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**Datasheet for the interlocutory decision  
of 25 June 2010**

**Case Number:** T 1068/07 - 3.3.08

**Application Number:** 98920015.9

**Publication Number:** 0981646

**IPC:** C12Q 1/68

**Language of the proceedings:** EN

**Title of invention:**  
Enzymatic DNA molecules

**Applicant:**  
THE SCRIPPS RESEARCH INSTITUTE

**Headword:**  
Enzymatic DNA/SCRIPPS

**Relevant legal provisions:**  
EPC Art. 123(2)

**Keyword:**  
"Main request and auxiliary request I - added subject-matter (yes)"  
"Auxiliary requests II and III - disclaimer"  
"Referral to the Enlarged Board of Appeal - yes"

**Decisions cited:**  
G 0001/03, G 0002/03, G 0001/07, T 1050/99, T 1139/00,  
T 0795/05, T 1107/06

**Catchword:**  
Question referred to the Enlarged Board of Appeal:  
"Does a disclaimer infringe Article 123(2) EPC if its subject-matter was disclosed as an embodiment of the invention in the application as filed?"



Case Number: T 1068/07 - 3.3.08

**I N T E R L O C U T O R Y   D E C I S I O N**  
of the Technical Board of Appeal 3.3.08  
of 25 June 2010

**Appellant:**

THE SCRIPPS RESEARCH INSTITUTE  
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**Representative:**

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**Decision under appeal:**

Decision of the Examining Division of the  
European Patent Office posted 2 February 2007  
refusing European patent application  
No. 98920015.9 pursuant to Article 97(1) EPC  
1973.

**Composition of the Board:**

**Chairman:** L. Galligani  
**Members:** P. Julià  
D. S. Rogers

## Summary of Facts and Submissions

- I. The applicant (appellant) lodged an appeal against the decision of the examining division dated 2 February 2007, whereby European patent application No. 98 920 015.9, published as International patent application WO 98/49346 (referred to in this decision as "*the application as filed*"), was refused.
- II. The decision was based on a main request and a first auxiliary request. The examining division considered that both requests did not to fulfil the requirements of Article 123(2) EPC because the application as filed provided no basis for the disclaimers introduced in claim 1. It was held that the said disclaimers did not meet the criteria laid down by the Enlarged Board of Appeal in decision G 1/03 (OJ EPO 2004, page 413) because prior art document D1 (WO 96/17086), which disclosed the subject-matter of these disclaimers and thus belonged to the same technical field of the application, was not so unrelated and remote from the claimed invention to be considered as an accidental anticipation.
- III. A notice of appeal and the statement setting out the appellant's grounds of appeal were filed. The appellant requested to grant a patent on the basis of the main request or the auxiliary request I before the examining division.
- IV. The board summoned the appellant to oral proceedings and, in a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) (OJ EPO Supplement to Official Journal 1/2010, 29)

annexed to the summons, informed the appellant of its preliminary, non-binding opinion on the substantive issues of the appeal proceedings.

V. The appellant replied to the board's communication and filed auxiliary requests II and III.

VI. Appellant's **main request** contained 46 claims, wherein claim 1 read as follows:

"1. A catalytic DNA molecule having site-specific endonuclease activity specific for a nucleotide sequence defining a cleavage site in a preselected substrate nucleic acid sequence, said catalytic molecule having first and second substrate binding regions flanking a core region, said molecule having the formula:



wherein

each X is any nucleotide sequence,  
(X-R) represents said first substrate binding region,  
(X) represents said second substrate binding region,  
R is a nucleotide capable of forming a base pair with a pyrimidine in the preselected substrate nucleic acid sequence,

T<sup>8</sup> may be replaced by C or A,

said first substrate binding region having a sequence capable of binding through complementary base-pairing to a first portion of said preselected substrate nucleic acid sequence,

said second substrate binding region having a sequence capable of binding through complementary base-pairing to a second portion of said preselected substrate nucleic acid sequence,

wherein the first substrate binding region does not have the sequence 5' CTTTGGTTA 3' or 5' CTAGTTA 3', wherein the second substrate binding region does not have the sequence 5' TTTTTC 3' and wherein the said catalytic DNA molecule does not show site-specific endonuclease activity for the sequence:

5' - GGAAAAGUAACUAGAGAUGGAAG - 3' (SEQ ID NO 135)."

