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Datasheet for the decision of 1 March 2018

Case Number: T 1047/12 - 3.3.08

Application Number: 01922870.9

Publication Number: 1309726

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
RNA SEQUENCE-SPECIFIC MEDIATORS OF RNA INTERFERENCE

Patent Proprietors:
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Massachusetts Institute of Technology
University of Massachusetts

Opponents:
Silence Therapeutics AG
BASF SE

Headword:
RNA interference mediators/WHITEHEAD INSTITUTE

Relevant legal provisions:
EPC Art. 54, 56, 83, 87, 113(1), 123(2), 123(3)

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It can be changed at any time and without notice.

Keyword:
Main request - added matter (no)
Scope of protection extended (no)
Lack of clarity (no)
Invention sufficiently disclosed (yes)
Priority valid (yes)
Novelty and inventive step (yes)

Decisions cited:
G 0006/88, G 0003/14, T 0059/87, T 0609/02, T 0903/05

Catchword:

This datasheet is not part of the Decision.
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Beschwerdekammern

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Case Number: T 1047/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 1 March 2018

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 30 March 2012 concerning maintenance of the European Patent No. 1309726 in amended form.**

Composition of the Board:

Chairman B. Stolz
Members: M. R. Vega Laso
D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 309 726 with the title "RNA sequence-specific mediators of RNA interference" was granted from the European application No. 01922870.9, which had been filed as an international application under the Patent Cooperation Treaty and published as WO 01/75164 (in the following "the application as filed").

II. The patent, which was granted with 19 claims, was opposed on the grounds for opposition of Article 100(a) in conjunction with Articles 54, 56, and 53(c); 100(b) and 100(c) EPC.

III. In an interlocutory decision pursuant to Article 101(3)(a) and 106(2) EPC posted on 30 March 2012, an opposition division found that, account being taken of the amendments introduced into claims 1 to 14 and the adapted description according to the main request filed at the oral proceedings, the patent and the invention to which it relates met the requirements of the EPC.

IV. Claims 1, 3, 9, 10, 12 and 13 according to the main request read as follows:

"1. A method of producing double stranded RNA of from 21 to 23 nucleotides in length comprising:

(a) combining double-stranded RNA with a soluble extract that mediates RNA interference, thereby producing a combination;

(b) maintaining the combination of (a) under conditions in which the double stranded RNA is

processed to double stranded RNA of from 21 to 23 nucleotides in length; and

(c) further comprising isolating the double stranded RNA of from 21 to 23 nucleotides in length from the combination.

3. An in vitro method of mediating RNA interference of mRNA of a gene in a cell comprising:

(a) introducing double stranded RNA of from 21 to 23 nucleotides in length and corresponding to a sequence of the gene which targets the mRNA of the gene for degradation into the cell in vitro;

(b) maintaining the cell produced in (a) under conditions under which degradation of the mRNA occurs, thereby mediating RNA interference of the mRNA of the gene in the cell.

9. A method as claimed in any one of claims 1-8 wherein the double stranded RNA of from 21 to 23 nucleotides in length comprises a terminal 3’ hydroxyl group.

10. A method as claimed in any one of claims 3-9 wherein the double stranded RNA of from 21 to 23 nucleotides in length is chemically synthesized RNA.

12. A method as claimed in any one of claims 1-11 wherein the double stranded RNA of from 21 to 23 nucleotides in length is isolated using gel electrophoresis.

13. A method as claimed in any one of claims 1-12 wherein the double stranded RNA of from 21 to 23

nucleotides in length is complementary to one of mammalian cellular mRNA or viral mRNA."

Claims 2, 4 to 8, 11 and 14 are directed to variants of the method of claim 1.

V. Opponents 01 and 02 lodged an appeal against the interlocutory decision of the opposition division and submitted statements setting out their grounds of appeal. However, on 15 January 2013 opponent 01 withdrew its opposition. Opponent 02 is thus the sole appellant.

