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D E C I S I O N
of 19 June 2000

Case Number: W 0010/99 - 3.3.4

Application Number: PCT/EP 98/00497

Publication Number: WO 98/33904

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/BIOGNOSTIK

Relevant legal provisions:
PCT Art. 17(3)(a)
PCT R. 13, 40.2(c)

Keyword:
-

Decisions cited:
W 0013/87, G 0001/89

Catchword:
-

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Case Number: W 0010/99 - 3.3.4
International Application No. PCT/EP 98/00497

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 19 June 2000

Applicant: Biognostik Gesellschaft für Biomolekulare Diagnostik mbH
Gerhard-Gerdes-Str. 19
D-37079 Göttingen (DE)

Representative: Meyers, Hans-Wilhelm
P.O. Box 10 22 41
D-50462 Köln (DE)

Subject of the Decision: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fee) of the European Patent Office (International Searching Authority) dated 14 July 1998.**

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: L. Galligani
C. Holtz

Summary of Facts and Submissions

I. International patent application PCT/EP 98/00497 was filed on 30 January 1998 with seventeen claims.

Claims 1 and 7 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."

"7. An antisense oligonucleotide or derivative thereof obtainable according to the method according to any one of the claims 1 to 6 except oligonucleotides represented in Fig. 4."

Claims 2 to 6 were directed to particular embodiments of the method of claim 1; claims 8 to 13 concerned embodiments of the oligonucleotide according to claim 7. Claims 14 and 15 concerned, respectively, a composition and a medicament comprising the said oligonucleotides, while claims 16 and 17 were directed to the use of the said oligonucleotides.

II. On 14 July 1998 the European Patent Office (EPO), acting as an International Search Authority (ISA), invited the Applicant to pay within a time limit of 30 days 88 additional search fees pursuant to Article 17(3)(a), Rule 40.1 and 40.3 PCT and issued a partial search report on claims 1 to 17 (all partially)

relating to the invention first mentioned, ie group 1. The invitation stated the 89 groups of inventions of which the following are of relevance for the purposes of the present decision:

1. Claims 1 to 17 (all partially): A method for preparing antisense oligonucleotides and antisenses obtained. Antisense oligonucleotide against the TGF-beta 1 gene and having SEQ ID 41, modified forms thereof, composition containing it and its therapeutic or diagnostic uses.

39. Claims 1 to 17 (all partially): Antisense oligonucleotides against the TGF-beta 2 gene.

III. The invitation stated that there was no single inventive concept underlying the plurality of claimed inventions. Reference was made in particular to the following prior art documents:

(1) WO-A-94/25588

(2) Biochem. Pharmacol., 1996, vol. 51. pages 173 to 182

(3) WO-A-96/39415

It was found that, due to the fact that the preparation and use of modified antisense oligonucleotides meeting the criteria specified in the first claim for inhibiting TGF-beta 1 nucleic acids as well as their modifications were known in the art, there was no special technical feature which could link the inventions of the different groups together, also in consideration of the fact that there were essential

differences in the primary structure of the different targets.

The Applicant's attention was furthermore drawn to the fact that if any of the inventions of groups 34 to 89 was to be chosen as subject-matter for a subsequent search, further objections of non-unity of invention could be raised depending on the results of the search.

IV. On 13 August 1998 the Applicant paid one additional fee for the invention of group 39. The additional fee was paid under protest pursuant to Rule 40.2(c) PCT. The Applicant submitted that the common inventive concept was represented by the method of claim 1 which provided rules for selecting suitable antisense oligonucleotide sequences. None of the cited prior art documents provided a similar method, although they disclosed compounds that could also be synthesised by the method now claimed. The method allowed the synthesis of oligonucleotides which had surprisingly increased effectivity and/or reduced toxicity and/or reduced non-selective effects.

V. On 20 November 1998 the European Patent Office (EPO), acting as an International Search Authority (ISA), invited the Applicant to pay within a time limit of 30 days 129 additional search fees pursuant to Article 17(3)(a), Rule 40.1 and 40.3 PCT and issued the International Search Report on claims 1 to 17 (all partially) relating to the inventions of groups 1 and 39.01. The invitation stated the 131 groups of inventions of which the following are of relevance for the purposes of the present decision:

1. same as No. 1 referred to in Section II above.

39.01 Claims 1 to 17 (all partially): Antisenses oligonucleotides against the TGF-beta 2 gene and having SEQ ID 519.

Groups of inventions 2 to 38 and 40 to 89 were the same as identified in the previous invitation (cf Section II above), the remaining groups 39.02 to 39.43 resulted from a lack of unity objection within the previous group 39.

VI. Apart from repeating the previous reasons for the finding of non-unity (cf Section III above), the invitation stated that, due to the fact that the use of modified antisense oligonucleotides for inhibiting TGF-beta 2 nucleic acids was known in the prior art, and that the adverse biological effects of oligonucleotides containing runs of guanosines was well documented in the prior art, there was no single inventive concept underlying the plurality of inventions also within the group 39, which related to 43 different inventions, namely groups 39.01 to 39.43. Reference was made to document (1) as well as to the following additional documents:

(4) Int. J. Cancer, 1996, vol. 65, pages 332 to 337;

(5) TIBTECH, 1996, vol. 14, pages 376 to 387;

(6) Mol. Biol. Reports, 1993, vol. 18, pages 217 to 221.