Claims 2 to 23 related to embodiments of claim 1. Claims 24 and 25 were directed to a composition comprising two or more populations of catalytic DNA molecules according to claim 1, wherein each population of catalytic DNA molecules was capable of cleaving a different nucleotide sequence in a substrate (claim 24) or of recognizing a different substrate (claim 25). Claims 26 to 29 concerned a method of cleaving a target nucleic acid molecule using a catalytic DNA molecule according to claim 1. Claims 30 to 46 related to a method of engineering a catalytic DNA molecule that cleaved a preselected substrate nucleic acid sequence in a target nucleic acid molecule comprising the steps of selecting a substrate nucleic acid sequence of from 10 to 26 nucleotides in length in a target nucleic acid molecule and synthesizing a deoxyribonucleic acid molecule comprising first and second substrate binding regions flanking a core region, wherein said molecule had the formula of claim 1.

VII. Appellant's **auxiliary request I** read as the main request, except for the deletion of claims 2 and 3 of the main request and the incorporation of the subject-matter of claim 2 ("R" representing A or G) into claim 1.

VIII. Appellant's **auxiliary requests II and III** read as the main request, except that the final portion of claims 1 and 30 reading "wherein the first substrate binding region does not have the sequence [...] (SEQ ID No. 135)" was replaced by a disclaimer which in Auxiliary request II read:

"... with the proviso that said catalytic molecule is not a molecule in which the first and second binding regions can bind through complementary base-pairing to a substrate nucleic acid which is:

5' - GGAAAAAGUAACUAGAGAUGGAAG - 3' (SEQ ID NO 135).";

and in auxiliary request III read:

"... with the proviso that said catalytic molecule is not a molecule which shows site-specific intermolecular catalytic cleavage of the substrate:

5' - GGAAAAAGUAACUAGAGAUGGAAG - 3' (SEQ ID NO 135)

under conditions of 2 mM MgCl<sub>2</sub>, 150 mM KCl, pH 7.5, 37°C, for a rate of about  $k_{\text{cat}} = 0.01 \text{ min}^{-1}$ ."

IX. Oral proceedings took place on 25 June 2010.

- X. The submissions made by the appellant may be summarized as follows:

*Article 123(2) EPC*

*Main request and auxiliary request I*

The positive features of claim 1, namely a catalytic core and the substrate binding sequences flanking the 5' and 3' regions of this catalytic core, defined a generic class of catalytic DNA molecules designated "10-23" in the application as filed (class A molecules). The substrate binding sequences could be any nucleotide sequence (X-R) and (X), except those recited in claim 1 in the form of negative features. Claim 1 also excluded catalytic DNA molecules with site-specific endonuclease activity for the SEQ ID NO 135 sequence. These negative features corresponded to those defining the prototype "10-23" enzymes described in Example 5 of the application as filed which were a sub-class (sub-class B molecules) of the more generic class A molecules. In the decision under appeal, the examining division considered claim 1 to be directed to "class A minus sub-class B molecules" and, since there was no indication in the application as filed that the "sub-class B molecules" were to be excluded, the negative features in claim 1 were considered to have no basis under Article 123(2) EPC. However, the examining division also acknowledged that Example 6 of the application disclosed a second sub-class of molecules of the more generic class A molecules, namely the "further derivatives" (sub-class C molecules). Thereby, it was acknowledged that class A and sub-classes B and C were all disclosed in the application as filed.

The appellant considered that claim 1 was directed to the sub-class C molecules of Example 6. The support or basis for the negative features of claim 1 did not come from an explicit statement in the application as filed that the sub-class B molecules were to be excluded, but rather from an explicit disclosure of the sub-class C itself, namely on page 87, lines 1 to 3 and 24 to 28 together with Figures 8 and 9, where it was stated that further derivatives (sub-class C molecules) could be obtained by changing the substrate and the substrate binding sequences of the prototype "10-23" molecules shown in Figures 8 and 9. The substrate and the substrate binding sequences of the sub-class C molecules were thus described in the application as filed in terms of what they were not, namely they had neither the substrate nor the substrate binding sequences of the prototype "10-23" molecules. The claimed molecules were not prototype "10-23" molecules and they did not have the same substrate sequence of these prototype "10-23" molecules. They had site-specific endonuclease activity against a new, wide range of substrate sequences, unlike the prototype "10-23" molecules which had activity only against the single substrate sequence SEQ ID NO 135. The combination of the substrate and the binding sequences of the prototype "10-23" molecules shown in Figures 8 and 9 with the passages on page 87, lines 1 to 3 and 24 to 28 of the application as filed provided an explicit support for the negative features of claim 1.

