the relevant date. In my view the addressee would have known that gene duplication has resulted in gene families, comprising related genes with similar sequences, in the same species, for example humans. Thus, the addressee would recognise the possibility of not just one but a family human genes which express sodium phosphate co-transporters.

57 The application also states:

> "Homologs of *Npt2B* are identified by any of a number of methods. A fragment of the provided cDNA may be used as a hybridization probe against a cDNA library from the target organism of interest, where low stringency conditions are used. The probe may be a large fragment, or one or more short degenerate primers. …… . Sequence identity may be determined by hybridization under stringent conditions, for example, …… . Nucleic acids having a region of substantial identity to the provided *Npt2B* sequences, e.g. allelic variants, genetically altered versions of the gene, *etc*., bind to the provided *Npt2B* sequences under stringent hybridisation conditions. By using probes, particularly labeled probes of DNA sequences, one can isolate homologous or related genes."

58 Although this passage relates to the use of probes, based on the nucleic acid of the invention, it is my understanding that it has been common laboratory practice over many years to use hybridisation probes to isolate genes which are homologous or related to a known nucleic acid. Even if the nucleic acid, and hence its nucleotide sequence, is not available, common general knowledge would allow the skilled addressee to produce an effective hybridisation probe from a corresponding known amino acid sequence. At the hearing Ms Richardson did not seek to suggest otherwise, indeed she stated that she thought the common general knowledge of the addressee would include techniques to detect homologs in most situations.

59 Hybridisation probes are used to screen cDNA libraries and, in my view, the skilled but unimaginative addressee would also know how to construct a cDNA library from, for example, a tissue sample. Furthermore, it would also be common general knowledge that cDNA libraries for specific types of tissue already existed.

60 Once the addressee had isolated a clone from a cDNA library using a hybridisation probe, it would be within his common general knowledge to sequence it and deduce the amino acid sequence of the corresponding polypeptide. It would also be within his common general knowledge to use cDNA to express a corresponding recombinant polypeptide.

61 Now that I have established what in my view would have been common general knowledge to the skilled, unimaginative addressee at the relevant date, I can turn to the third *Windsurfing* step. This requires me to identify the differences between the alleged invention and what is disclosed in the European application and the Hilfiker paper.

62 I will start by comparing the European application with the alleged invention. In the agent's letter, dated 28 May 2004, it is stated that it has never been shown that the IPT-1 of the European application is a functional sodium phosphate co-transporter in mammalian cells, nor has there been any working example showing the activity of IPT-1 in an appropriate mammalian system, either in the European application itself or since. Ms Richardson made the

same point at the hearing. However, it is clear to me that I must consider what the skilled but unimaginative addressee would have thought and done on the basis of what was known at the priority date. The skilled person has many attributes but it has never been suggested that crystal ball reading is one of them. Therefore, I have to consider what the skilled person would have made of the disclosure in the European application in the light of any additional, relevant information that was made available after its publication but before the priority date of the present invention. The applicant has not identified any such additional information and so I need only consider the disclosure of the European application. The addressee would have seen immediately from the title that the European application relates to a human sodium dependent phosphate transporter. On reading the specification of the European application he would have noted that the invention relates to an IPT-1 polynucleotide which comprises the nucleotide sequence SEQ ID NO: 1 encoding an IPT-1 polypeptide comprising a sequence SEQ ID NO: 2. He would have also noted that IPT-1 is structurally related to other proteins of the sodium depended phosphate transporters family, as shown by the results of sequencing the cDNA encoding human IPT-1, and that one polynucleotide of the invention in the European application may be obtained, using standard cloning and screening, from a cDNA library derived from mRNA in cells of human small intestine and lung. The addressee would also have read that the IPT-1 polypeptides and polynucleotides are expected to have, *inter alia*, similar biological functions/properties to their homologous polypeptides and polynucleotides. At the hearing Ms Richardson suggested that the addressee reading the European application would have doubted that the IPT-1 polypeptide had the function and the activity of an intestinal sodium phosphate co-transporter because the European application states that IPT-1 is shown to be most homologous in sequence to a bovine renal sodium dependent phosphate transporter. In view of what I have already said concerning the addressee's common general knowledge of gene families, I do not believe this comparison would have led him to doubt, for example, the statement that a polynucleotide encoding IPT-1 may be obtained from a cDNA library derived from cells of human small intestine.

