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# D E C I S I O N
## of 14 November 2000

**Case Number:** T 0838/97 - 3.3.4

**Application Number:** 84112647.7

**Publication Number:** 0140308

**IPC:** C12N 15/11

**Language of the proceedings:** EN

**Title of invention:**
Regulation of gene expression by employing translational inhibition utilizing mRNA interfering complementary RNA

**Patentee:**
THE RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK

**Opponent:**
Calgene Inc.

**Headword:**
Translational inhibition/RESEARCH FOUNDATION

**Relevant legal provisions:**
EPC Art. 54(1)(2), 56, 83

**Keyword:**
"State of the art - Gordon Research Conference - public (no) - confidentiality agreement"
"Novelty (yes)"
"Inventive step (yes)"
"Sufficiency of disclosure (yes)"

**Decisions cited:**
T 0204/83, T 0677/91, T 0830/90, T 0877/90, T 0739/92, T 0776/96, T 0636/97

**Headnote:**

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**Case Number:** T 0838/97 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 14 November 2000**

**Appellant:** (Opponent 02)
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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 27 June 1997 rejecting the opposition filed against European patent No. 0 140 308 pursuant to Article 102(2) EPC.**

**Composition of the Board:**

**Chairperson:** U. M. Kinkeldey
**Members:** L. Galligani
C. Holtz
R. E. Gramaglia
S. C. Perryman

## Summary of Facts and Submissions

I. The appeal was lodged against the decision of the opposition division dated 27 June 1997 whereby the opposition was rejected. The patent had been opposed by two parties, one of which (opponents 01) later withdrew the opposition.

Claims 1, 22 and 23 as granted in the version for all designated Contracting States except Austria (non-AT States) read as follows:

"1. An artificial nucleic acid construct which, upon introduction into a cell containing a gene, antagonizes the function of said gene, said artificial nucleic acid construct containing the following nucleic acid segments:

(a) a transcriptional promoter segment;

(b) a transcription termination segment; and therebetween

(c) a nucleic acid sequence segment;

whereby transcription of the nucleic acid sequence segment produces a ribonucleotide sequence which does not naturally occur in the cell, is complementary to at least a portion of a ribonucleotide sequence transcribed by said gene, and said non-naturally occurring ribonucleotide sequence antagonizes the function of said gene."

"22. A micro-organism containing a nucleic acid construct according to any one of claims 1 to 12 or a

vector according to any one of claims 13 to 15."

"23. The micro-organism according to claim 22, which is a bacterium, a yeast or a virus."

Dependent claims 2 to 4 concerned particular embodiments of the construct of claim 1. Independent claim 5 was directed to an artificial nucleic acid construct in which item (c) was an inverted segment of the gene to be antagonized. Dependent claims 6 to 12 concerned embodiments of the preceding claims. Claims 13 to 17 were directed to nucleic acid or vectors containing the nucleic acid construct, claim 18 concerned a pharmaceutical composition and claims 19 to 21 a method for antagonizing the function of a gene in a microorganism.

In the corresponding set of claims 1 to 23 for AT some claims were formulated as process claims. Claims 22 and 23 thereof were identical to claims 22 and 23 for the non-AT States.

II. The opposition division considered that, as shown also by later evidence, the invention as claimed was disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The report by one of the inventors (Dr Inouye) of inconclusive experiments (cf documents (8) and (9) referred to in Section VIII infra)) was not considered to be a proof of failure. Moreover, the opposition division considered that the claimed subject-matter was novel over the following documents:

(1) The EMBO Journal, 1983, Vol. 2, No. 1, pages 93 to 98;

(2) Cell, September 1983, Vol. 34, pages 683 to 691;

(3) Nature, 17 December 1981, Vol. 294, pages 623 to 626;

(4) Methods in Enzymology, Edited by Ray Wu, Academic Press, New York USA, 1979, Vol. 68, pages 482 to 493.

As regards the presentation of Dr H. Weintraub at the Gordon Research Conference on 25 to 29 July 1983, it was decided that, although the presentation was considered to be public, the evidence available did not allow a reliable answer to the question: "What was really disclosed?". Thus, it was decided that the presentation was not state of the art.

The claimed subject-matter was also considered to involve an inventive step as the combination of any of the documents (1) to (4) with

(6) WO-A-83/01451

did not even remotely suggest it.

