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D E C I S I O N
of 27 June 2006

Case Number: T 1190/05 - 3.3.08

Application Number: 98908022.1

Publication Number: 1012267

IPC: C12N 15/11

Language of the proceedings: EN

Title of invention:
An antisense oligonucleotide preparation method

Applicant:
BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK mbH

Opponent:
-

Headword:
Antisense oligonucleotide/BIOGNOSTIK

Relevant legal provisions:
EPC Art. 54

Keyword:
"Main request - novelty - (yes)"

Decisions cited:
T 0601/92

Catchword:
-

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Case Number: T 1190/05 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 27 June 2006

Appellant: (Applicant)
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 28 April 2005 refusing European application No. 98908022.1 pursuant to Article 97(1) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent application No. 98 908 022.1 published as International application No. WO 98/33904 with the title "An antisense oligonucleotide preparation method" was refused by the examining division.

The main request then on file comprised claims 1 to 6 as filed on 31 March 2004 which were identical to claims 1 to 6 as originally filed. Claim 1 read as follows:

" 1. A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of

- selecting a target nucleic acid, if necessary elucidating its sequence

- generating the antisense oligonucleotide with the proviso that

  - the oligonucleotide comprises at least 8 residues,

  - the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases,

  - the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (*CCCC*) within the target molecule, or alternatively four or more consecutive elements of GGGG,

  - the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of

forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG, and

- the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications:

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R + 2H-bond-R}} \geq 0.29$$

- and synthesizing the oligonucleotide thus generated in a per se known manner."

Dependent claims 2 to 6 related to further features of the method of claim 1.

Three auxiliary requests were also on file.

II. The grant of a patent was refused for lack of novelty, an objection which in the view of the examining division applied to all requests on file. No documents were cited as novelty-destroying. The examining division reasoned that none of the three steps of selecting a target nucleotide, generating the antisense oligonucleotide and synthesizing the oligonucleotide "comprised any (special) features which could distinguish the claimed method from a (any) method for the preparation of an antisense oligonucleotide...".

The remark was also made that oligonucleotides which followed the requirements of the rule were known in the art.

Finally, the examining division considered that no parallel could be drawn between the present case and the case dealt with in decision T 601/92 of 20 April 1995 where novelty was acknowledged to a process for the production of a known product. The reasons therefor were that this earlier case was in a totally unrelated field and, beside, the two cases differed by the fact that the invention as now claimed was not for the preparation of a single compound (oligonucleotide), but comprised the preparation of a list of an (uncountable) number of different oligonucleotides.

III. The appellant (applicant) filed a notice of appeal against this decision, paid the appeal fee and submitted a statement of grounds of appeal together with a main request and three auxiliary requests. The claims of the main request were identical to the claims refused by the examining division.

IV. The appealed decision was not rectified by the examining division and the case was remitted to the board of appeal (Article 109(2) EPC).

V. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal wherein a number of observations were made in particular under Article 84 EPC.

VI. On 26 May 2006, the appellant sent a further submission together with the same main request as already on file

and eight auxiliary requests in substitution of the previous ones.

VII. On 22 June 2006, the board informed the appellant by telephone that auxiliary request IV would be allowable under Articles 84 EPC and 54 EPC provided that claim 1 was further amended.

VIII. On that same day, the appellant sent a fax letter in reply together with a request corresponding to auxiliary request IV and comprising an amended claim 1. The appellant requested the board to consider this new claim request as the main request. It was also requested that the oral proceedings be cancelled, should the new main request be considered allowable.

Claim 1 of the **new main request** read as follows:

" 1. A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of

- selecting a target nucleic acid, if necessary elucidating its sequence

- synthesizing the antisense oligonucleotide to said target sequence in a per se known manner wherein the antisense oligonucleotide has the following features

- the oligonucleotide comprises at least 8 residues,

- the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases,

- the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (*CCCC*) within the target molecule, or alternatively four or more consecutive of GGGG,

- the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG, and

- the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications:

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R + 2H-bond-R}} \geq 0.29"$$

Dependent claims 2 to 6 remained as originally filed (section I, supra).

IX. Oral proceedings which were to take place on 27 June 2006 were cancelled on 23 June 2006.

X. The following documents are mentioned in the present decision:

(1) : WO 94/25588;

(6) : WO 95/00103;

(8) : Hatzfeld, J. et al., J. Exp. Med., Vol. 174, pages 925-929, October 1991,

(11) : Agrawal, S., Trends in Biotechnology, Vol. 14, No. 10, pages 376 to 387, October 1996;

(13) : WO 95/02422.

XI. The appellant's arguments insofar as relevant to the present proceedings may be summarized as follows:

The claimed invention taught the skilled person that in order to be good antisense oligonucleotides, oligonucleotides should fulfil certain design criteria, in particular that they should have a certain mixture of C/G and A/T nucleotides in the sequence but should avoid large amounts of G, especially "runs" of G.