63 I am therefore satisfied that the addressee would recognise that the European application relates, in part, to a human intestinal sodium phosphate co-transporter and to this extent there is no difference between what is disclosed in the present application and in the European application. This leaves just the specific differences between the sequence of the polypeptide disclosed in the European application and the sequence of the polypeptide of the present inventive concept.

64 Ms Richardson seemed to dismiss the Hilfiker paper as a starting point because it did not provide a fair starting point. I consider it would be wrong to dismiss this prior art on these grounds, particularly since in some respects it could be regarded as closer to the invention than the European application. Only by applying a structured approach, such as that established in *Windsurfing*, can the relevance of this prior art be established.

65 The Hilfiker paper discloses work done to identify a new sodium phosphate co-transporter expressed in the small intestine of mouse. Thus, the Hilfiker paper and the alleged invention both concern intestinal sodium phosphate co-transporters but they have their origins in different species, namely mice and humans. Not surprisingly the amino acid sequence of the new sodium phosphate co-transporter, which is the subject of the Hilfiker paper, is different from that of the polypeptide of the present inventive concept. However, I note that the applicant has acknowledged in the present application that a high degree of homology exists between the two sequences.

66 I can now move on to the fourth and final *Windsurfing* step: whether, viewed without any knowledge of the alleged invention, the differences constitute steps which would have been

obvious to the skilled man or whether they require any degree of invention?

67 I do not take this to mean that the addressee should be able to predict the amino acid sequence SEQ ID NO: 01 of the Npt2B polypeptide of the invention directly from the amino acid sequences disclosed in the European application and the Hilfiker paper. This is the approach Ms Richardson took at the hearing and I think it is flawed, not the least because the addressee would not necessarily think in this way. To reach a conclusion on the fourth *Windsurfing* step I need to answer three questions:

(a) would it have been obvious to the addressee to try and obtain an alternative human intestinal sodium phosphate co-transporter?

(b) would a route to this goal have required any degree of invention on the part of the addressee?

(c) assuming there was an obvious route, would the addressee have obtained a polypeptide comprising SEQ ID NO: 01 as the inevitable consequence of following this route?

Obvious to try?

68 To answer this question I will start by considering the European application which Ms Richardson identified as the closest of piece of prior art. Under a heading "Background of the invention" the European application states (my emphasis):

> "Phosphate retention has been shown to play a critical role in the development of uremic bone disease. Blockade of intestinal absorption of phosphate could provide an important target for prevention of uremic bone disease in patients who have end stage renal disease (ESRD) and possibly a target for slowing the progression of renal disease itself. Patients with ESRD cannot excrete phosphate and they develop hyperphosphatemia, secondary hyperparathyroidism and uremic bone disease. Current treatment of these patients involves dietary phosphate restriction and phosphate binders, both of which have severe drawbacks. **Blockade of phosphate absorption with a specific inhibitor of the intestinal phosphate transporter would provide a major advance in the treatment of these patients. This indicates that the sodium dependent phosphate transporters family has an established, proven history as therapeutic targets. Clearly there is a need for identification and characterization of further members of the sodium dependent phosphate transporters family which can play a role in preventing, ameliorating or correcting dysfunctions or diseases, including, but not limited to, chronic renal failure, end stage renal disease, uremic bone disease, and cancer**."

From this it seems that before the priority date of the application there was both a need and scope for the identification of further sodium phosphate co-transporters. Moreover, the European application flags up in the clearest of terms that the identification of a specific inhibitor of the intestinal phosphate transporter would constitute a major advance. I have no reason to suppose that the European application misrepresents the situation as it existed in the late 1990s, and in my view the prospect of making a major advance would have provided ample motivation for the addressee to identify, characterise and obtain a human intestinal sodium phosphate co-transporter.