Importantly, all the catalytic DNA molecules derived from the prototype "10-23" enzymes that were disclosed in Example 6 had substrate binding sequences different from those of the prototype "10-23" molecules and they



were active on substrate sequences different from that of the prototype "10-23" enzymes - as shown, for instance, in Table 4 of Example 6. The substrate sequence of the prototype "10-23" enzymes was disclosed in Example 5 and shown in Figures 8 and 9. This was the only substrate sequence used in Example 5 to exemplify the intermolecular cleavage reaction of the prototype "10-23" molecules. There was no reference to any other substrate sequence for the prototype "10-23" enzymes in that example. All references in Example 5 to other target sequences and to alterations and changes of the initial substrate nucleotide sequences were found, only and exclusively, within the context of self-cleavage reaction and of the method disclosed in the application as filed for generating and isolating (by rounds of amplification) suitable individual clones of catalytic DNA molecules, such as the exemplified prototype "10-23" molecules - as shown in Table 3.

In summary, the passage on page 87, lines 24 to 28 of the application as filed defined a sub-group of variants of the prototype "10-23" molecules (sub-class C molecules). When read in the light of Example 6 as a whole, this passage was a clear and unambiguous teaching to change the substrate-binding sequences of the enzyme with respect to those of the prototype "10-23" molecule in order to cleave substrates different from the prototype "10-23" substrate. This passage taught a process for producing catalytic DNA molecules active on substrate sequences different from that of the prototype "10-23" sequence by changing the substrate binding sequences of the prototype "10-23" enzyme in a complementary manner. The inevitable product of such a process was a generic subgroup or

sub-class of catalytic DNA molecules that differed from the prototype "10-23" enzymes in their substrate binding sequences and in the substrate they were capable of cleaving, i.e. the subject-matter of claim 1.

According to the established case law, the disclosure of a process inevitably resulting in a product which was not *per se* explicitly described, made available the product thus produced. For the purpose of Article 123(2) EPC, the amendment of a claim - by inclusion of a feature that was implicitly disclosed - was acceptable if the implicit disclosure was the clear and unambiguous consequence of an explicit disclosure. The catalytic DNA molecules claimed in the main request and in the auxiliary request I were disclosed as an implicit consequence of the explicit disclosure found in the passage on page 87, lines 24 to 28 of the application as filed. Therefore, the requirements of Article 123(2) EPC were fulfilled.

*Auxiliary requests II and III*

In both requests the disclaimer defined the catalytic molecules having the structure of the prototype "10-23" molecules disclosed as an embodiment of the invention in Example 5 and in Figures 8 and 9 of the application as filed. Such a disclaimer should be allowed when the approach of decisions T 1107/06 of 3 December 2008 and T 1139/00 of 10 February 2005 was followed, according to which the criteria laid down in decision G 1/03 (*supra*) did not apply to cases where the subject-matter to be excluded was originally disclosed as an embodiment of the invention. However, if the board intended to follow the approach adopted *inter alia* in

decision T 1050/99 of 25 January 2005, which considered disclaimers based on embodiments disclosed in the original application as being part of the invention to be undisclosed disclaimers in accordance with G 1/03 (*supra*), the attention of the board was drawn to the comments of the Enlarged Board of Appeal in its decision G 1/07 of 15 February 2010 (to be published in the OJ EPO), wherein the divergence in the case law on disclaimers in relation to disclosed embodiments was acknowledged (cf. point 4.2.3 of the Reasons). In the light thereof and before any decision adverse to the appellant was taken, a referral to the Enlarged Board of Appeal was requested. In this respect the following question was proposed by the appellant:

"1. Is an amendment to a claim by the introduction of a disclaimer unallowable under Article 123(2) for the sole reason that the subject matter excluded by it from the scope of the claim is disclosed in positive terms in the application as filed?."