The decision under appeal did not identify any documents disclosing a method such as claimed.

The examining division had reached a conclusion of lack of novelty by simplifying claim 1 to the extent of only taking into account that the claimed method comprised three steps: selecting the target oligonucleotide, generating and synthesizing the antisense oligonucleotide thereto. All claimed features which defined the step of generating the antisense oligonucleotide had been ignored. This approach was obviously insufficient to draw a negative conclusion as regards novelty.

It was true that some oligonucleotides of the prior art could be the products of the method of the present invention. Yet, a process for the preparation of compounds could be novel even if the compounds were known. There was established case law to this point such as T 601/92 (supra). Admittedly, this case and the present application were in very different technical fields. Yet, the legal conclusion which was drawn in T 601/92 was of general applicability.

As no document on file disclosed the method of claim 1, this claim and, consequently, the claim request as a whole fulfilled the requirements of Article 54 EPC.

XII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claim request filed on 22 June 2006.

Reasons for the decision:

Main request
Articles 123(2) and 84 EPC; added subject-matter, clarity

1. Claim 1 differs from claim 1 as originally filed by the following features:

- the antisense nucleotide is unambiguously identified as being antisense **to** the target sequence, which leaves no doubt that one of its property is to hybridize to the target sequence.

- the step of generating the antisense sequence has been combined with that of synthesizing it. It is

now clear that features of the oligonucleotide produced by the claimed method reflect method features, ie the synthesis of the antisense oligonucleotide requires that specific choices are made each time a nucleotide is added to the growing chain which, when completed, will become the antisense oligonucleotide.

2. The board is satisfied that the claim wording is clear and that the claimed method only comprises technical features which were disclosed in the originally filed application (see eg. originally filed claim 1). The requirements of Articles 123(2) and 84 EPC are fulfilled.

Article 54 EPC; novelty

3. There are 15 documents on file. One of them describes a method for producing cellular products comprising thermoplastic or rubber materials. Four are essentially concerned with methods for derivatizing oligonucleotides eg. linking them to substituents such as steroids, alkylating agents, antibodies etc..., (see eg. document (13)). None of these documents are of any relevance to novelty.

4. The other ten documents disclose antisense oligonucleotides as modulators of gene expression, for example that of fibrogenic cytokines (document (6)), or as potential therapeutic agents, for example for the treatment of the immunosuppressive effects of transforming growth factor (document (1)). In each of them, antisense oligonucleotides are identified by their sequences. Whenever mention is made of the method which led to their synthesis, it is described as the

conventional and well-known technique of solid-phase synthesis. None of them teaches that specific measures must be taken during synthesis to obtain an antisense oligonucleotide specifically suited to the tasks it is intended to perform. At most, reference is made to which part of the target sequence the antisense oligonucleotide should bind to (eg. document (1), page 4: to areas of a gene coding region or to areas of a gene coding and non-coding regions; document (8), page 926: to regions flanking the translation initiation region). In fact, it is only in document (11), a review on antisense oligonucleotides, that it is mentioned (page 379), that the antisense oligonucleotide primary structure (eg. the presence of four Gs or of palindromes) may have an influence on its properties. Yet, no specific instructions are given as to the A/T, G/C content of the antisense oligonucleotide, nor is the skilled person cautioned against some types of primary structures.

5. In the absence of any documents on file disclosing the claimed method, novelty has to be acknowledged.

6. As is also apparent from the examination procedure, novelty seems to have been challenged by the examining division on the basis that there existed in the prior art oligonucleotides which could have been made by the claimed method. The board understands this argument of the examining division as meaning that the skilled person who synthesized the oligonucleotides of the prior art must have used the claimed method. In the board's judgment, the adventitious and unknowing use of a method does not amount to providing a clear and unambiguous disclosure of this method. Therefore, the

mere statement that a defined method must have been used to prepare a known product does not constitute a sound basis on which to deny novelty of this method.

7. The board agrees with the appellant that a process may result in the synthesis of known compounds and nonetheless be novel. In its decision (page 5, point 2.3 of the reasons), the examining division discussed the present case in relation to the earlier case dealt with in decision T 601/92 (supra) where this legal principle has been applied (point 6.2 of the "Reasons"). The examining division's reasoning seemed at least to imply that the principle did not apply in the present case because the claimed process resulted in the preparation of a great number of compounds (oligonucleotides) whereas the process claimed in T 601/92 led to the preparation of one product. Irrespective of the validity of this statement, the board fails to see that it has any relevance as the number of products made (whether known or unknown) is in both cases immaterial to the novelty of the claimed method.

8. For the above reasons, it is concluded that the requirements of Article 54 EPC are fulfilled.

Order

For these reasons it is decided that:

- The decision under appeal is set aside.

- The case is remitted to the first instance for further prosecution on the basis of the main request filed on 22 June 2006.

The Registrar The Chairman

A. Wolinski L. Galligani