69 At the hearing there was some discussion whether the addressee would have considered it worthwhile to search for an alternative human sodium phosphate co-transporter when the

European application had seemingly already identified one. In considering this point I note that the European application itself envisages the identification and isolation of further full-length human and non-human cDNAs and genomic clones encoding IPT-1 polypeptide by employing polynucleotides, which are identical or sufficiently identical to a nucleotide sequence contained in SEQ ID NO: 1, as hybridization probes. In my view this is consistent with the addressee's common general knowledge about gene families and I do not believe he would have been deterred by the disclosure in the European application of one human sodium phosphate co-transporter from seeking others of the same family. This appears to be confirmed in the application in suit which states (again my emphasis):

> "Because of the wide variety of disease conditions characterized by the presence of abnormal Pi metabolism, there is **continued interest** in the identification of the molecular components responsible for Pi metabolism. **Of particular interest would be the identification of the intestinal transporter responsible for absorption and uptake of Pi in the intestine**."

70 The Hilfiker paper, published at more or less the same time as the European application, notes that so far proteins involved in mammalian small intestinal Na/Pi co-transport had not been described. This paper also identifies the small intestine as an important control site to maintain and balance the extracellular concentration of inorganic phosphate. As I have indicated above the addressee would have known that for the most part there is a one-to-one correspondence between human and mouse genes. Set against this background, the suggestion in the Hilfiker paper that the authors had identified and characterised a new type of sodium phosphate co-transporter, which is expressed in the small intestine of mouse, would be enough in my view to motivate the addressee to seek a human counterpart.

71 Thus, on the balance of probabilities I find that the addressee would have considered it obvious at the relevant time to try and obtain:

(a) a variant of the human intestinal sodium phosphate co-transporter disclosed in the European application; and

(b) a human homolog to the type IIb sodium phosphate co-transporter expressed in the small intestine of mice, as described in the Hilfiker paper.

Moreover, whilst I accept that success would not have been certain, I consider the potential major benefits, which would come from success, would have outweighed any thought of failure.

Would the route have been obvious?

72 In my view the disclosure in the European application and the Hilfiker paper would have led the skilled person to look specifically to the human small intestine for an alternative sodium phosphate co-transporter. I have already referred to Ms Richardson's comment at the hearing that she thought the common general knowledge of the addressee would include techniques to detect homologs in most situations. Whilst I cannot take Ms Richardson's general comment as signalling her acceptance that these techniques could have been used to obtain the cDNA of SEQ ID NO: 02 of the invention, I have no reason to suppose that the techniques for obtaining this cDNA would have required any inventive ingenuity on the part of the addressee. He would have known how to produce a cDNA library from mRNA in cells of the human small intestine and how to screen that library, using hybridisation probes derived from the cDNA sequences disclosed in the European application and the polypeptide sequence disclosed in the

Hilfiker paper. Using these techniques he would have been able to look for a full length coding sequence. Alternatively, the sequence information, provided in the European application and in the Hilfiker paper, would have allowed the addressee to conduct database searches, such as in the LifeSeq® database, for a related EST cDNA clone. Once again he could have identified a full length coding sequence using just his common general knowledge. Thus, in my view the addressee had not one but two obvious routes for obtaining a cDNA with the nucleotide sequence of SEQ ID NO: 02 and hence a polypeptide of SEQ ID NO: 01.

Would the skilled person have obtained the polypeptide by following an obvious route?

73 I believe on the balance of probabilities that the addressee using no more than his common general knowledge could and would have found the cDNA of SEQ ID NO: 02 provided the cells of the human small intestine actually expressed the corresponding protein. I have already quoted a passage from the application which appears under the heading "EXPERIMENTAL". This passage includes the statement:

> "Experiments using RT-PCR confirmed the expression of this gene in cDNA derived from human small intestine samples ……."