III. With their statement of grounds of appeal, the appellants filed two statutory declarations by Dr M. Neuberger.

IV. The respondents filed their comments to the statement of grounds of appeal and submitted two new documents.

V. On 18 July 2000, the board issued a communication with an outline of the points to be discussed and a preliminary opinion on some issues.

VI. Both parties made further submissions in reply to the board's communication. The appellants filed therewith an additional document. The respondents filed additional documents (27) to (33), of which document (27) was a table listing 100 examples of successful control of biological functions in cells by antisense RNA as evidenced by 100 published articles supplied as enclosures.

VII. Oral proceedings took place on 14 November 2000. The respondents filed as a new main request claims 1 to 23 in two different sets, one for all non-AT States and one for AT. These claims differed from the claims as granted only in that in claim 23 the embodiment "a yeast" was deleted.

VIII. In addition to the documents already referred to the in previous sections, the following documents are referred to in the present decision:

(8) Gene, 1988, Vol. 72, pages 25 to 34;

(9) Extracts from the deposition of Dr M. Inouye before the U.S. District Court Eastern District of California on 16 September 1993;

(10) Cell, April 1984, Vol. 36, pages 1007 to 1015;

(18) Extracts from the testimony of Dr S. Molin before the U.S. District Court District of Delaware.

IX. The appellants objected to novelty on the basis of: i) the oral disclosure of Dr Weintraub at the Gordon Research Conference in July 1983; and ii) document (1).

As regards the question whether or not there was an actual duty of confidentiality in relation to i), they argued that the participants to Gordon Research Conferences were not subject to a blanket prohibition from disseminating the information they received. There were in the file declarations of scientists to this effect (cf declarations S1 to S8). Moreover, those attending the conference were afterwards free to discuss what they had learnt with colleagues of the same or other laboratories. The only restrictions binding the participants at Gordon Research Conferences concerned "printed" publications, as the aim was to prevent written references to preliminary communications presented at the conferences, unless the individual making the contribution provided permission. This could be deduced from Exhibits B and D annexed to the declaration by Dr Cruickshank, which had not to be given a broader interpretation than their wording allowed.

Having regard to document (1), the appellants argued that, as claim 1 at issue was a product claim directed to an artificial construct comprising the three elements a) to c), there was anticipation if such a construct was described therein. This was indeed the case as the chimeric plasmids described on page 96, namely pOU565, pJ242 and pJ232, contained the same three structural elements, namely **a)** a transcriptional promoter segment, this being either the tet, deo or lac promoter segment from which copT transcription was driven; **b)** a transcription termination segment which would lie downstream of the copT sequence (cf document (18)) and **c)** a nucleic acid sequence segment which did not naturally occur in the cell a gene of which was antagonised by its transcript, said sequence

being represented by the copT sequence that was complementary to the copARNA of plasmid pJL99 and thus titrated out copA from the latter plasmid, thereby causing an increased ß-galactosidase expression via the repA-lac sequence (cf second statutory declaration dated 4 November 1997 by Dr M. Neuberger).

The appellants also denied the presence of an inventive step. In their view, the patent in suit was not the first to propose the use of "anti-sense" sequences for inhibiting a gene. Document (6) had already proposed making oligonucleotides complementary to target sequences, which was the same concept as that of the patent in suit, and had pointed to the problem of introducing them from the exterior (cf page 17). Document (1) had introduced the idea of producing within the cells nucleic acid transcripts which antagonised a gene, and had shown this to be experimentally feasible. The combination of the two documents, one relating to the concept, the other to the experimental way to put it into practice, readily suggested the claimed subject-matter to the skilled person.

The appellants also submitted that the patent in suit did not provide a sufficient disclosure because it failed to show that its teaching extended to organisms (eg yeast) other than bacteria as exemplified. Among the 100 examples provided by the respondents in document (27) there was not a single example with yeast. As a matter of fact, documents (8) and (9) showed that experiments were not successful in yeast.

X. The respondents argued that the patent-in-suit related to a pioneering and milestone invention which had been

exemplified in E. coli as a model system. They submitted that later evidence, and also the work of the appellants themselves (EP-A-0240 208 - Exhibit CC), showed that it was widely successful. The patent specification enabled the skilled person to put the invention into practice over the broad area claimed. As for novelty, they argued that the presentation of Dr Weintraub at the Gordon Research Conference was given under a confidentiality obligation and that, in any case, it was totally unclear what was exactly said. They submitted that the said obligation to confidentiality was comparable to that of panel reviewers of scientific publications. Furthermore, the claimed subject-matter was new over document (1) which in fact taught away from it by suggesting a protein interaction as a regulatory mechanism. Moreover, the claimed subject-matter was not obvious vis-à-vis document (6) alone or in combination with any of the documents (1) to (4).