XI. The appellant (applicant) requested that the decision under appeal be set aside and that a patent be granted on the basis of either the main request filed on 30 May 2005 or auxiliary request I filed on 19 December 2006 or auxiliary requests II or III filed on 25 May 2010, or that the question submitted at the oral proceedings be submitted to the Enlarged Board of Appeal.

## Reasons for the Decision

*Article 123(2) EPC*

*Main request and auxiliary request I*

1. In claim 1 of these two requests the catalytic DNA molecule is characterised by a number of positive features then limited by three negative features ("wherein [...] does not [...]") (cf. points VI and VII *supra*). For the latter the examining division found neither explicit nor implicit support in the application as filed. Moreover, it considered that, when seen as disclaimers, the features in question could not be allowed because they were not in line with the criteria laid down in G 1/03 (*supra*). Thus, the application was rejected under Article 123(2) EPC (cf. point II *supra*).
2. The appellant submits that the decision was incorrect. In its view, the subject-matter of claim 1 is disclosed as such in the application as filed. This includes the negative features, which although not explicitly disclosed, are nevertheless implicitly and unambiguously derivable from the original disclosure, in particular, from page 87, lines 1 to 3 and 24 to 28, Example 6 and Figures 8 and 9 (cf. point X *supra*).
3. Example 6 of the application as filed, which has the title "*Preparation of of (sic) a Universal Substrate Enzyme*", begins with a reference to the "*foregoing*" disclosure showing that an enzyme can be prepared having the ability to catalytically cleave target nucleic acids having preselected sequences, and ends with the statement "*(i)n addition, it is seen that the*

- substrate can be altered and an enzyme is prepared which can cleave that substrate" (cf. page 86, lines 5 to 13).*
4. The first paragraph on page 87 indicates that "(t)he following section describes the preparation of improved enzymes based on the "10-23" and the "8-17" motifs described above. These improved enzymes are generic enzymes which can cleave any preselected target sequence, and that target specificity depends solely on the sequence of the substrate binding regions of the enzyme, as described further herein". The reference to "any preselected target sequence" outlines the broad purpose of the example and certainly includes (i.e. it does not exclude) the target sequence or substrate molecule selected in Example 5 for generating and isolating (by intramolecular self-cleavage evolution) the prototype "10-23" motif as well as for measuring (by intermolecular cleavage reaction) its enzymatic activity, as shown in Figures 8 and 9 of the application as filed.
  5. On page 87, after a reference to Example 5 and to the cleavage mechanism of the prototype "10-23" motif and the resulting cleavage products, it is stated in lines 24 to 28 that "(f)or both the 8-17 and 10-23 motif enzymes, the sequence of the substrate can be changed without loss of catalytic activity, so long as the substrate-binding arms of the enzyme were changed in a complementary manner" (the "8-17" motif enzyme being another specific catalytic DNA molecule isolated in Example 5).

6. The appellant relies on this passage of the description as a form of positive support for the negative features used in limiting the definition of the claimed catalytic DNA molecule. This is because, in its view, changing the substrate of the "10-23" motif enzyme implies the exclusion from the ambit of protection of the specific substrate binding arms and the specific substrate sequence of said prototype molecule shown in Figures 8 and 9, this being effected by the three negative features in claim 1. The said view is allegedly further corroborated by the fact that all the enzymes derived from "10-23" disclosed in Example 6 (cf. Table 4) which have a substrate different from that of the "10-23" prototype also have arms which are different from this prototype. Under these circumstances, according to the appellant, the product of claim 1 is the implicit consequence of said explicit disclosure and thus, no issue under Article 123(2) EPC arises.
7. The board cannot agree with the appellant's reasoning. There is no explicit disclosure of any specific substrate in the passage referred to by the appellant nor an indication linking this substrate to that specifically illustrated in Figures 8 and 9. There is also no limitation or restriction as regards the nature and type of changes that may be introduced into the substrate or, in a complementary manner, into the substrate-binding arms of the prototype "10-23" motif enzyme. The passage in question is thus to be regarded as relating to a generic group of catalytic DNA molecules derived from the prototype "10-23" motif enzyme. Furthermore, the board considers that the passage in question has also to be understood within

the context and in the light of the information and teaching provided in Example 5 to which Example 6 makes reference.