This is adequate confirmation for me that the relevant gene is expressed in cells of the human small intestine and as such I am satisfied that the addressee would have obtained the cDNA of SEQ ID NO: 02 without the need for any inventive ingenuity, by constructing a cDNA library from mRNA expressed in human small intestinal cells and by screening this library using hybridisation probes derived from the sequence information published in the European application and/or the Hilfiker paper. I am also satisfied that by using these published sequences to screen EST databases, including the LifeSeq® database, the addressee would have identified the cDNA of SEQ ID NO: 02 in at least Incyte's cDNA library using no more than his common general knowledge. Once he had identified and obtained the cDNA of SEQ ID NO: 02 it would a straightforward matter, not involving any inventive ingenuity, to express the cDNA to produce the polypeptide of SEQ ID NO: 01.

74 Thus, for the above reasons I found that the Npt2B polypeptide claimed in claims 1 and 2 and the nucleic acid of claims 3 to 5 do not have an inventive step having regard to the prior disclosure of the European application and the Hilfiker paper.

75 I have already mentioned that Ms Richardson acknowledged that an expression cassette of claim 6, cells of claims 7 and 8 including the expression cassette of claim 6, the method of producing Npt2B claimed in claim 9 and the non-human transgenic animal model claimed in claim 10 would not be independently inventive if I found any of claims 1 to 5 lacked novelty or an inventive step. I agree and I do not believe I need to give my reasons in view of the position Ms Richardson took on this matter. However, Ms Richardson's concession did not extend to claims 11 to 17 and so I must give my reasons for finding the subject matter of these claims obvious.

Inventive step based on the activity of the Npt2B polypeptide?

76 In her submission to me Ms Richardson maintained that the subject matter of claims 11 to 17 was independently inventive over the subject matter of claims 1 to 10 because the prior art cited by the examiner does not demonstrate a human Type IIb sodium phosphate intestinal co-transporter. However, Ms Richardson did not explain to me in any detail how this specific activity of the Npt2B polypeptide provides or contributes to an inventive step for the matter of claims 11 to 17. Moreover, it seems to me that the activity of the polypeptide of the invention is

obviously that of a sodium phosphate co-transporter on the basis of its homology with the sodium phosphate co-transporters disclosed in the European application and the Hilfiker paper.

77 Claims 11 to 13 of the application relate to a method of screening to identify Npt2B modulatory agents. It seems to me that the claimed screening protocol has not been designed specifically for the Npt2B polypeptide and it would be equally effective for identifying modulatory agents to sodium phosphate co-transporters in general. Moreover, the European application discloses a screening assay which uses cell lines expressing recombinant IPT-1 in a similar phosphate uptake assay to identify inhibitors of phosphate transport. Thus, I fail to see how the claimed screening method depends specifically on the activity of a human Type IIb sodium phosphate intestinal co-transporter. The only difference between the screening method of claim 11 and the phosphate uptake assay disclosed in the European application is the choice of target, that is the use of the Npt2B polypeptide instead of the IPT-1 polypeptide. However, in my view this difference does not provide an inventive step for the screening method of claims 11 to 13 because the Npt2B polypeptide itself lacks an inventive step and is obviously a sodium phospate co-transporter.

78 Claim 14 concerns the use of the Npt2B polypeptide for screening Npt2B modulating agents but again the European patent discloses the use of the IPT-1 polypeptide in assays which involve, for example, mixing a candidate compound with a solution containing a IPT-1 polypeptide. Thus, it seems that claim 14 relies solely on the use of the Npt2B polypeptide for its inventive step but as before this cannot impart any inventiveness to the matter of claim 14 because it is not inventive itself and its activity is obvious.

79 Claim 15 claims a pharmaceutical composition comprising Npt2B polypeptide or a nucleic acid encoding this polypeptide and claim 16 claims the polypeptide and nucleic acid for use in therapy. In my opinion, the addressee would recognise that virtually any biologically active substance, particularly a sodium phosphate co-transporter, would have potential for use in therapy on the basis of his common general knowledge. Moreover, the European application envisages the use of the NPT-1 polypeptide and the corresponding polynucleotide in prophylactic and therapeutic methods, as well as in pharmaceutical compositions. Thus, the only difference between what is claimed in claims 15 and 16 of the application and what is known is the Npt2B polypeptide itself. Once again this difference is not inventive.

