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# D E C I S I O N
## of 18 February 1999

**Case Number:** T 0994/95 - 3.3.4

**Application Number:** 82903424.8

**Publication Number:** 0092574

**IPC:** C07H 21/02

**Language of the proceedings:** EN

**Title of invention:**
Oligonucleotide therapeutic agent and methods of making same

**Patentee:**
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**Opponent:**
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Applied Biosystems, Inc.
Hoechst Aktiengesellschaft Zentrale Patentabteilung
Gen- Probe Inc.
Novartis AG Patent and Trademark Dept.
Genta Inc.

**Headword:**
Oligonucleotide therapeutic agent/MOLECULAR BIOSYSTEMS

**Relevant legal provisions:**
EPC Art. 83

**Keyword:**
"Sufficiency of disclosure (no)"

**Decisions cited:**
T 0409/91, T 0694/92, J 0007/90, T 0639/95, T 0158/91

**Catchword:**

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0994/95 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 18 February 1999**

**Appellant:** (Proprietor of the patent) Molecular Biosystems, Inc.
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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 16 October 1995 revoking European patent No. 0 092 574 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** L. Galligani
**Members:** F. L. Davison-Brunel
C. Holtz

## Summary of Facts and Submissions

I. European patent No. 0 092 574 with the title "Oligonucleotide therapeutic agent and methods of making same" was granted with 2 claims on the basis of European patent application No. 82 903 424.8

The claims as granted for eight contracting states (non-AT States) read as follows:

"1. Therapeutic agent for selectively blocking the translation of mRNA into a targeted protein, comprising a stabilized oligonucleotide of 14 to 23 bases having a base sequence substantially complementary to a portion of the coding region of the mRNA coding for said targeted protein."

"2. Therapeutic agent according to claim 1, characterized in that the oligonucleotide is in a phosphotriester form."

The corresponding method claims were granted for AT.

II. Seven notices of opposition were filed requesting the revocation of the patent under Article 100(a) and/or Article 100(b) EPC. Opponents 1 later withdrew their opposition.

III. By a decision within the meaning of Article 102(1) EPC, the Opposition Division revoked the patent for lack of sufficient disclosure. In particular, it was found that in the absence of any example, the invention could not be carried out in a reliable way starting from the

instructions given in the patent specification. The experimental evidence which had been provided during substantive examination had not been performed with materials directly derivable from the originally filed application and therefore could not be considered relevant for the purpose of sufficiency of disclosure.

IV. The Appellants (Patentees) filed an appeal, paid the appeal fee and submitted the grounds for the appeal.

V. The Respondents I, V and VI (Opponents 2, 6 and 7) answered to the Appellants' submissions. Respondents V filed with their reply the declaration of Dr F. Natt with accompanying evidence.

VI. The Appellants filed on 14 July 1998 four auxiliary requests together with an answer to the Respondents' submissions.

Claim 1 of the first auxiliary request (non-AT States) read as follows:

"1. Therapeutic agent for selectively blocking the translation of mRNA into a targeted protein, comprising a stabilized oligonucleotide of 14 to 23 bases having a base sequence substantially complementary to a portion of the coding region of the mRNA coding for said targeted protein

wherein said agent is obtainable by:

determining the sequence of the mRNA whose expression is to be blocked;

selecting a portion of 14 to 23 nucleotides of said sequence;

making a stabilized oligonucleotide complementary

to said portion;

introducing said stabilized oligonucleotide into a cell expressing said mRNA;

determining whether synthesis of protein encoded by said mRNA can be substantially inhibited without inhibiting the synthesis of other proteins in the cell; and

selecting as a therapeutic agent said oligonucleotide if it is capable of said inhibitory activity."

Claim 1 of the second auxiliary request (for all States) related to a method for identifying a therapeutic agent for selectively blocking the translation of mRNA into a targeted protein, said method comprising the same steps as in claim 1 of the first auxiliary request (non-AT States).

Claim 1 of the third auxiliary request (for all States) read as follows: "A method providing the down-regulation of expression in a cell culture of host cells of a target vital protein of a viral or bacterial organism foreign to said cells, which method comprises treating said cells with an effective amount of a stabilized oligonucleotide of 14 to 23 bases having a base sequence substantially complementary to a portion of the coding region of the mRNA coding for said target vital protein."

