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D E C I S I O N
of 20 April 2005

Case Number: T 0931/01 - 3.3.8

Application Number: 88901380.1

Publication Number: 0291533

IPC: C07H 17/02

Language of the proceedings: EN

Title of invention:
RNA ribozyme restriction endoribonucleases and methods

Patentee:
UNIVERSITY PATENTS, INC.

Opponent:
GENE SHEARS PTY LIMITED
Immusol Incorporated

Headword:
Ribozyme/UNIVERSITY PATENTS

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
"Added subject-matter - main and auxiliary requests - yes"

Decisions cited:
G 0001/03, T 0157/90

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0931/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 20 April 2005

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 13 June 2001 concerning maintenance of European patent No. 0291533 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent No. 0 291 533 with the title: "RNA ribozyme restriction endoribonucleases and methods" was granted with 13 claims on the basis of the international application No. PCT/US87/03161 published as WO 88/04300.

Originally filed claims 2, 12 and 44 read as follows:

"2. RNA enzyme wherein the enzymatic activity is selected from the group consisting of nucleotidyltransferase, dephosphorylase, and sequence specific endoribonuclease activities.

12. RNA ribonuclease enzyme wherein ribonuclease activity occurs at pH 5-9.0.

44. RNA endoribonuclease enzyme of claims 1-24 wherein activity is specific for single-stranded RNA."

II. Of the three oppositions which were filed, that of opponent 2 was later withdrawn. The grounds of opposition were failure to comply with the requirements of Article 123(2) EPC (Article 100(c) EPC), lack of novelty and inventive step (Article 100(a) EPC) and lack of sufficiency of disclosure (Article 100(b) EPC). The patent was maintained on the basis of the first auxiliary request then on file.

Claim 1 thereof read as follows:

"1. An enzymatic ribonucleic acid molecule which is capable of cleaving by transesterification a separate

RNA molecule at a predetermined phosphate ester bond in a single-stranded target nucleotide sequence within the separate RNA molecule, which enzymatic molecule consists of:

(i) a substrate binding portion of a wild-type self-splicing IVS RNA which is capable of binding with the target nucleotide sequence and the specificity of which is changed by altering its wild-type sequence; and

(ii) an enzymatic portion of said self-splicing IVS RNA having endonuclease activity independent of any protein in vitro;

wherein said enzymatic molecule can only cleave the single-stranded target sequence without forming a covalent bond between said enzymatic molecule and any portion of said separate RNA molecule."

Claims 2 to 5 related to further features of the enzymatic ribonucleic acid of claim 1 and claim 6 was directed to a method for specifically cleaving in vitro a separate RNA molecule at a target nucleotide sequence comprising contacting said molecule with the enzymatic ribonucleic acid molecule as defined in any one of claims 1 to 5 under specific conditions.

III. Appellants I and II (respectively, patentee and opponent 1) filed an appeal against this decision. Opponent 03 was party to the proceedings as of right. Both appellants submitted statements of grounds of appeal in due time and paid the appeal fee. Appellant I's statement of grounds of appeal was

accompanied by a new request to be considered as main request.

Claim 1 of the new main request read as follows:

"1. An enzymatic ribonucleic acid molecule which is capable of cleaving by transesterification a separate RNA molecule at a predetermined phosphate ester bond in a single-stranded target nucleotide sequence within the separate RNA molecule, which enzymatic molecule comprises:

(i) a substrate binding portion capable of binding with the target nucleotide sequence; and

(ii) an enzymatic portion having endonuclease activity independent of any protein in vitro, wherein said enzymatic molecule can only cleave the single-stranded target sequence without forming a covalent bond between said enzymatic molecule and any portion of said separate RNA molecule;

with the proviso that said molecule is not L-19 IVS-beta from *Tetrahymena thermophila* or L-19 IVS-beta with the guanosine-co-factor attached to the 5'-end."

IV. Appellants I and II each submitted observations on the other's statement of grounds of appeal.

V. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal, indicating its preliminary non-binding opinion.

VI. In its letter dated 18 March 2005, appellant I informed the board that it did not intend to attend oral proceedings.

VII. Appellant II sent a further submission in answer to the board's communication.

VIII. Oral proceedings took place on 20 April 2005. Opponent 3 was not present despite having been duly summoned.

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

(15): Tanner, N.K. and T.R. Cech, Abstract 177 of a paper presented at the 1986 meeting on RNA processing, May 14 to May 18, 1986, arranged by R.P. Perry, H.D. Robertson and S.M. Berget, Cold Spring Harbor Lab., Cold Spring Harbor, New York;

(81): Waring, R.B. and R.W. Davies, Gene, Vol. 28, pages 277 to 291, 1984;

(83): Cech, T.R. et al., Cell, Vol. 27, pages 487 to 496, December 1981 (Part 2);

(85): van der Horst, G. and H.F. Tabak, Cell, Vol. 40, pages 759 to 766, April 1985;

(86): Chu, F.K. et al., J. Biol. Chem., Vol. 260, No. 19, pages 10680 to 10688, September 1985.