80 Finally claim 17 is a claim of the second medical use format, often described as a "Swiss type" claim, for Npt2B polypeptide and the corresponding nucleic acid. The disease conditions specified in this claim are those commonly associated with abnormal serum phosphate levels, such as hypo- and hyperphosphatemia. The European application similarly recognises the potential of the IPT-1 polypeptide and the corresponding nucleic acid for the treatment of abnormal conditions related to both an excess of and insufficient amounts of IPT-1 polypeptide activity. Thus, as with the earlier claims, claim 17 is reliant on the use of the novel Npt2B polypeptide for an inventive step but as before this polypeptide cannot provide that step because the polypeptide itself and its activity as a sodium phosphate co-transporter are obvious. Therefore, the use of Npt2B and the corresponding nucleic acid claimed in claim 17 lacks an inventive step.

81 So far I have not mentioned claim 18, which is an omnibus claim directed at all of the various aspects of the invention claimed in the earlier claims. Ms Richardson did not make any submissions in respect of claim 18 at the hearing and I have not identified any specific disclosure in the application which seemingly could provide an inventive step. Therefore, in my view claim 18 does not relate to anything which is inventive.

Support

Finding on support

82 I found that there was no support for:

(a) claims 16 and 17 in so far as they relate to the use of the Npt2B polypeptide of the invention in therapy; and

(b) claim 17 in so far as it also relates to the use of the nucleic acid of the invention for the treatment hyperphosphatemia, including hyperphosphatemia resulting from renal insufficiency, hyperparathyroidism, hypocalcemia, vitamin D deficiency, or soft tissue or metastatic calcification.

This finding was not as wide ranging as the examiner's objection for reasons which will be clear from what follows.

The examiner's objection

83 The examiner had objected that there was no support for claims 16 and 17 to first and second medical uses of the Npt2B polypeptide of claims 1 and 2, and the nucleic acid of claims 3 to 5. In particular, the examiner had noted that the application did not contain any experimental evidence to establish that the polypeptide and the nucleic acid would work as therapeutic agents, especially for the range of disease conditions listed in claim 17.

The applicant's response

84 The applicant responded in the agent's letter, dated 28 May 2004, by arguing that if a therapeutic effect is generally outlined in biochemical and physiological terms in an application and/or can be deduced by means of common general knowledge and no practical complications are expected, then little or no experimental evidence may be needed in the originally filed specification in order to substantiate a therapeutic effect. The applicant maintained that in the present case the application identifies the Npt2B polypeptide as a sodium phosphate co-transporter and gives the physiological background and biochemical mechanisms underlying the claimed therapeutic effects based on this activity of the polypeptide. Thus, in the applicant's view it is immediately evident from the teaching of the present invention that the claimed compounds may be used in therapeutic applications to yield the claimed therapeutic effects.

85 Ms Richardson submission to me at the hearing on this matter was along the same lines. However, Ms Richardson also referred me to "Examination Guidelines for Patent Applications relating to Medical Inventions in the UK Patent Office" which were published recently by the Office. In particular, she drew my attention to paragraphs 76 and 111 of these Guidelines, which relate to support for first and second medical use claims, where it is stated that the form of evidence is not critical and that the application may provide *in vivo* or *in vitro* data or even *in silico* modelling data if it is considered to provide a credible basis for support. Ms Richardson also made the point that claims 16 and 17 were based on therapeutic uses of compounds, where compounds themselves were novel and inventive.

86 At the hearing Ms Richardson also commented that the applicant had received no feed back why the examiner considered that the polypeptide and nucleic acid of the invention would not be expected to have the claimed therapeutic activity. In this regard she referred me to decision

T 484/92 (Takiron Co. Ltd.) of the Technical Boards of Appeal of the European Patent Office, where the Board found that an allegation of lack of "evidence" or "proof" should be backed by an argument as to why it is considered that an example is inherently unlikely to achieve the specified result.