VI. By letter dated 7 January 2013, the patent proprietors (respondents) replied to the grounds of appeal. They re-filed the set of claims according to the main request underlying the decision under appeal, and submitted three additional sets of claims as first to third auxiliary requests as well as new documentary evidence.

VII. In a communication in preparation of the oral proceedings, the board expressed a provisional opinion on procedural issues and various substantive issues concerning Articles 123(2)(3), 83, 87, 54 and 56 EPC.

VIII. In reply to the board's communication, the appellant (opponent 02) and the party as of right (opponent 03) informed the board that they would not attend the oral proceedings. They did not make any substantive submissions.

IX. Oral proceedings were held on 1 March 2018 in the presence of the respondents.

X. The following documents are referred to in this decision:

(6): T. Tuschl et al., 1999, Genes & Development, Vol. 13, pages 3191 to 3197;

(23): WO 00/44895, published on 3 August 2000;

(24): WO 99/32619, published on 1 July 1999;

(27): WO 94/01550, published on 20 January 1994;

(28): WO 99/53050, published on 21 October 1999; and

(29): M. K. Montgomery and A. Fire, July 1998, Trends in Genetics, Vol. 14, No. 7, pages 255 to 258.

XI. The submissions made by the appellant concerning issues relevant to this decision, were essentially as follows:

Article 123(2) EPC - added matter

The subject-matter of claim 3 extended beyond the content of the application as filed. There was no basis in the application as filed for the feature "double stranded" characterising an RNA of from 21 to 23 nucleotides in length in the context of a method of mediating RNA interference. It was apparent from the passage on page 2, lines 22 to 24 that, according to the invention, not only double stranded RNA, but also single stranded RNA was capable of mediating RNA interference. There was no hint in that passage that the particular definition of RNA as ssRNA or dsRNA applied to each and any aspect disclosed in the application as filed. Rather to the contrary, it was evident from the passages on page 2, lines 30 and 31

and page 3, lines 8 to 10 that the definition applied only to the "isolated RNA molecules". A person skilled in the art would not have immediately and unambiguously derived from those passages the teaching of a method of mediating RNA interference making use of double stranded RNA of from 21 to 23 nucleotides in length.

There was no proper basis in the application as filed for the feature that the double stranded RNA of from 21 to 23 nt in length corresponded to a sequence of the gene. The passage on page 16, lines 25 and 26 of the application as filed indicated that there was no upper limit on the length of the dsRNA that can be used. This suggested that the dsRNA to which it was referred there was the starting RNA, rather than the dsRNA of from 21 to 23 nt in length used in the method of claim 3. The aspect of complementarity was only disclosed in connection with the specific method of assessing the ability of 21 to 23 nt RNAs to mediate RNA interference disclosed on page 18, lines 30 and 31.

Article 123(3) EPC - extension of the scope of protection

The amendments introduced into the claims contravened Article 123(3) EPC. Compared to claim 14 as granted from which it was derived, the amendment introduced into claim 9 was not a limitation. Rather, its subject-matter was an *aliud* and the scope of protection conferred by the amended claim extended beyond that of the patent as granted. While in claim 14 as granted there was a clear reference to the input dsRNA, amended claim 9 referred to the output dsRNA, i.e. the 21-23 nt dsRNA. The same applied, *mutatis mutandis*, to amended claims 10, 12 and 13 when compared to claims 15, 17 and 18 as granted.

Article 84 EPC - clarity

The passage on column 2, lines 5 to 8 of the adapted description which specified RNA of from about 21 to about 23 nucleotides caused an inconsistency and a lack of clarity. As there was no indication in claim 3 that the double stranded RNA molecule used was not one which was produced by the "method of the invention", it was evident that the dsRNA in claim 3 was not really limited to a length of precisely 21 to 23 nucleotides.