Claim 1 of the fourth auxiliary request (for all States) read as follows: "Use of a therapeutic agent comprising a stabilized oligonucleotide of 14 to 23 bases having a base sequence substantially complementary to a portion of the coding region of an

mRNA coding for a targeted protein for selectively blocking the translation of mRNA into a targeted protein in cell culture."

In all of the auxiliary requests, claim 2 related to the subject-matter of the respective claim 1 characterized in that the oligonucleotide is in a phosphotriester form.

VII. A communication was sent according to Article 11(2) of the Rules of Procedure of the Boards of Appeal, setting out the Board's provisional, non-binding opinion.

VIII. Respondents VI replied thereto and filed with the reply the same declaration of Dr F. Natt with accompanying evidence as earlier filed by Respondents V (cf. Section V above).

IX. Oral proceedings took place on 18 February 1999.

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

(15) S. T. Crooke, Ann.Rev.Pharmacol.Toxicol., Vol. 32, pages 329 to 376, 1992;

(39) Liebhaber, S.A. et al., in "Gene Regulation: Biology of Antisense RNA and DNA", edited by R. P. Erickson and J. G. Izant, Raven Press Ltd, New York, pages 163 to 174, 1992;

(47) Stull, R.A. et al., Nucleic Acids Res., Vol. 20, No. 13, pages 3501 to 3508, 1992.

(48) Barton, C. M. and N. R. Lemoine, British Journ. of Cancer, Vol. 71, pages 429 to 437, 1995.

XI. The submissions in writing and during oral proceedings by the Appellants can be summarized as follows:

There were two aspects to enablement: firstly, the patent had to teach the practical steps necessary to perform the invention, and, secondly, the teaching provided had to be sufficient for the invention to be performed over the whole area claimed.

With regard to the first aspect, it could not be doubted that the specification provided sufficient instructions for the subject-matter of the claims to be put into practice because:

- Two ways were shown how to determine the coding sequence of a target mRNA.

- The skilled person would have no difficulty in selecting a portion of 14 to 23 nucleotides as several such portions would be equally suitable.

- At the filing date, how to stabilize oligonucleotides was a matter of common knowledge.

- Finally, there were no experimental difficulties in testing whether the therapeutic agent thus obtained would block translation, at least to some extent.

The burden of proof was on the Respondents to show that this teaching could not be followed to arrive at the

claimed invention.

With regard to the second aspect, reference was made to the case law of the Boards of Appeal, in particular to T 694/92 (OJ EPO 1997, 408). This decision made it clear that the issues of support of the claims, sufficiency of disclosure and inventive step were closely interrelated, in particular, in cases where a balance had to be found between on the one hand, the technical contribution to the state of the art by the invention and, on the other hand, the manner of claiming. This finding applied to the present case since the invention lay in a concept for a new class of compounds. Thus, it was not possible to decide the issue of sufficiency without taking into account the prior art i.e. without deciding the issues of novelty and inventive step. Yet, the Opposition Division considered sufficiency of disclosure in isolation, its findings were, thus, erroneous. The case had, therefore, to be sent back to the first instance.

After the filing date of the patent in suit, it was shown that the therapeutic oligonucleotide may advantageously include the 5' end of the target sequence or a site for RNAse H. These features were to be regarded as improvements of the invention. Neither of them was essential for reproducibility.
In post-published document (15), the oligonucleotides complementary to the region comprising the initiation codon were identified on page 353 as the most potent. This did not mean that other oligonucleotides would not work. In the same manner, it was clear from page 340 that most stabilized oligonucleotides would enter cells although with different efficiencies. Finally, many

cases of the successful uses of oligonucleotides were listed on pages 362 to 366.

In document (47) (page 3506), it was shown that oligonucleotides which did not complement the ATG region would nonetheless inhibit cytokine induced expression of IC-AM-cDNA although to a lesser extent. The failure of a phosphorothioate antisense oligonucleotide to specifically suppress p53 protein production disclosed in document (48) (page 433) was an isolated case, not to be taken into account.

Enablement was factual. The time when it was proven was irrelevant. If a late document was sufficient to invalidate a patent, then it should also be possible to use a late document to validate sufficiency. Thus, the experimental evidence submitted by the Appellants after the filing date of the patent, to prove enablement had to be taken into account. It showed, in particular, that stabilized 15 mer-oligonucleotides could inhibit translation of the beta-globin gene in vivo. Sufficiency of disclosure could be acknowledged.