The law

87 Section 14(5)(c) requires that the claim or claims shall be supported by the description. This requirement has been considered in the context of "Swiss-type" claims on a number of occasions in the past and I was referred to one of these cases, *Prendergast's Applications* [2000] RPC 446. In this case Neuberger J (as he was then) held that:

> "In relation to a "Swiss-type" application, it appears to me that, in the absence of any practical evidence of the idea working (that is the idea of using a well-established drug for the treatment of a condition for which it has not so far been used), the absence of any evidence of the idea working involves the absence of a description."
>
> "There is obvious force in the contention that, where you have a claim for the use of a known active ingredient in the preparation of a medicament for the treatment of a particular condition, the specification must provide, by way of description, enough material to enable the relevantly skilled man to say this medicament does treat the condition alleged, and that pure assertion is insufficient."
>
> "The tests can, where appropriate, be very rudimentary. It would be wholly inappropriate, and indeed impractical, to lay down what the tests should be in each case, but it is clear that, in general, relatively rudimentary tests will do."

88 Whilst the judgment in *Prendergast's Applications* concerned claims of the "Swiss-type", I see no reason why it should not apply in equal measure to claims of the "first medical use" type. Such claims are to known substances which have been found for the first time to have a use in a method of treatment of the human or animal body by surgery or therapy or of diagnosis practiced on the human or animal body. Thus, as with "Swiss-type" claims, it appears to me that support for first medical use claims depends on the applicant including in his application enough material to enable the relevantly skilled person to say that the substance has, for example, the therapeutic activity alleged by the applicant. Ms Richardson seemed to accept that the judgment in *Prendergast's Applications* was also relevant to the question of support for first medical use claims.

89 Finally, I should mention the Examination Guidelines referred to by Ms Richardson. Although a great deal of thought went into their production, they are no more than guidelines and I am not bound by their content.

Assessment and conclusions on support

90 Before I turn to consider whether claims 16 and 17 are supported, I should address Ms Richardson's comment that the examiner did not back his objection with some argument as to why he considered the polypeptide and nucleic acid of the invention did not have the claimed therapeutic activity. With respect to Ms Richardson this was not the objection the examiner made. The applicant had supplied data after filing the application to confirm that the Npt2B polypeptide of the invention was indeed a sodium phosphate co-transporter and the examiner had accepted this. Moreover, the examiner was not challenging whether there was a credible link between this function of the Npt2B polypeptide and the medical uses claimed for it. His

objection was that the necessary evidence was not to be found in the application as filed. Whether, the examiner was right in this was something I had to decide.

91 Moreover, I do not consider a distinction Ms Richardson sought to make on the basis of the facts of the present case and the facts as they were in relation to *Prendergast's Applications* is relevant to the question of support. Support is needed for claims to the use of compounds for therapy, regardless of whether the compounds are themselves new or inventive. In any event, I found that the nucleic acid of the present invention is not new and the polypetide of the invention is not inventive.

92 At the hearing Ms Richardson did not contradict the examiner's view that the application does not contain any experimental evidence to support claims 16 and 17. Rather she argued that such experimental evidence is unnecessary because the application establishes that the claimed Npt2B polypeptide is a sodium phosphate co-transporter and as such plays an important role in the Pi metabolism. Furthermore, the particular disease conditions specified in claim 17 are all associated with disorders in the Pi metabolism.

93 The judgment in *Prendergast's Applications* established that full, rigorous, detailed and conclusive tests are not required to provide support for a particular therapeutic use. In his judgment Neuberger J did not seek to lay down what the tests should be in each case and he recognised that rudimentary tests are acceptable where appropriate. Often *in vitro* tests have been accepted in the past, as an alternative to *in vivo* tests, where they demonstrate that a substance in question has a biological activity relevant to the claimed therapy. However, *in vitro* or *in vivo* testing is not the only way the biological activity of a substance can be determined and one alternative is *in silico* modelling, as mentioned in the Examination Guidelines. A further alternative of particular relevance to polynucleotides and polypeptides is the use of homology comparisons to determine biological activity by reference to polynucleotides and polypeptides of known activity. In my opinion results, obtained from any of these alternative approaches, could provide support for first and second medical use claims, provided they are not speculative. In the application the applicant describes how the Npt2B polypeptide was identified as a membrane protein having the function of a sodium phosphate co-transporter in its native environment. Thus, the application establishes a link between the Npt2B polypeptide, its role in the Pi metabolism and disease conditions associated with disorders in the Pi metabolism. Whilst I have no reason to doubt the relationship between the Npt2B polypeptide and its specified function as a sodium phosphate co-transporter, this is not be enough to provide support for the therapeutic applications of the Npt2B polypeptide as claimed in claims 16 and 17.