Article 83 EPC - sufficiency of disclosure

The invention as claimed in claim 3 was not sufficiently disclosed in the application as filed. In the patent and the experiments described in document (6) the same soluble extract was used. However, as apparent from page 3194, right column, last sentence of document (6), a 49 bp dsRNA was not effective in generating a dsRNA molecule which mediates RNA interference. Thus, either particular reaction conditions were required, or successful performance of the invention depended on chance.

Article 87 EPC - priority

The subject-matter of amended claim 3 did not enjoy the priority of an earlier US application filed on 30 March 2000, because the amendments introduced into claim 3 did not conform to Article 123(2) EPC. Moreover, the earlier application suffered in terms of enablement of the same shortcomings as the patent in dispute. For this reason, the priority of 30 March 2000 could not be validly claimed.

Article 54 EPC – novelty

Document (23)

The subject-matter of claim 3 lacked novelty over document (23), which constituted prior art under Article 54(3)(4) EPC 1973. The L-dsRNA described in this document was a double stranded RNA of from 21 to 23 nucleotides in length. It was used for specifically inactivating gene function. As apparent from Figure 4e, no YFP fluorescence could be observed upon administration of the dsRNA molecule to a cell containing an mRNA coding for YFP.

The teaching of document (23) had been incorrectly represented in the decision under appeal. In view of the disclosure on page 3, lines 23 to 25, which referred to the interferon response, it was evident that document (23) related to RNA interference and that the 21 nt double stranded RNA was actually effective in gene silencing. It was irrelevant to the assessment of novelty that Example 2 of document (23) did not demonstrate degradation of mRNA. First, there was no requirement under the EPC that a novelty-destroying document provided experimental evidence. Second, the sole condition required for RNA interference to occur was a double stranded RNA of a length within certain ranges and having a certain degree of complementarity to the target mRNA. Since this condition was fulfilled by the L-dsRNA molecule, there was no need to show that any mRNA degradation actually occurred.

Document (27)

The content of document (27) was prejudicial to the novelty of claim 3. This document described RNA

molecules which were active as antisense molecules and thus suitable for mediating the degradation of a targeted mRNA. As is apparent from Figure 1, the RNA molecules consisted of two distinct regions, the first region hybridizing to the target sequence and the second being self-complementary. The length of the first region ranged from 8 to 50 nucleotides in length. Assuming that 4 nucleotides would be required for the "hinge", a base-paired double strand of 23 bp would be formed. A method of inhibiting gene expression using such a dsRNA was the subject-matter of claims 15 and 16 of document (27).

Article 56 EPC – inventive step

The subject-matter of claim 3 did not involve an inventive step in view of document (24) as the closest state of the art, combined with document (28). The sole difference between the method of claim 3 and that described in document (24) was the use of a dsRNA of 21 to 23 nucleotides in length. The problem to be solved could be formulated as providing a method for the inhibition of the expression of a given target gene using a double-stranded RNA structure with one strand having a region which is complementary to a target gene, which imposes less efforts in the manufacturing process. From page 9, lines 11 to 29 of document (28), a person skilled in the art could derive that a dsRNA having at least 10 consecutive nucleotides could generate an effective inhibition of the expression of a given target gene.

Alternatively, the skilled person could combine document (24) with document (29) which stressed that shorter oligodeoxyribonucleotides with specific

secondary structure would be desirable as potential antagonists to target nucleic acid-binding proteins.

XII. The submissions by the respondents, insofar as they are relevant to the present decision, may be summarised as follows:

Article 123(2) EPC - added matter

The feature "double stranded RNA" in claim 3 had a basis on page 4, lines 14 to 20; page 2, lines 16 to 18 and 22 to 30 of the application as filed. The definitions in these passages were not restricted to one specific aspect of the invention. Further support could be found on page 16, line 22 to page 17, line 13, Figures 14B, 15 and 16, and Example 5.

It was clearly and unambiguously derivable from the passage on page 16, line 22 to page 17, line 13, in particular on page 16, lines 25 and 26 that the dsRNA corresponded to a sequence of a gene. If the dsRNA corresponded to an mRNA, as disclosed on page 17, lines 1 to 13, then it necessarily also corresponded to the sequence of a gene, since the mRNA was transcribed from the gene.