XI. The appellants requested that the decision under appeal be set aside and that the patent be revoked.

The respondents requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 23 as submitted in the oral proceedings in two different sets, one for all non-AT States and one for AT and pages 2, 4 to 15 of the description as granted and page 3 as submitted in the oral proceedings, and Figures 1 to 8 as granted.

## Reasons for the Decision

*The state of the art: The presentation of Dr H. Weintraub at the Gordon Research Conference on 25-29 July 1983*

1. As stated eg in T 877/90 of 28 July 1992, an oral disclosure is regarded as made available to the public if the person(s) exposed to it was (were) able to understand it and was (were) potentially able to further distribute it to others, **and** there was no bar of confidentiality or secrecy agreement restricting the use or dissemination of the disclosure.

2. Thus, the first important question in relation to the presentation of Dr H. Weintraub at the Gordon Research Conference in July 1983, which was given before an audience qualified in the relevant technology, is whether it was given under any form of confidentiality agreement. In deciding this question, it should be kept in mind that an agreement which rules out availability to the public does not necessarily have to be a contract made in writing, as an implicit or implied agreement can also be taken into account (cf eg T 830/90 of 23 July 1993).

3. The question of the confidentiality of a Gordon Research Conference was posed already in the case of T 739/92 of 16 July 1996 where it was decided, in agreement with the first instance finding, that the participants at the Gordon Research Conference then in question had to be regarded as normal members of the public who were free to disseminate the information they obtained. However, it is noted that the body of evidence on the basis of which the said decision was taken did not include all the documents available in the present case, in particular it did not include the affidavit of the director of the Gordon Research

Conferences and annexes thereto which are now on file (cf affidavit of Dr Cruickshank). It is in any case necessary for this board to examine the question on the basis of the evidence available before it, and to come to its own conclusion on this issue of fact.

4. In his affidavit, Dr Cruickshank, who was Director of the Gordon Research Conferences from 1968 to 1993, expresses the belief that all participants of the conferences were generally aware of the policies, guidelines and restrictions governing them and that there was a general understanding among the participants that the materials presented were to be treated as confidential. Indeed, as it is clearly stated eg in the announcement of the Gordon Research Conferences published in Science, 4 March 1983, Vol. 219, pages 1095 to 1131 (Exhibit C annexed to the affidavit), the purpose of the conferences is to foster and promote discussion among scientists by providing a unique forum for open communication on the latest developments in science thereby stimulating advanced thinking in research at universities, research foundations, and industrial laboratories. It is explicitly stated that the review of known information is not desired. In view of this, in order to protect the rights of scientific priority, it is an established requirement of each conference that no information presented or discussed is to be used or cited without the specific authorization of the individual(s) making the contribution (ibidem). The limited number of conferees (approximately 100), who are selected upon application by the chairperson of the conference so as to ensure the widest possible attendance, are explicitly instructed *inter alia* that "*information presented at the conferences is not to be used without*

*the specific authorisation of the individual who makes the contribution, whether in formal presentation or in discussion*" (ibidem). By having the application for registration accepted, each participant agrees to these regulations (cf Exhibit D annexed to the affidavit).

5. The opposition division decided "on the balance of probabilities" that the participants at the Gordon Research Conferences were merely prohibited from making **printed** reference to conference papers and discussion, **not** from further discussing publicly these matters. This is also the position of the appellants who, in support of this view, filed declarations S1 to S7 of scientists who attended such conferences (however, not the one in which Dr Weintraub gave his presentation) and express their personal belief that the restrictions do not concern the oral dissemination of the information obtained at a conference to others, eg co-workers or colleagues, who did not attend it (cf declarations S1 to S7). In the further declaration of Dr M. Levine (S8), who attended the 1983 Gordon Research Conference in which Dr Weintraub made his presentation, nothing is said about the issue of confidentiality.

