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D E C I S I O N
of 23 September 2004

Case Number: T 0769/03 - 3.3.8

Application Number: 95907214.1

Publication Number: 0737075

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Language of the proceedings: EN

Title of invention:

Ileal bile acid transporter compositions and methods

Applicants:

WAKE FOREST UNIVERSITY

Opponent:

-

Headword:

Ileal bile acid transporter/WAKE FOREST UNIVERSITY

Relevant legal provisions:

EPC Art. 56

Keyword:

"Inventive step - no"

Decisions cited:

T 0455/91, T 0207/94

Catchword:

-



Case Number: T 0769/03 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 23 September 2004

Appellants:

WAKE FOREST UNIVERSITY
Medical Center Boulevard
Winston-Salem
NC 27157-1023 (US)

Representative:

Wallinger, Michael, Dr.-Ing.
Wallinger & Partner
Patentanwälte
Zweibrückenstrasse 2
D-80331 München (DE)

Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 17 February 2003
refusing European application No. 95907214.1
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
M. B. Günzel

Summary of Facts and Submissions

I. European application No. 95 907 214.1 published as WO 95/17905 with the title "Ileal bile acid transporter compositions and methods" was refused by the Examining Division for lack of inventive step.

II. The Appellants (Applicants) lodged an appeal against this decision, paid the appeal fee and filed a statement of grounds of appeal together with a new request. Claims 1, 23 and 34 of this request read as follows:

"1. A nucleic acid segment comprising an isolated gene encoding a mammalian ileal/renal bile acid cotransporter polypeptide, further defined as comprising:

(a) a nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:3; or

(b) an isolated nucleic acid segment encoding a mammalian ileal/renal bile acid cotransporter coding sequence, wherein the segment hybridizes to (a) under conditions of hybridization in 50% formamide buffer, followed by washing in 0.2 X SSC at 65°C for 30 minutes."

"23. A polypeptide comprising an amino acid sequence according to SEQ ID NO:2 or SEQ ID NO:4."

"34. A method of detecting heterozygous ileal/renal bile acid cotransporter gene alleles in a subject comprising the following steps:

amplifying the ileal/renal bile acid cotransporter genes from said subject; and
subjecting the amplified nucleic acid segments to denaturation followed by electrophoresis under nondenaturing conditions."

Dependent claims 2 to 19 and 22 related to further features of the nucleic acid segment of claim 1. Claims 20 and 21 related to recombinant host cells comprising the nucleic acid segments of any preceding claims. Dependent claims 24 to 28, 29 and 30 respectively related to further features of the polypeptide of claim 23 and to antibodies immunoreactive with said polypeptides. Claim 31 related to a method of screening substances as modulators of ileal/renal bile acid cotransport activity making use of the polypeptides of claims 23 to 28 and dependent claims 32 and 33 related to further features of this method. Dependent claims 35 to 37 related to further features of the method of claim 34.

- III. A communication was sent by the Board pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal setting out the Board's provisional, non binding opinion.
- IV. The Appellants informed the Board on 14 September 2004 that they would not be attending the oral proceedings. They further requested that a decision be taken based on the content of the file.
- V. The state of the art comprised *inter alia* the following documents:

(1): Wong, M.H. et al., Hepatology, Vol 18, No.4 Pt.2, Abstract 348, page 143A, 4-7 November 1993,

(7): Hagenbuch, B. et al., Proc.Natl.Acad.Sci.USA, Vol.88, pages 10629 to 10633, December 1991.

VI. The Appellants' arguments with regard to inventive step were essentially as follows:

(a) The closest prior art was document (1) insofar as it postulated the isolation of a cDNA expressing a bile acid transport activity (IBAT cDNA). Yet, it only made the suggestion of using an expression cloning strategy and this was not sufficient to arrive at the claimed sequences with some expectation of success. In fact, document (1) was not enabling: it did not provide any instructions how to construct the specific ileal cDNA library which was indispensable for the cloning of the transporter cDNA, ie that a size selected cDNA library was necessary. Furthermore, it did not mention the specific experimental conditions under which the screening of the positive clones needed to be carried out.