VII. On 24 March 1999 the ISA communicated to the Applicant the result of its review under Rule 40.2(e) PCT. The finding of lack of unity was confirmed because it was held that, since, as also admitted by the Applicant,

oligonucleotides which satisfied all the necessary criteria stated in claim 1 and which could be prepared also by the claimed method were known from the prior art (cf document (1)), the method of claims 1 to 6 was not specifically necessary for the preparation of the said compounds, being only an alternative method to other known methods of synthesis. Therefore, the method itself could not be seen as the special technical feature which would form an unifying concept between all the claimed compounds. Under these circumstances, each single compound related to separate inventive concepts.

Therefore, the Applicant was invited to pay within one month the protest fee.

VIII. The protest fee was paid by the Applicant on 23 April 1999.

Reasons for the Decision

1. The protest is admissible.

2. According to Rule 13.1 PCT, the international patent application shall relate to one invention only or to a group of inventions so linked as to form a single inventive concept. If the ISA considers that the claims lack this unity, it is empowered, under Article 17(3)(a) PCT, to invite the Applicant to pay additional fees.

3. Lack of unity may be directly evident *a priori*, ie before the examination of the merits of the claims in comparison with the state of the art revealed by the

search (cf., for example, decision W 13/87 of 9 August 1988). Alternatively, having regard to decision G 1/89 of the Enlarged Board of Appeal, dated 2 May 1990 (OJ EPO 1991, 155), the ISA is also empowered to raise an objection *a posteriori*, ie after having taken the prior art revealed by the search into closer consideration. This practice is laid down in the PCT Search Guidelines, Chapter VII, 9 (PCT Gazette 30/1992, 14025) which are the basis for a uniform practice of all International Searching Authorities. The Enlarged Board of Appeal indicated that such consideration represents only a provisional opinion on novelty and inventive step which is in no way binding upon the authorities subsequently responsible for the substantive examination of the application (point 8.1. of the Reasons for the decision). In point 8.2 of the Reasons, the Enlarged Board mentioned that such invitation to pay additional fees should always be made "with a view to giving the Applicant fair treatment" and should only be made in clear cases.

4. According to Rule 13.3 PCT, the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

5. The question here is whether or not the subject-matter of the claims of the groups 1 and 39 (cf Section II above) can be considered to be part of the same general inventive concept.

6. Antisense oligonucleotides both against the TGF-beta 1 and TGF-beta 2 genes which satisfy the structural criteria outlined in the method claim 1 as well as

compositions containing them and their use in the preparation of medicaments are known in the art (cf, for example, document (1), see claims and sequence listing on pages 24 to 63). These oligonucleotides can be synthesised by a method known per se. The fact that known oligonucleotides which fulfil the criteria defined in claim 1 are disclaimed in the product claim 7 (cf the feature "except oligonucleotides represented in Fig. 4"), while reinstating novelty of the claims vis-à-vis the quoted prior art, is per se not sufficient to provide **a common inventive link** between, on the one hand, antisense oligonucleotides against the TGF-beta 1 gene with sequence SEQ ID 41 and modified forms thereof (invention of group 1), and, on the other hand, antisense oligonucleotides against the TGF-beta 2 gene (invention of group 39). This is because: firstly, a number of antisense oligonucleotides specific for both said genes were already known from the quoted document (1), and, secondly, the two genes are structurally different from each other and thus any further antisense oligonucleotide according to product claim 7 constitutes a structurally different solution to the technical problem of finding alternative oligonucleotides specific for either one of the two genes.

7. The argument put forward by the Applicant that the unitary link is constituted by the method whereby the claimed antisense oligonucleotides are prepared cannot be accepted. As shown by document (1), antisense oligonucleotides which by satisfying the criteria set in claim 1 fall under product claim 7, can be prepared by known methods, eg solid phase synthesis, based on the sequence of the selected target nucleic acid. Thus,

the method of claim 1 is not a "special" method whereby antisense oligonucleotides having the defined structural characteristics can be made. Consequently, the features of the said method cannot be seen as "special technical features" in the sense of Rule 13.2 PCT which define the contribution to the art made by each of the claimed antisense oligonucleotides against the TGF-beta 1 or 2 genes of claim 7 of the respective groups 1 or 39. Thus, the said method cannot serve as unitary link between the subject-matter of the claims of groups 1 and 39.

8. For the foregoing reasons, the international application does not comply with the requirement of Rule 13.1 PCT and the invitation to pay one additional fee was justified.

Order

For these reasons it is decided that:

The protest according to Rule 40.2(c) PCT is dismissed.

The Registrar: The Chairwoman:

A. Townend U. Kinkeldey