6. In the board's judgment, since the purpose of the Gordon Research Conferences is to encourage free, informal and open discussion exclusively on the latest developments among scientists from various institutions and laboratories, the restrictions which the participants are invited to accept upon registration cannot be narrowly interpreted as being limited to printed references, but have to be understood as meaning that any information presented at a Gordon Research Conference, whether in a formal talk, poster

session or discussion, amounts to **a private communication** from the individual making the contribution and is presented with the restriction that such information is **not for public use**. Otherwise, the stated purpose of the conferences would fail. In this respect, it is observed that, since the chairperson of a conference will select applicants so as to distribute the attendance as widely as possible among the various institutions and laboratories, the audience is likely to include also the closest scientific (and possibly commercial) rivals. This is also admitted by the declarers in S1 to S7. Under these circumstances, a profitable discussion is possible only under a confidentiality agreement, such as the one issued by the organisers.

7. In statements S1 to S7, the scientists express their personal **belief** that the restrictions set forth by the organisers do not prohibit participants from further disclosing information learned at a Gordon Research Conference to colleagues from their or other laboratories. However, the circumstances under which this alleged further dissemination is made (in closed circles? under a form of confidentiality? publicly?) are not specified. Moreover, none of the declarers actually admits to have actually disseminated publicly information received at a Gordon Research Conference. For this reason, the board considers that the said statements by a limited numbers of scientists cannot prevent the board from concluding that the presentation of Dr H. Weintraub at the Gordon Research Conference in July 1983, whatever its contents, amounted to a private communication within a closed circle of persons bound by a confidentiality agreement, and thus is not to be considered to be part of the state of the art.

*Novelty*

8. The appellants argue that the plasmid constructs described on page 96 of document (1) fall within the wording of claim 1, which consequently is not novel.

9. In order to be novelty-destroying, a prior art document has to contain a clear and unmistakable disclosure for the skilled person of the subject-matter of a claim in question (cf eg T 204/83 OJ EPO 1985, 310; T 776/96 of 23 September 1997 and T 677/91 of 3 November 1992). Novelty assessment is not based on a mere photographic comparison with a prior art document, but requires consideration of both the explicit and implicit disclosure of the document. However, there must be no doubt that the prior disclosure, as read by the skilled person, unambiguously corresponds in all its technical features to the subject-matter as claimed. In the board's judgement such is not the case here. In order to demonstrate that the plasmid constructs of document (1) correspond to the one of claim 1 at issue, the appellants have to "interpret" the features derivable from document (1) beyond what can be reasonably implied therefrom. Feature b) is a typical example in this respect. Nowhere in document (1) is there any mention of a transcription termination sequence. Dr Molin in his testimony (document (18)) states that a terminator was not inserted. Dr Neuberger in his second declaration indicates in general terms that the transcription termination site "will lie" downstream of the copT insert (where exactly is not indicated), and in this respect he has to refer to additional prior art documents concluding: "Indeed, I really cannot conceive of any other reasonable interpretation of the information" (cf. item 7.5). In the board's view, such

evidence is not sufficient for allowing the conclusion that the skilled person would have considered the plasmid constructs of document (1) to be identical to the construct of claim 1 in all its features as he or she would not have recognised in the said document, for example, the presence of feature b), much less its presence in functional correlation with the features a) and c). The said feature per se constitutes already a sufficiently distinctive feature, so that it is not even necessary to examine in detail all other aspects of the matter.

10. For these reasons, the subject-matter of claim 1 is novel having regard to document (1). No other document on file was stated by the appellants to affect the novelty of this claim or of the other claims. Nor did the board find other novelty-anticipating documents. Therefore, the claim request at issue satisfies the requirements of Article 54 EPC.

*Inventive step*

11. The closest prior art is represented by document (6) which describes the use of stabilised (eg as a phosphotriester form) oligonucleotides capable of hybridising with a given mRNA for controlling biological functions in an organism, eg for blocking the synthesis of a protein at the level of translation.

12. In the light of this document, the underlying technical problem can be defined as being the provision of an alternative approach for regulating (eg blocking) expression of proteins in a host cell.

13. As a solution, the claims at issue propose a method and

means for antagonising the function of a gene essentially based on the use of a construct with the features recited in claim 1. The proposed approach is exemplified in E. coli where the expression of the genes for the major outer proteins is shown to be decreased.

14. The relevant question is whether the skilled person, starting from document (6) and considering further prior art documents, would have readily devised a nucleic acid construct as claimed in order to antagonise the function of a given gene in a cell.