(b) Even if a cDNA encoding a protein with bile transporter activity could eventually be cloned by following the teachings of document (1), this would not at all guarantee that the sequence of this cDNA would be that of the IBAT cDNA of the present invention. Indeed, many different positive clones had been isolated in document (1) and it was more than likely that each one of them carried

a cDNA encoding a different protein with bile acid transport activity. It would, thus, only be by chance that the clone carrying the said IBAT cDNA could be isolated. In line with the established case law, random techniques were not recognized as destroying inventive step.

- (c) As was pointed out in the application, document (7) described the cloning of the rat liver bile acid transporter but it had not been possible to show that the recombinant protein was functional. This created a prejudice against cloning the hamster IBAT cDNA using the expression of the IBAT protein as a mean for screening the positive clones.

For these reasons, the skilled person who was by nature cautious would not have started on the cloning project and if he/she nonetheless did, he/she would not have had a reasonable expectation of success to arrive at the claimed cDNA.

- VII. The Appellants requested that the decision under appeal be set aside and a patent be granted on the basis of the claims submitted with the statement of grounds of appeal.

Reasons for the decision

1. Claims 1 and 2 of the request filed with the grounds of appeal respectively correspond to originally filed claims 3 and 2; claims 3 to 18, 19 to 33 and 34 to 37 respectively correspond to originally filed claims 4 to

19, 27 to 41 and 48 to 51. The requirements of Article 123(2) EPC are fulfilled.

2. The only issue to be discussed is that of inventive step. The closest prior art is document (1), a short abstract from the group the inventor belongs to. It describes in general terms the isolation of the ileal bile transporter cDNA from hamster ileal cells and teaches that expression cloning should be used as a screening method whereby the positive clones are identified in the Na⁺-dependent [³H] taurocholate assay. The cDNA is defined by its size: 2.2 Kb but not by its sequence.
3. Starting from the closest prior art, the problem to be solved can be defined as determining the structure of a DNA encoding an ileal/renal bile acid transporter.
4. One of the solutions provided in claim 1 is the IBAT cDNA obtained from hamster cells characterized by its specific sequence: SEQ ID NO:1.
5. Taking into account the teachings of document (1) that an IBAT cDNA can be cloned starting from hamster ileal cells, it would have been obvious for the skilled person wanting to solve the above mentioned problem to attempt constructing a cDNA library starting from such cells. The argument was, however, presented by the Appellants that the teachings of document (1) were too scanty so that the skilled person aware of them would, nonetheless, have had to exercise inventive skills to obtain the hamster IBAT cDNA. More specifically, it was pointed out that document (1) did not teach the necessity for constructing a cDNA library mostly

comprising high molecular weight (MW) molecules (ie resulting from the reverse transcription of high MW mRNAs obtained by size fractionation). This argument, however, fails to take into account the teachings in document (1) that the positive clone contains a 2.2Kb cDNA (ie a high MW cDNA), and in document (7) (page 10269, right-hand column), that cDNAs of between 1.5Kb and 2.3Kb can be obtained by constructing a cDNA library from size fractionated mRNAs. At this point, it is, of course, important to emphasize that document (7) discloses the isolation of IBAT cDNA from rat liver and, thus, would necessarily have come to the attention of the skilled person wanting to clone the hamster IBAT cDNA. Otherwise stated, the combination of the teachings of document (1) and (7) makes it obvious to size fractionate the hamster mRNAs in order to construct a "good" cDNA library.