Article 123(3) EPC - extension of the scope of protection

The scope of protection had not been extended. To the extent that claim 14 as granted was considered ambiguous, it could refer to the input RNA or the output RNA. The skilled person would note that page 14, lines 6 and 7 of the application as filed indicate that the 21-23 nt RNA molecules of the invention can also comprise a 3' hydroxyl group.

Article 83 EPC – sufficiency of disclosure

The requirements of Article 83 EPC were fulfilled. Claim 3 did not mention any soluble extract. There were no serious doubts substantiated by verifiable facts that the use of 21 to 23 nt dsRNA for inducing RNA interference was insufficiently disclosed.

Article 87 EPC – priority

The subject-matter of claim 3 was disclosed on page 3, lines 14 to 19; page 2, lines 3 to 16, and page 11, line 18 to page 12, line 17, as well as claim 16 of the earlier US application filed on 30 March 2000. Thus, the priority was valid.

Article 54 EPC – novelty

Document (23)

The subject-matter of claim 3 was novel in view of document (23). While claim 3 required that the claimed method involves mRNA degradation, in Example 2 of document (23) only inhibition of gene expression was referred to. As stated in decision T 59/87 (OJ EPO 1991, 561), a line had to be drawn between what is in fact made available to a skilled person reading the application, and what remains hidden or otherwise has not been made available.

There was no clear and unambiguous disclosure in document (27) of a double stranded RNA molecule of from 21 to 23 nucleotides in length, nor of methods involving mRNA degradation by such a double stranded molecule. Hence, claim 3 was novel.

Article 56 EPC - inventive step

The subject-matter of claim 3 was inventive over document (24) combined with document (28). Document (24) did not disclose the use of 21 to 23 nt dsRNA to mediate RNA interference or mRNA degradation. A motivation to specifically arrive at the use of such dsRNAs to mediate RNA interference, or a suggestion that such dsRNAs may be tried, was not provided in document (28). The suggestion of a paired region of at least 10 consecutive nucleotides was insufficient to lead the skilled person to a 21 to 23 nt dsRNA, particularly when the examples in document (28) made use only of significantly longer molecules for reducing gene expression. Similarly, document (29) made no mention of shortening dsRNA for use as a mediator of RNA interference.

XIII. The appellant (opponent 02) requested in writing that the decision under appeal be set aside and the patent be revoked.

XIV. The respondents (patent proprietors) requested that the appeal be dismissed.

Reasons for the Decision

Article 123(2) EPC - added matter

1. In the decision under appeal, the opposition division found that the subject-matter of the amended claims according to the main request does not extend beyond the content of the application as filed. These findings were contested by the appellant only insofar as they related to amended claim 3, in particular as regards

the features "***double stranded** RNA of from 21 to 23 nucleotides in length*" and "*corresponding to a sequence of the gene*" (see section XI above).

2. Amended claim 3 is derived from claim 17 of the application as filed, which is directed to a method of mediating RNA interference of mRNA of a gene in a cell (or organism) by (a) introducing RNA from about 21 to about 23 nucleotides which targets the mRNA of the gene for degradation into the cell (or organism), and (b) maintaining that cell (or organism) under conditions under which degradation of the mRNA occurs. While claim 17 of the application as filed does not specify that the introduced RNA is double-stranded, it is stated on page 2, lines 22 to 24 of the application as filed that:

> "*As used herein, the terms RNA, RNA molecule(s), RNA segment(s) and RNA fragment(s) are used interchangeably to refer to RNA that mediates RNA interference.* ***These terms include double-stranded RNA****, single-stranded RNA,...*" (emphasis added by the board).