Use of the Npt2B polypeptide in therapy

94 It is clear from the description of the application that the polypeptide of the invention is present in a non-naturally occurring environment, for example separated from its naturally occurring environment. If this were not the case, the polypeptide of claims 1 and 2 would be anticipated by the polypeptide in its native state and the invention would be no more than an unpatentable discovery. The description also states that the polypeptide of the invention may be present as an isolate, which is substantially free of other naturally occurring biological molecules, and in certain embodiments it may be present in substantially, usually at least 99%, pure form. Thus, I had to decide whether the support provided in the application concerning the activity of the polypeptide in its native state could be read across to the claimed polypeptide in a non-naturally occurring environment, for example in at least 99% pure form.

95 When considering inventive step above, I referred to Ms Richardson's submission that protein

function is dependent on the three dimensional structure of the protein. I agree with this entirely. In the case of a membrane protein, the three dimensional structure will be dependent not only on its underlying amino acid sequence, as explained by Ms Richardson, but also on its location within the cell membrane. For example, the present application states:

> "The Npt2B protein of the subject invention is a membrane protein having a number of transmembrane regions, where the number of putative transmembrane regions based on the amino acid sequence is 10 ……."

Thus, the applicant has predicted that the Npt2B protein or polypeptide is folded so that it crosses the cell membrane a number of times, possibly 10 times. It is very unlikely in my view that the protein would retain this configuration when isolated from its native environment within the cell membrane, for example when it is at least 99% pure. If the Npt2B polypeptide retains any of its native state structure when isolated from the cell membrane, e.g. in at least 99% pure form, it is also unlikely that this structure would be such that the polypeptide retains its function as a sodium phosphate co-transporter. Therefore, I must conclude on the balance of probabilities that even though the description provides support for the function of the Npt2B polypeptide in its native state, this support cannot be read across to the polypeptide in a non-naturally occurring environment. Moreover, in the absence of any description in the application of a test demonstrating that the polypeptide retains its function as a sodium phosphate transporter when in a non-naturally occurring environment, I conclude that claims 16 and 17 are not supported at least so far as they relate to therapeutic uses of the Npt2B polypeptide claimed in claims 1 or 2.

Use of the Npt2B polypeptide and the corresponding nucleic acid in association with hyperphosphatemia

96 There is one further matter I must consider in relation to the alleged therapeutic activity of the Npt2B polypeptide and the corresponding nucleic acid. The description identifies various diseases associated with disorders in the Pi metabolism. These diseases are characterised as those associated with abnormally low Pi absorption or the presence of hypophosphatemia and those associated with abnormally high Pi absorption or the presence of hyperphosphatemia. The description also states that nucleic acid compositions of the invention find use as therapeutic agents in situations where one wishes to enhance Npt2B activity in a host, e.g. disease conditions associated with hypophosphatemia. This suggests to me that the expression of Npt2B polypeptide in its native environment can act to increase Pi absorption. However, there is nothing in the description to indicate credibly that the Npt2B polypeptide or the corresponding nucleic acid could be used alternatively to inhibit Pi absorption and so be used to treat disease conditions associated with the presence of hyperphosphatemia. In the absence of anything to suggest that this alternative use is other than speculation, I can only conclude that there is no support for the reference in claim 17 to the use of a Npt2B polypeptide and to the use of the corresponding nucleic acid for the production of a medicament for the treatment of disease conditions characterised by the presence of hyperphosphatemia, specifically hyperphosphatemia resulting from renal insufficiency, hyperparathyroidism, hypocalcemia, vitamin D deficiency, and soft tissue or metastatic calcification.

Appeal

97 Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days of the decision already issued on 23 June 2004.

R J WALKER
Deputy Director acting for the Comptroller