X. Appellant I's written arguments insofar as relevant to the present decision may be summarised as follows:

Article 123(2) EPC
Main request, claim 1; allowability of the disclaimer

The opposition division had found the disclaimer allowable under Article 123(2) EPC because its purpose had been to exclude from the scope of the claim molecules disclosed in document (15) which happened to be an accidental anticipation of the claimed subject-matter under Article 54(2) EPC. These findings were correct and should be followed by the board.

Auxiliary request, claim 1

The subject-matter of claim 1 was a generalisation from the exemplified Tetrahymena L-19 IVS-beta RNA enzyme to RNA enzymes with the same characteristics. It had a basis in the application as filed for the following reasons:

- The skilled person would be well aware that the invention did not concern the discovery of a particular RNA structure but the unexpected finding that it was possible to prepare RNA enzymes which had sequence-specific endoribonuclease activities.

- Originally filed claims 2, 12 and 44 (referring to RNA enzymes having endoribonuclease activities) provided an explicit disclosure of a generalisation from the Tetrahymena ribozyme to any potential class of ribozymes.

- The functional features exemplified for the Tetrahymena IVS RNA could be transferred to

substantially different RNA molecules such as group II introns and, therefore, to any potential class of ribozymes. This was supported by and confirmed in the last two sentences on page 32, third paragraph of the application as filed.

- Others in the field had followed the teachings of the patent to generate further RNA-cleaving enzymatic RNA molecules from self-cleaving RNA introns.

- In accordance with the case law, it was not necessary to provide examples for each and every embodiment that was covered by the teaching of an invention. This case law which was established in relation to Article 83 EPC could equally be applied under Article 123(2) EPC.

For these reasons, the requirements of Article 123(2) EPC were fulfilled.

XI. Appellant II's arguments in writing and during oral proceedings insofar as relevant to the present decision may be summarised as follows:

Article 123(2) EPC
Main request, claim 1; allowability of the disclaimer

Claim 1 contained a disclaimer to exclude from the scope of the claim molecules disclosed in document (15) which was state of the art under Article 54(2) EPC. This document was concerned with the self-splicing activity of the Tetrahymena IVS RNA and also with the effect of beta-elimination on the capacity of the molecule to form covalent bonds, ie with the mechanisms which were at the basis of the presently claimed

invention. It could not have been ignored by the skilled person interested in enzymatic RNA molecules and, thus, it was not to be considered as an accidental anticipation of the claimed subject-matter. Consequently, in accordance with the case law, the disclaimer was not allowable under Article 123(2) EPC.

Auxiliary request, claim 1

The application as filed (pages 26 to 31) disclosed a specific enzymatic RNA molecule: L-19 IVS-beta with the following characteristics:
- it comprised a substrate-binding portion and enzymatic portion originating from the Tetrahymena wild-type, self-splicing IVS RNA,
- it exerted its endoribonuclease activity without forming a covalent bond with its RNA substrate, and
- its substrate-binding portion could be altered so as to change the specificity of the cleavage reaction.

The subject-matter of claim 1 was a generalisation from this specific teaching to any and all enzymatic RNA molecules having the above mentioned features, yet there was no basis in the application as filed for such a generalisation. In this respect, Appellant I had made reference to the third passage on page 32 but this passage had no technical content.

In accordance with the case law (T 157/90 of 12 September 1991), a generalisation of a feature expressly mentioned in the application as filed could not be allowed if it had only "formal" support inasmuch as the technical teaching disclosed in said application related to the one feature which was disclosed.

In the present case, the application as filed (page 32) provided evidence by reference to the work of Waring and Davies (document (81) on file) that not all of the wild-type VIS RNA had a defined substrate-binding portion. This implied that the technical teaching relating to Tetrahymena IVS RNA - a recognisable substrate binding portion which might be altered - could not generally be applied. In addition, there was no evidence that enzymatic RNA molecules could be derived from the wild-type IVS RNAs other than that of Tetrahymena. Finally, the feature that the enzymatic molecule would be unable to form a covalent bond with its target substrate which, in L-19 IVS-beta RNA, resulted from the molecule having lost its terminal G was not transferable to other IVS RNAs such as that of Neurospora crassa which ended in A rather than G.