3. The wording "*As used herein*" is often found in patent documents with the meaning "as used in this application/patent". Accordingly, a person skilled in the art reading the passage of the application as filed quoted above understands that the definition in lines 22 to 24 applies not only to the isolated RNA molecules described in lines 16 to 22 of the same page, but to any RNA mentioned in connection with other aspects of the disclosed invention, including a method of mediating RNA interference as defined in claim 17 and disclosed on page 4, lines 14 to 20 of the application. Contrary to the appellant's view, the fact

that the passages on page 2, lines 30 and 31 and page 3, lines 8 to 10 of the application as filed refer to, respectively, "*RNA molecules of the present invention*" and "*RNA molecules of about 21 to about 23 nucleotides*" without specifying that these molecules are double-stranded, is not in contradiction with the previous definition of the term RNA molecule as including, *inter alia*, dsRNA.

4. As regards the feature "*corresponding to a sequence of the gene*", the board concurs with the opposition division's view that a *verbatim* basis is found in the passage on page 16, lines 25 and 26 of the application as filed (see section 5.5.2 of the decision under appeal). The passage in question does not refer exclusively to the precursor dsRNA, but rather to any dsRNA that can be used in the invention, including the 21 to 23 nt dsRNA. This is apparent from the fact that dsRNA of 21 or 22 base pairs is mentioned in the same paragraph (see lines 28 and 31, respectively), and that dsRNA of this length is clearly disclosed in the application in connection with a method for mediating RNA interference (see, e.g., page 17, lines 1 to 3).

5. For the sake of completeness, the board observes that it can be derived from the statements on page 16, lines 25 to 31 read in connection with those on page 13, lines 24 to 28, and page 3, lines 20 to 23 of the application as filed, that the dsRNA may be complementary to mammalian cellular mRNA or viral mRNA. Hence, also the findings in the decision under appeal concerning claim 13 are considered to be correct.

6. For these reasons, the appellant's objections to the findings on Article 123(2) EPC in the decision under appeal fail to convince the board.

Article 123(3) EPC - extension of the scope of protection

7. In the decision under appeal, the opposition division found that the amendments introduced into claims 9, 10, 12 and 13 did not result in the protection conferred by the patent as granted being extended (see section 4.3 of the decision). This finding has been contested by the appellant.

8. Claim 14 of the patent as granted, from which present claim 9 is derived, does not specify whether the dsRNA comprising a terminal 3' hydroxyl group is the input (i.e. precursor) dsRNA specified in claim 1, step (a), or the 21 to 23 nt dsRNA produced by the method of claim 1 and used in the method of claim 3. As far as claim 14 of the patent as granted depends on claim 4 (or claims 5, 6, 8 and 9 referring to claim 4), it is clear that only the 21-23 nt dsRNA can be meant, as this is the sole dsRNA species mentioned in those claims. In contrast, as far as claim 14 of the patent as granted depends on claims 1 to 3, it must be interpreted as referring to either the input dsRNA **or** the produced dsRNA of from 21 to 23 nucleotides in length, as both are mentioned in claims 1 to 3. The same applies, *mutatis mutandis*, to amended claims 10, 12 and 13, which are derived from, respectively, claims 15, 17 and 18 of the patent as granted.

9. By the amendment introduced into the present claims 9, 10, 12 and 13, the double stranded RNA is defined as having from 21 to 23 nucleotides in length. Since this is, contrary to the appellant's view, in fact a limitation compared to claim 14 as granted, in which the input dsRNA was also included, the amendment does not result in an extension of the scope of protection

conferred by the claims of the patent as granted from which they are derived. Therefore, the objection that the amendment contravenes Article 123(3) EPC cannot be accepted.

Article 84 EPC - clarity

10. The appellant contested the opposition division's adverse findings on an alleged inconsistency between the passage on column 2, lines 5 to 8 of the adapted description and the amended claims (see section 11.1 of the decision under appeal). The board shares the opposition division's view that there is no such inconsistency, in particular as regards claim 3. It should be noted that the passage indicated by the appellant relates to the small dsRNAs resulting from the processing of the input dsRNA, rather than to the dsRNA used in the method of claim 3. In any case, since the alleged non-compliance with Article 84 EPC does not arise from the amendments introduced into claim 3, it does not need to be considered (see decision G 3/14, OJ EPO 2015, 102, Order).