6. In the application, the same cells are used as recipient for the individual recombinant cDNAs as are used in document (1): COS cells, and the positive clones are identified by the same assay: the Na⁺-dependent [³H] taurocholate assay. The experimental conditions in which the assay is carried are said to have been modified (page 62 of the application as filed), and the appellants see there an indicia of inventive step. The Board cannot agree. It is true that document (1) does not provide any details as how to carry out the assay. Yet, this assay seems to have been well-known at the priority date: the application as filed (page 2) refers to it being carried out as early as 1983 and also cites numerous documents where the assay is made use of (eg. on page 25). Finding out the best incubation time and temperature, the optimum

substrate concentration and taking care not to loose the substrate on the sides of the reaction vessels are, in the Board's judgment, initiatives which are well within the abilities of the skilled person in the field of biotechnology. In this respect, attention is drawn to eg T 455/91 (OJ EPO 1995, 684) where the skilled person's likely attitude to possible changes to known procedures was discussed. The then competent Board concluded that within the normal design procedures, the skilled person would readily seek appropriate manifest changes, modifications and adjustments involving little trouble. For this reason, the Board does not accept that the changes made to the taurocholate assay are indicative of inventive step.

7. A third argument by the Appellants was that:
"...Hagenbuch et al. (1991) already tried unsuccessfully to identify a functional IBAT by expression cloning (see specification: page 4, paragraph 1). These stated uncertainties corroborate the prejudice of a skilled person that simply using an expression cloning strategy for identifying this transporter would not work.". It should be noted here that the Appellants refer to a passage in the specification of the patent application and that, of course, the specification of the application per se is not a piece of prior art likely to create a prejudice. As for Hagenbuch et al. (1991), ie document (7), it discloses the successful isolation of a liver IBAT cDNA clone by expression cloning using the taurocholate assay (page 10630, Results). It also describes the characterisation of the protein product encoded by the cDNA in in vitro translation experiments but only insofar as its structure is concerned (molecular weight,

glycosylation, page 10632, left-hand column). The functionality of the protein per se is **not** tested. For this reason, the Appellants' argument is not found convincing and it is concluded that document (7) does not constitute a prejudice against isolating the IBAT cDNA by expression cloning. To the contrary, as already explained in point 5 supra, document (7) provides a useful information which when combined with the teaching of document (1) makes obvious the construction of the IBAT cDNA library.

8. Finally the Appellants argued on the basis of the seven positive clones identified in document (1) that these represented cDNAs encoding different proteins with bile acid transport activity and that, therefore, the skilled person following document (1) had no reasonable expectation of success to isolate the specific, claimed IBAT cDNA. It was thus stated: "**It is normally assumed**, when working with libraries that each result represents one individual clone. **This assumption can be accepted as correct.... It is highly probably** (and meanwhile also proven by experimental data of in the inventors) that not all of them are related with each other... **Moreover, it is highly probable** that at least some of the positive clones will encode polypeptides, which fall under the structural definitions as disclosed in D1,..., and still would not comprise the claimed sequence!" (emphasis added by the Board). No experimental data were submitted in support of these allegations which thus remain unfounded.
9. In accordance with the case law (eg T 207/94, OJ EPO 1999, 273), the question whether a reasonable expectation of success exists or not can be evaluated

only by taking into account real difficulties. In order to be considered, any allegation that features jeopardize a reasonable expectation of success has to be based on technical facts. From what precedes, it is clear that the difficulties of isolating the IBAT cDNA are in the realm of conjectures rather than facts. Thus, the argument cannot be taken into account when assessing inventive step.

10. The Board's conclusions may, thus, be summarised as follows: the skilled person wanting to determine the structure of an IBAT DNA knew from document (1) that one such DNA could be isolated starting from hamster ileal cells. He/she would infer in a straightforward manner from the combination of the teachings of documents (1) and (7) how to proceed. No specific problems had been reported in the prior art which would prejudice the skilled person against starting the experiment. No difficulties arose while cloning which could not have been solved by the skilled person as understood for the purpose of patent law, in particular, no evidence is forthcoming that the IBAT cDNA clones would be difficult to distinguish. For these reasons, inventive step is denied to the subject-matter of claim 1 related to the IBAT cDNA as obtained from hamster ileal cells: a nucleic sequence of SEQ ID NO:1. Consequently, the request as a whole cannot be allowed.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar:

The Chairman:

A. Wolinski

L. Galligani