As for the argument that the subject-matter of originally filed claims 2, 12 and 44 provided a basis for the claimed enzymatic RNA molecules, it was even less convincing as none of these claims referred to RNA enzymes having the features now claimed.

Accordingly, the generalisation in claim 1 had no support in the application as filed and, thus, was not allowable under Article 123(2) EPC.

XII. Opponent 3 did not make any substantive submissions at any point during the appeal proceedings.

XIII. Appellant I requested that the decision of the opposition division be set aside and that the patent be maintained on the basis of the main request filed with

the grounds of appeal or, in the alternative, that the appeal filed by appellant II be dismissed.

Appellant II requested that the decision under appeal be set aside and that the European patent No. 0 291 533 be revoked.

Reasons for the decision:

Article 123(2)EPC
Main request, claim 1, admissibility of the disclaimer

1. Document (15) is an abstract of a presentation made at a meeting which took place between 14 and 18 May 1986. It, thus, is state of the art pursuant to Article 54(2) EPC. It describes results obtained while studying the self-splicing **IVS** RNA from Tetrahymena thermophila. It is shown that under cyclisation conditions, the self-splicing IVS RNA is cleaved to shorter forms respectively lacking 15 and 19 nucleotides: L-15 IVS RNA and **L-19 IVS** RNA. Another possible modification of the self-splicing IVS RNA is the elimination of the 3' terminal guanosine via a mechanism involving oxidation and beta-elimination to give **IVS-beta** RNA. Like the IVS RNA, the IVS-beta RNA is cleaved in the presence of free guanosine and under cyclisation conditions into shorter RNA molecules. It was never in dispute that one of the shorter molecules thus obtained is **L-19 IVS-beta** RNA ie the enzymatic ribonucleic acid molecule described on page 38 of the application as filed to illustrate the invention.

2. In claim 1, an attempt was made to delimitate the claimed subject-matter from the teaching of document (15) by introducing into the claim the disclaimer:

"...with the proviso that said molecule is not L-19 IVS-beta from Tetrahymena thermophila *or L-19 IVS-beta with the guanosine-co-factor attached to the 5'-end".*

3. In accordance with the Enlarged Board of Appeal decision G 1/03 (OJ EPO 2004, 413, point 2.1 of the Order), "a disclaimer may be allowable in order to restore novelty by delimiting a claim against an accidental anticipation under Article 54(2) EPC; an anticipation is accidental if it is so unrelated to and remote from the claimed invention that the person skilled in the art would never have taken it into consideration when making the invention."

4. In the present case, it is not possible to consider document (15) as an accidental anticipation as it is on the basis of the findings which it describes (more specifically, the mechanisms by which L-19 IVS-beta RNA is produced) that the present invention was developed. Thus, it is not a document of such a kind as may be disposed of by way of a disclaimer.

5. Claim 1 contains an unallowable disclaimer. Consequently, the main request is rejected under Article 123(2) EPC.

Article 123(2) EPC
Auxiliary request (claim request accepted by the opposition division), claim 1

6. The subject-matter of claim 1 is a generalisation from the Tetrahymena enzymatic L-19 IVS-beta RNA to RNA enzymes obtained from any class of RNA introns. Appellant I points, in particular, to the end of the second full passage on page 32 of the application as filed as a basis for this generalisation. This passage is part of a section entitled *"Variant Ribozymes (or other versions of the ribozyme that retain activity)"* where future work to be done with the L-19 IVS RNA is discussed, such as the identification of the regions necessary for endoribonuclease activity and the possibility to alter its cleavage specificity by mutagenesis. The entire passage reads as follows:

"Waring, R.B. and Davies, (1984) Gene 28: 277 show a class of IVS RNA molecules with similar structure. This work is similar to that of Cech, T.R., et al. (1983) Proc. Natl. Acad. Sci. USA 80: 3903 showing a class of fungal mitochondrial RNA IVS molecules. Some of these other IVS molecules have been found to be self-splicing. (Cech, T.R., et al. (1981) Cell 27:487; Kruger, K., et al. (1982) ibid. 31:147; Garriga, G., et al. (1984) ibid 39:631; Van der Horst, G., et al. (1985) ibid 40:759; Chu, F.K., et al. (1985) J. Biol. Chem. 260:10680; Peebles, C.L., et al. Cell in press; Van der Veen, R., et al., ibid. in press). Thus a series, or many series or class, or family of endoribonucleases from the same or other natural sources can be based on the work of the invention.

Those skilled in the art will be able to search out other RNA enzymes from various natural sources."