Article 83 EPC - sufficiency of disclosure

11. While the appellant did not contest the findings in the decision under appeal concerning Article 83 EPC (see section 10 of the decision), it raised an objection to claim 3 under Article 83 EPC relying on document (6) as evidence that a 49 nt dsRNA incubated with the same *Drosophila* soluble extract used in the examples of the patent in suit is not effective in mediating RNA interference.

12. The evidence on which the appellant relied does not support its objection. Claim 3 requires that the dsRNA

introduced into the cell is of from **21 to 23** nucleotides in length. Since a dsRNA of **49** nt in length as used in the experiment described in document (6) is clearly not within this range, the fact that such a dsRNA does not mediate RNA interference cannot be accepted as evidence that a person skilled in the art cannot carry out a method of mediating RNA interference according to the invention as defined in claim 3. Hence, the appellant's argument fails.

13. The appellant's further contention that the patent does not disclose the mechanism underlying RNA interference mediated by 21 to 23 nt dsRNA also fails, because there is no requirement under Article 83 EPC that the mechanism underlying an invention must be disclosed in the application as filed. As regards the objection that, at the filing date, the inventors were not in possession of the technical teaching of the claims, the appellant, except for pointing to paragraph 13 of the reasons of decision T 609/02 of 27 October 2004, did not put forward any arguments or evidence in this respect. The circumstances underlying decision T 609/02 (*supra*) differed substantially from those in the present case, because in that case the patent specification provided no evidence at all relating to the claimed invention, but only a vague indication of a possible medical use for a chemical compound yet to be identified. Hence, the *ratio decidendi* of T 609/02 (*supra*) is, in the board's view, not applicable to the present case.

14. In view of the evidence and arguments brought forward in appeal proceedings, the board has no doubts that the information provided in the application - supplemented by the common general knowledge in the field – enabled the skilled person to carry out the invention, without

applying inventive skills or being confronted with an undue burden of experimentation. Hence, the objection of lack of sufficient disclosure is not justified.

Article 87 EPC – priority

15. The findings in the decision under appeal on Article 87 EPC in respect of claim 3 were contested by the appellant by referring to the arguments it put forward in connection with Articles 123(2) and 83 EPC.

16. Claim 16 and the passages on page 2, lines 5 to 7; and page 3, lines 14 to 19 of the first priority application are literally identical to claim 17 and the passages of the application as filed which are regarded as basis for the feature "*double stranded RNA of from 21 to 23 nucleotides in length*" (see paragraphs 2 and 3 above in connection with Article 123(2) EPC). Moreover, the passage from line 21 on page 11 to line 2 on page 12 of the priority document is identical to that on page 16 of the application as filed, from which the feature "*corresponding to a sequence of the gene*" can be derived (see paragraph 4 above).

17. As regards the appellant's allegation that a method as claimed in present claim 3 is not sufficiently disclosed in the priority document, the board refers to the findings in connection with Article 83 EPC in paragraphs 12 to 14 above. Contrary to appellant's view, the fact that the earlier application does not include experimental evidence corresponding to Example 5 of the application as filed, cannot be considered to be prejudicial to the right to priority claimed for the patent as amended. In order for a right to priority to be valid, it is not required that the earlier application provides experimental evidence that the

disclosed invention in fact works (see decision T 903/05 of 30 August 2007, paragraphs 8 to 11 of the reasons).

18. For these reasons, the appellant's argument that the priority of the earlier application cannot be validly claimed for the method of claim 3 fails. Hence, document (23) constitutes prior art under Article 54(3) EPC 1973 which is relevant to the assessment of novelty of the claimed method, but cannot be considered for assessing whether the claimed method involves an inventive step.