In view of the substantial procedural violations by the Opposition Division, the appeal fee had to be reimbursed. Furthermore, the evidence filed by Respondents V had to be thrown out as inadmissible. If not, a question of its inadmissibility had to be referred to the Enlarged Board of Appeal.

XII. The submissions by the Respondents were as follows:

The patent disclosed an interesting concept which could not be put into practice without undue burden. The

examples provided in the patent specification were incomplete. Furthermore, they were written in the present rather than in the past tense. This indicated that they had never been carried out. Consequently, it was impossible for the Respondents to discharge their burden of proof by reproducing the invention as described.

In fact, the question was not whether the Respondents failed to provide proof that the invention was not enabled but, rather, whether the invention could be reproduced without undue burden. At the filing date, the stabilisation of long oligonucleotides was extremely difficult. The declaration by Dr F. Natt showed that it was not possible to obtain phosphotriesters by the method disclosed in the patent specification. Furthermore, the specification left many important points unanswered, amongst them, which of the known stabilizing groups should be chosen so that the stabilized oligonucleotides would be able to enter the cells, and which part of the mRNA sequence should serve as target. Solving each of these points involved a separate research programm which may succeed or not. Performing the invention as a whole required that each step be carried out in a successful manner. This clearly involved undue burden of experimentation when working on the basis of the teaching of the patent.

The principles set out in decision T 694/92 (supra) in a case where the patent in suit provided some examples that the claimed invention was reproducible, at least in some specific experimental conditions, did not apply to the present case where the problem simply was that it was not possible to reproduce the invention under

any form without undue burden. Accordingly, there was not even a possibility of looking for a balance between sufficiency of disclosure and inventive step.

The statements in post-published document (39), page 165: "some but not all antisense cDNAs can block translation", and in post-published document (48), page 435: "...it is important that a subtle difference in experimental techniques can significantly affect the result of an antisense experiment" underscored the fact that in antisense technology no generic concept was applicable.

The experiments filed by the Appellants in an attempt to prove sufficiency of disclosure should not be taken into account because their protocol had taken into account knowledge acquired after the filing date of the patent.

XIII. The Appellants requested that the decision under appeal be set aside and that the case be remitted to the first instance for further prosecution of novelty and inventive step on the basis of the patent as granted (main request) alternatively on either of the first to fourth auxiliary requests, filed on 14 July 1998, that the appeal fee be reimbursed, and that a question be referred to the Enlarged Board regarding the admissibility of the submissions by Respondents V as regards sufficiency of disclosure.

XIV. The Respondents requested that the appeal be dismissed.

## Reasons for the Decision

1. The appeal is admissible.

*Main request: sufficiency of disclosure (Article 83 EPC)*

2. The claimed invention is defined as a therapeutic agent for selectively blocking the translation of an mRNA into a targeted protein comprising a stabilized oligonucleotide of 14 to 23 bases having a base sequence substantially complementary to a portion of the coding region of the mRNA coding for said targeted protein. Pursuant to Article 83 EPC, adequate instructions should be given in the specification or on the basis of common knowledge for the skilled person to be able to prepare without undue effort such a therapeutic agent. This does not necessarily mean that it should be proven that the invention was actually carried out at the filing date. However, the written description of the invention should be such as to enable the person skilled in the art to make and use it without undue difficulties (cf eg T 639/95 of 21 January 1998). In particular, the patent specification should teach:

(a) how to identify the relevant portion of the mRNA encoding the targeted protein (mRNAs being longer than 14 to 23 bases),

(b) how to devise an oligonucleotide of 14 to 23 bases of substantial complementarity and synthesize it,

(c) how to stabilize said nucleotide and

(d) how to test for its ability to enter the cells and to selectively block translation of the target

mRNA.

3. With regard to feature (a), the patent specification teaches that the sequence of an mRNA may be deduced from that of the DNA it is derived from, or from the sequence of the protein it encodes. This last approach is illustrated in the second example starting from the protein sequence of the FSH hormone situated between the 33rd and the 44th amino-acids. No reasons for choosing this specific part of the protein sequence are given. Nor is evidence given that an oligonucleotide complementary to this region selectively blocks mRNA translation. The skilled person is left in doubt as to whether any portion of an mRNA is suitable as a target and as to which criteria, other than trial and error, can be used to select a specific region.