15. In the appellants' view, the answer to the above question is in the affirmative because the skilled person would have derived from document (1) the idea of producing the "anti-sense" oligonucleotides in the cells, instead of having to introduce them from the exterior through the cell membrane.

16. In the board's judgment, such an analysis is based on hindsight. This is because the skilled person, knowing from document (6) that one of the problems of the approach was the **in vivo** degradation of the oligonucleotides (cf page 3, line 13 to 15; page 17, lines 13 to 23) and knowing that, in order to avoid this, stabilised forms thereof had to be used, would not have readily taken into consideration the idea of producing them in the cells where they would have been exposed immediately to various degradative enzymes. He or she would have rather looked for further ways for stabilising the oligonucleotides and for increasing at the same time their penetration through the cell membrane. Thus, under normal circumstances, the skilled person would not have taken the teaching of document (1) into consideration. For the same reasons, the skilled person would not have taken the teaching of document (2) into consideration, which was concerned with the rather specific teaching of the inhibition of transposase translation by a small complementary regulatory RNA. As a matter of fact, there were no "real life" links between these three documents which could have lead the skilled person to any form of combination of their teachings.

17. Under these circumstances, the board finds that the claims at issue propose a technical solution which was not obvious to the skilled person and which, failing proof of the contrary, and as confirmed by later evidence, was valid over the whole area claimed. Thus, the requirements of Article 56 EPC are satisfied.

*Sufficiency of disclosure*

18. In respect of this issue, the appellants relied on reports on unsuccessful experiments in yeast (cf documents (8) and (9)) in order to support their contention that the teaching of the patent in suit is not applicable over the whole area claimed.

19. The board notes firstly that yeast is no longer specifically recited in claim 23 and, secondly, that the said lack of sufficient disclosure objection is understood to be mainly directed to the product claim 22, which might be considered to encompass also yeast without specifically referring to it, as no doubts can exist that an artificial nucleic acid construct according to claim 1 can be assembled without difficulties by the skilled person.

20. The question here is whether the teaching of the patent in suit can be considered to be of general application to microorganisms, having been successfully exemplified only in E. coli bacteria as a model. The respondents have provided a large number of later documents showing the validity of the model across a broad area of host cells (cf document (27) and enclosures).

21. The patent in suit provides the concept which constitutes the essence of the invention. Experimental guidance is provided in particular in respect of a bacterial model system, which is said to provide the basis for accomplishing the same in other host cells, eg eukaryotes. In view of the nature of the invention, it can be stated that, notwithstanding the guidance provided in the patent specification, a certain amount of trial and error is always needed, and the skilled

person performing the invention in a given host cell can not tell with absolute certainty whether the teaching will be successfully applicable until the experiment is actually carried out. This conclusion can be drawn inter alia from documents (8) to (10). However, this is not necessarily indicative of undue burden, if the results can be readily tested and no further concepts have to be developed in order to achieve the desired result. In the board's judgement. the latter considerations are applicable here. In this respect it is also observed that a claim can validly cover broad subject-matter, even though the description does not enable every method of arriving at that subject-matter to be carried out (cf T 636/97 of 26 March 1998, see point 4.5 of the reasons).

22. For these reasons, it is considered that the requirements of Article 83 EPC are satisfied.

*Adaptation of the description*

23. The appellants raised an objection under Article 123(2) EPC against the amendment on page 3, namely the deletion on line 30 of the term "yeast". In their view, as yeast was an integral part of the application as filed (cf the expression "including...yeast.." on page 6, line 22), in their view the deletion amounts to new information not originally disclosed.

24. The board does not share the appellants' view. Yeast was one of the microorganisms referred to in particular as possible hosts within the more general concept of "microorganisms". Its deletion from the description is merely the consequence of the fact that this particular embodiment of the invention is no longer specifically

claimed (cf claim 23 at issue vs claim 23 as granted) and does not result in the creation of subject-matter which was not originally disclosed. Thus, adapted page 3 of the description raises no issues under Article 123(2) EPC.

## Order

## For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the two sets of claims 1 to 23 submitted in the oral proceedings, pages 2, 4 to 15 of the description as granted and page 3 as submitted in the oral proceedings, and Figures 1 to 8 as granted.

The Registrar: The Chairperson:

U. Bultmann U. Kinkeldey