Article 54 EPC - novelty

19. The appellant contested the findings in the decision under appeal as regards Article 54 EPC only as far as they concerned the novelty of claim 3 in view of either document (23) or document (27) (see section 8.5.2 of the decision).

20. Claim 3 defines an *in vitro* method of mediating RNA interference of mRNA in a cell. The mediation of RNA interference of mRNA in a cell is thus a technical feature of the claimed method (see decision G 6/88, OJ EPO 1990, 114, Order).

Document (23)

21. Document (23) describes a method of inhibiting the expression of a target gene by introducing into a cell a double stranded RNA molecule, one strand being complementary to at least a portion of the target gene over a stretch of no more than 49 consecutive nucleotides. In Example 2, the YFP gene encoding yellow fluorescent protein and a dsRNA molecule are

microinjected simultaneously into the cell nucleus of murine fibroblasts. After injection of either a dsRNA homologous to the YFP gene over a length of 315 bp (see page 17, lines 25 to 28 and SEQ ID NO: 5 in the Sequence Listing), or a dsRNA of 21 bp in length corresponding to a sequence of the YFP gene, in which the two strands of the dsRNA are linked to each other *via* a C18 linker (L-dsRNA; see page 18, lines 13 to 15), YFP fluorescence could not be detected (see Figures 4c and 4e, and the passage on page 20, lines 12 and 13, and 15 to 17, respectively). The authors then conclude:

> "*Dieses Ergebnis belegt, dass auch kürzere dsRNAs zur spezifischen Inhibition der Genexpression bei Säugern verwendet werden können, wenn die Doppelstränge durch chemische Verknüpfung der Einzelstränge stabilisiert werden*." (page 20, lines 17 to 21)
>
> [This result shows that shorter dsRNAs can be used to specifically inhibit mammalian gene expression, if the double strands are stabilized by chemically linking the single strands] (translation by the board)

22. The board shares the opposition division's view that document (23) does not disclose or even suggest – let alone provide any evidence - that the double stranded RNA of 21 nt in length having the two strands linked *via* a C18 linker (L-dsRNA) targets the YFP mRNA for degradation. In fact, the passage quoted above mentions only inhibition of gene expression, and the fact that the L-dsRNA is injected into the nucleus casts doubts as to whether the L-dsRNA could possibly mediate degradation of the YFP mRNA which is expected to be in

the cytoplasm. Therefore, the board concurs with the opposition division that it cannot be established beyond reasonable doubt from the information provided in document (23) that the reported lack of YFP fluorescence is due to the degradation of the YFP mRNA by the mechanism of RNA interference, rather than to a different silencing mechanism. Thus, the content of document (23) does not anticipate the subject-matter of claim 3.

Document (27)

23. Neither a dsRNA molecule of from 21 to 23 nucleotides in length, nor a method in which RNA interference is mediated by such a molecule can be derived, directly and unambiguously, from document (27). The oligonucleotides described in document (27) are proposed for use as antisense agents (see, e.g., page 1, lines 7 to 9, and page 5, lines 2 to 4), the double stranded region having the function of stabilizing the molecule and making it more resistant to nucleolytic degradation (see sentence bridging pages 8 and 9). Hence, the finding in the decision under appeal that document (27) is not prejudicial to the novelty of the method of claim 3 is considered to be correct.

Article 56 EPC - inventive step

24. In the decision under appeal (see section 9.2.4), the subject-matter of claims 1 and 3 (as well as that of the remaining claims which either depend on or refer to claim 1 or 3) was found to involve an inventive step within the meaning of Article 56 EPC. These findings were contested by the appellant only as far as they concerned claim 3.

25. The appellant relied on document (24) as the closest state of the art. This document describes methods of inhibiting the expression of a target gene by introducing into a cell an RNA molecule comprising a double stranded structure with a nucleotide sequence which is identical to a portion of the target gene. It is stated on page 11, lines 27 and 28 that the length of the identical nucleotide sequences may be at least 25, 50, 100, 200, 300 or 400 bases. It should be noted that these numbers characterize the length of the nucleotide sequence identical to the target gene, rather than the length of the RNA itself which may, in principle, be longer.