4. With regard to feature (b), the patent specification makes reference to two methods of synthesizing oligonucleotides, i.e. by known synthetic techniques or as part of a cDNA. The possibility that the oligonucleotide be substantially rather than fully complementary to the target mRNA is not discussed. It is, however, advised to test it in vitro for its cross-reactivity with other mRNAs than the target mRNA.

5. Furthermore, according to page 3, column 2 line 58, the oligonucleotide should preferably be stabilized as a phosphotriester (cf. feature (c)). This does not mean, of course, that other stabilizing groups cannot be taken into consideration.

6. Feature (d) is a testable feature. However, the specification provides no experimental evidence in

respect of any suitable target mRNA. Nor is any stabilized oligonucleotide shown to enter cells and to block translation of the corresponding mRNA.

7. Thus, the teachings of the patent can be summarized as being that an oligonucleotide stabilized in any known way and complementary to a portion of an mRNA will have to be tested in respect of its ability to enter a cell and hybridize to said mRNA in such a way as to block translation, methods being available to characterize any mRNA portion and to isolate and stabilize any oligonucleotide. Whenever such an oligonucleotide is found, it is a therapeutic agent according to claim 1. The Appellants themselves defined this teaching as conceptual in nature and the Board certainly agrees that it is so.

8. In the absence of any tangible proof in the patent specification that the claimed concept can be put into practice, post-published documents can be used as evidence whether the invention merely disclosed at a general conceptual level was indeed reproducible without undue burden at the relevant filing date. A close survey of the scientific literature brings about the following information:

- document (15) published in 1992 (ten years after the filing date of the patent in suit) discusses the therapeutic application of oligonucleotides. On pages 338 to 342, the cellular uptake and distribution of stabilized oligonucleotides used in antisense technology are reviewed. On page 342, it is stated: "Clearly oligonucleotides of different types behave differently and there are

substantial variations as a function of cell type. Moreover, length and specific sequences may alter uptake and pendant modifications may profoundly influence cellular uptake.". On page 352 to 356, the mechanisms by which oligonucleotides can inhibit translation are described. It is found that "oligonucleotides complementary to the translation initiation codon were the most potent of the more than 50 compounds studied complementary to various other regions in the RNA". Other useful antisense oligonucleotides are identified as those which, when hybridized to mRNA, make it a substrate for RNAseH. Table 7 provides a listing of antisense oligonucleotides activities as measured in cell cultures. According to the authors, "the data presented in Table 7 support only a few generalisations". In particular, only the phosphorothioates but not the methylphosphonates are said to appear to have quite high therapeutic indexes in vitro. It is also stated that too few data are available to draw any conclusions on the properties of other classes of oligonucleotides.

- Document (47), published in 1992 discloses a study of the inhibitory efficacy of antisense phosphodiester oligonucleotides in a cell free translation system (in vitro) and shows that this efficacy much varies as a function of the oligonucleotide sequence (Table 4).

- In document (48) published in 1995, which is a study of the efficacy in cell cultures of antisense oligonucleotides directed against P53

mRNA (in vivo), it is stated: "...it is important to note that a subtle difference in experimental technique can significantly affect the results of an antisense experiment."

The Board concludes from the teachings of these documents that antisense technology applied to therapy had not become a matter of routine experimentation, more than ten years after the filing date of the patent.

9. The Appellants argued that each of the steps involved in the isolation and therapeutic functionality of antisense oligonucleotides could be made to work **to some extent** and that this should be enough to consider the whole invention as sufficiently disclosed. The Board, however, cannot agree. Firstly, there is no evidence that all potential methods of carrying out anyone step can be used indifferently. For example, although phosphotriesters are disclosed in the patent in suit as the preferred form of stabilized oligonucleotides, they are never accounted for as therapeutic antisense oligonucleotides in the post-published documents. Secondly, each of the necessary steps needs to be combined with the other steps to get to the therapeutic compound. If all steps can only be carried out with "some" efficiency, then it is to be expected that the overall efficiency of their combination will be dismally low. Moreover, even if each individual experimental step per se could be considered as being feasible with a certain amount of trial and error, the total amount of experimental effort necessary to successfully advance step by step towards the desired final goal is still to be regarded

as undue burden for a skilled person, especially in the absence of any concrete guidance and experimental verification. In the Board's judgment, this implies that the sole disclosure of the concept "therapeutic oligonucleotide" as provided by the patent in suit is not adequate for sustaining sufficiency of disclosure.