7. It cannot be denied that the last part of this passage ("*Thus, a series...can be based...")* which appellant I relies upon is very vaguely worded. Taken together with the information relating to Tetrahymena L-19 IVS RNA contained in the section as a whole, it could probably be considered as a disclosure of RNA enzymes having the claimed features **and** derived from L-19 IVS RNA, ie. obtainable **from Tetrahymena**. Yet, it is not prima facie an unambiguous disclosure of RNA enzymes having the claimed features **and** obtainable from IVS RNA sources **other than Tetrahymena**. Since the beginning of the paragraph mentions quite a few documents, it may be that, in light of the technical information they provide, the last part of the paragraph could nonetheless be regarded as a disclosure of RNA enzymes such as generically claimed.

8. Peebles et al., and Van der Veen et al., not having been published at the time the application was filed, need not be taken into consideration. The same is true of Cech et al., (document (83) on file) and of Kruger et al., (cited in document (85)), as both are concerned with Tetrahymena IVS RNA . Chu et al., (document (86) on file) reports the finding of an intron in the T4 phage thymidylate synthase gene and provides evidence in support of an RNA processing mechanism involving intron excision and splicing but it is wholly silent as to what this mechanism might be, let alone as to whether or not the intron RNA would, if modified, have enzymatic activity.

9. Van der Horst et al., (document (85) on file) and Garriga et al., (summarized in document (85), page 762, right-hand column) describe the self-splicing of yeast and Neurospora IVS RNAs. The similarities between the self-splicing mechanisms of both these molecules and that of Tetrahymena IVS RNA are discussed in detail in the "Discussion". It is also reported that other introns exist which are spliced by a different mechanism (Class II introns, page 763, right-hand column). These would not be expected to serve as starting molecules for producing RNA enzymes such as claimed.

10. Finally, Waring and Davies, (document (81) on file) teaches (page 289, right-hand column) that some introns belonging to the same class as the Tetrahymena IVS RNA may nonetheless differ in structure: the internal guide sequence (IGS) (corresponding to the substrate-binding portion in the RNA enzyme) is in some instances more diffuse, in others entirely lost. These do not have the characteristic feature (i) of the claimed RNA molecule.

11. Thus, even taking into account the documentary information which is cited in the application as filed, it must be concluded that the mere mentioning that a series or many series or class or family of endoribonucleases from other natural sources (than Tetrahymena) can be based on the work of the invention does not constitute an adequate basis on which to allow a generalisation from the Tetrahymena L-19 IVS-beta RNA to the claimed RNA enzymes.

12. As for originally filed claims 2, 12 and 44 (insofar as they relate to RNA enzymes as endoribonucleases), they do not mention any of the characteristics of the RNA endoribonucleases now claimed. They do not amount to a disclosure of the claimed subject-matter as is necessary for the requirements of Article 123(2) EPC to be fulfilled (eg. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition, pages 197 to 201).

13. One of appellant I's further arguments under Article 123(2) EPC was that the skilled person would, as a matter of fact, understand the invention as being directed to more than a particular RNA molecule. The board would agree that being aware of the endoribonuclease activity of Tetrahymena L-19 IVS-beta RNA, he/she could envisage that this teaching might be extendable to other RNA introns. However, such a mere observation cannot amount to acceptable evidence for the purpose of Article 123(2) EPC. What is required under this article is that the subject-matter of the European patent be disclosed in the application as filed. As shown in points 6 to 12 supra, this is not the case.

14. Finally, appellant I referred to the case law relating to Article 83 EPC - to the effect that it was not necessary to provide examples of each and every embodiment which would fall within the scope of a claim - and argued that this case law applied equally under Article 123(2) EPC. The board cannot agree: whether or not a claimed subject-matter is reproducible on the basis of the information contained in a patent (Article 83 EPC) is an entirely different issue from

that of whether or not information present in a patent was also present in the corresponding application as originally filed (Article 123(2) EPC). Thus, the case law relating to Article 83 EPC simply can not be applied to Article 123(2) EPC.

15. The present findings not to allow a generic claim to RNA enzymes having the specific features of L-19 IVS-beta RNA (claim 1, parts (i) and (ii)) when only L-19 IVS-beta is described in the application as filed is in accordance with earlier case law on Article 123(2) EPC. T 157/90 (supra) was cited by appellant II in this respect. There, the issue was whether a claim to human calcitonin having one additional amino acid at its C-terminal end (irrespective of which one) could be allowed under Article 123(2) EPC when the application as filed only disclosed glycine as the additional amino acid to be used. The claimed generalisation was refused although the appellant had argued that the skilled person would, as a matter of fact, consider glycine to be representative of all amino acids.

16. For these reasons, the auxiliary claim request is rejected for failing to fulfil the requirements of Article 123(2) EPC.

Order:

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

G. Röhn L. Galligani