26. It is undisputed that the method described in document (24) differs from the method of present claim 3 in that the latter comprises introducing into the cell a dsRNA of from **21 to 23** nucleotides in length which mediates RNA interference.

27. The decision under appeal is silent about the objective technical problem to be solved starting from document (24) as the closest state of the art. According to the appellant, there are no advantageous technical effects linked to the use of a dsRNA of from 21 to 23 nt in length and, consequently, the problem to be solved can only be the provision of an **alternative** method of inducing RNA interference. This was disputed by the respondents which, at the oral proceedings, contended that the problem to be solved was the provision of a method for mediating RNA interference that does not provoke an interferon response in mammals.

28. Even if the board were to accept the problem to be solved as formulated by the appellant, the arguments and evidence on which it relied fail to convince the board that, at the priority date, it was obvious to a person skilled in the art seeking an alternative to the method of inducing RNA interference described in document (24) to reduce the length of the dsRNA to, specifically, 21 to 23 nt. A person skilled in the art, starting from document (24), could have possibly tried to induce RNA interference using a 25 nt dsRNA - as suggested in this document -, but had neither the motivation to try shorter dsRNA molecules, in particular dsRNA molecules of from 21 to 23 nt in length, nor a reasonable expectation that these molecules may induce RNA interference. It should be noted that the dsRNA molecules used in the examples of document (24) are several hundreds of nucleotides in length.

29. Document (28), which the appellant regarded as a pointer towards the method of the present invention, describes methods for reducing the phenotypic expression of a nucleic acid sequence in eukaryotic cells, in particular plant cells by introducing into a cell chimeric genes encoding sense and antisense RNA molecules which are, respectively, homologous and complementary to at least part of the nucleotide sequence of interest. The passage on page 9 lines 11 to 29 on which the appellant relied, relates to a method in which the chimeric genes are transcribed into a sense and an antisense RNA molecule, each including at least 10 consecutive nucleotides and having between 75% and 100% sequence identity with the gene and the complement of the gene, respectively. The sense and antisense RNA molecules are capable of forming a double

stranded, duplex RNA by base-pairing between the regions which are complementary.

30. A skilled person reading document (24) in combination with document (28) could, in principle, try to mediate RNA interference using a dsRNA of at least 10 nucleotides in length. However, there is no apparent reason why the skilled person would choose specifically a length of 21 to 23 nt, as neither document (24) nor document (28) give any hint that would motivate him/her to use a dsRNA of this length, let alone arouse a reasonable expectation of being able to induce RNA interference using such a dsRNA.

31. The appellant relied further on the teachings of document (24) combined with those of document (29). However, neither document (29) as a whole nor the passage quoted by the appellant in section 2.3.1 of its statement of grounds of appeal – which the board was unable to find in document (29) - contain any pointer to the specific solution proposed in claim 3.

32. As stated in paragraph 18 above, document (23), which constitutes prior art under Article 54(3) EPC 1973, cannot be considered for the assessment of inventive step. Thus, the appellant's line of argument relying on a combination of document (24) with document (23) cannot be accepted.

33. Summarising the above, the arguments put forward by the appellant in support of its objection that the method of claim 3 does not involve an inventive step, fail to convince the board.

Article 113(1) EPC - right to be heard

34. In its communication under Article 15(1) RPBA, the board expressed a provisional opinion on the issues to be discussed at the oral proceedings. The reasons given by the board in the present decision are essentially those given in the communication. The appellant neither replied in substance to the board's communication, nor attended the oral proceedings. Since the appellant had ample opportunity to make any submissions it wished in respect of the grounds and evidence on which the present decision is based, the provisions of Article 113(1) EPC are complied with.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Stridde B. Stolz

Decision electronically authenticated