10. The Appellants further argued that sufficiency of disclosure need not be proven at the filing date and that, therefore, the experiments which they submitted after the filing date of the patent and which showed that 15mer stabilized oligonucleotides could inhibit globin synthesis should be accepted as proof that the invention was reproducible.

11. It is certainly true that in many occurrences patent applicants or proprietors file additional experimental evidence of the reproducibility of their invention. In all cases, the late filed evidence should constitute a bona fide attempt to reproduce the invention as filed, in order to be found relevant. In the present case, the in vivo experimental evidence filed already during examination in reply to a decision to refuse the application, decision which was consequently rectified under Article 109(1) EPC, discloses two 15mer oligonucleotides which are capable of inhibiting the translation of the beta-globin gene. One of them is stabilized with methylphosphonate, the other includes in its sequence the beta-globin gene initiation codon. Both these features have advantages for cellular uptake and translation inhibition which only became known in the art after the filing date of the application. Thus, in the Board's judgment, the experiments cannot be said to prove the reproducibility of the claimed subject-

matter **as disclosed** in the patent specification as originally filed.

12. As for the Appellants' arguments that the case should be sent back to the first instance because while deciding sufficiency of disclosure, the Opposition Division failed to make a proper assessment of the invention, in particular of its relationship with the prior art, the following is observed:

13. Sufficiency of disclosure is achieved when the skilled person following the instructions given in the patent specification is able to carry out the invention **without undue burden** (cf. point 2 supra). The amount of technical details to be provided will depend on the correlation of the facts of each particular case with certain general parameters, such as the character of the technical field, the date on which the disclosure was presented and the corresponding general knowledge, and the amount of reliable technical detail disclosed in a document (see decision T 158/91 of 30 July 1991). In situations where conflicting statements are made in respect of the value of the prior art versus the value of the actual disclosure, it may be appropriate to find a balance between the breadth of the claims and the actual contribution to the state of the art by the disclosure of the patent in suit (T 694/92 supra), However, the question of sufficiency can also be decided independently from the question of inventive step in such cases, as the present one, where the question is rather whether the quality and quantity of experimentation needed to perform the conceptual invention based on the scanty guidance provided in the patent specification was undue for the person of

ordinary skill in the art at the filing date. In view of the findings in points 3 to 9 above, the Board concludes that the fact that the prior art was not taken into account in the framework of an inventive step analysis has no bearing on the assessment of sufficiency of disclosure.

14. The requirements of Article 83 EPC are not fulfilled in relation to the subject-matter of the main request.

*First to fourth auxiliary requests*

15. The first claim in the first to fourth auxiliary requests are drafted as a product-by-process claim, method claims or use claim respectively (see point VI, above). All of them comprise an oligonucleotide made in a stabilized form and complementary to a portion of mRNA, which is able to enter cells and block translation.

16. The reasoning which led the Board to conclude that the disclosure in the specification was insufficient in relation to the subject-matter of claim 1 of the main request would equally apply in relation to the subject-matter of claim 1 of each auxiliary request, which merely incorporates features from the description, said features being considered insufficient to provide guidance for the skilled person in performing the invention. Accordingly, it is decided that the requirements of Article 83 EPC are also not fulfilled with regard to the subject-matter of the auxiliary requests.

*Other matters:*

The *request for referral of a question to the Enlarged Board of Appeal.*

17. The Appellant requested that a question be sent to the Enlarged Board of Appeal if the late filed evidence by Respondents V as regards sufficiency of disclosure was accepted into the proceedings. This evidence which in any case was also filed by Respondents VI, was not found decisive for the purpose of the present decision. Therefore, in accordance with the case law of the Boards of appeal (see eg J 7/90, OJ 1993, 133), the request is refused.

*The request for refund of the appeal fee*

18. Rule 67 EPC provides for the possibility for reimbursement of appeal fees "where the Board of Appeal deems an appeal to be allowable". In the present case, as the appeal is dismissed, the first condition for the reimbursement of the appeal fee is not fulfilled.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

U. Bultmann L. Galligani