8. Although in Example 5, the initial self-cleavage reaction used to generate and isolate the prototype "10-23" motif enzyme is then converted to an intermolecular cleavage reaction (by dividing the enzyme and the substrate domains into separate molecules) and, for that reaction, the specific substrate exemplified for the "10-23" motif enzyme is only that shown in Figures 8 and 9 (cf. page 84, line 2 to page 86, line 2), the example also explicitly contemplates the use of other alternative substrates. In the self-cleavage reaction, the target sequence (12 highly conserved nucleotides within the U5 LTR region of HIV-1 RNA) is actually found embedded in a longer substrate sequence which, as explicitly stated in Example 5, may optionally be altered. In fact, the exemplified substrate sequence derives from the originally given sequence (SEQ ID NO: 50) by adding an additional dA residue (cf. page 75, line 24 to page 76, line 10). Similar alterations, *"such as by length, nucleotide sequence, type of nucleic acid, and the like"*, are also addressed in a general way in Example 5, although admittedly only in the context of the self-cleavage reactions for generating enzymatic DNA molecules of alternative specificities (cf. page 83, line 2 to 24).
  
9. It may be argued that, in the absence of any explicit indication in Example 5, some of these substrate sequences might be considered, understood or seen by the skilled person as being also possible suitable

substrates for the prototype "10-23" motif enzyme in an intermolecular cleavage reaction (Figure 8 lends support to such a view by showing the presence of a certain degree of flexibility in the interaction between the substrate and the substrate binding arms through the standard Watson-Crick pairing). In any case, there can be no doubt that all these changes and alterations of the substrate sequence described in Example 5 may also be contemplated or comprised in the above passage relied upon by the appellant as providing a basis for the claimed subject-matter.

10. Thus, in the board's view, the disclosure of the passage in question embraces changes and alterations in the substrate of the prototype "10-23" motif enzyme that may not require any complementary change in any of the two substrate binding arms (when, for instance, shortening the 3' end or extending both the 5' and/or 3' ends of this substrate, changing the type of one nucleic acid, etc.) or at least in one of them. More substantial changes or alterations in the substrate may certainly require the introduction of substantial complementary changes in both or, at least in one, of the substrate binding arms. All these changes and, accordingly, all the resulting (sub)groups of catalytic DNA molecules, are implied by the generic disclosure on which the appellant relies.

11. Consequently, the exclusion through negative features from the ambit of protection of claim 1 of the specific (first and second) substrate binding arms and of the specific substrate sequence of the prototype "10-23" motif (cf. Figures 8 and 9) constitutes a selection within the broader outline of the changes proposed in



Example 6, in particular on page 87 lines 24 to 28. For this selection no direct and unambiguous support is found in the application as filed. For this reason, claim 1 in both requests under consideration offends against Article 123(2) EPC and the main request and auxiliary request I cannot be allowed.

*Auxiliary requests II to III*

12. In these two requests the negative features which characterised claim 1 of the preceding requests have been replaced by a disclaimer (cf. point VIII *supra*).
13. The appellant submits that in both cases the disclaimer is in conformity with the requirements of Article 123(2) EPC when the approach of e.g. T 1107/06 (*supra*) is adopted whereby a disclaimer does not infringe Article 123(2) EPC if its subject-matter is disclosed as an embodiment of the invention in the application as filed.
14. Indeed, in the two requests now under scrutiny the subject-matter of the disclaimer is disclosed as an embodiment of the invention because i) a catalytic molecule "in which the first and second binding regions can bind through complementary base-pairing to a substrate nucleic acid which is 5' - GGAAAAAGUAACUAGAGAUGGAAG - 3' (SEQ ID NO 135)" (cf. auxiliary request II) is described *inter alia* on page 85, lines 2 to 26 and Figure 9 of the application as filed;  
  
and ii) a catalytic molecule which shows site-specific intermolecular catalytic cleavage of the substrate

- 5' - GGAAAAAGUAACUAGAGAUGGAAG - 3' (SEQ ID NO 135)  
under conditions of 2 mM MgCl<sub>2</sub>, 150 mM KCl, pH 7.5, 37°C,  
for a rate of about  $k_{cat} = 0.01 \text{ min}^{-1}$  (cf. auxiliary  
request III) is described *inter alia* on page 87, lines  
13 to 18 and Figure 9 of the application as filed.
15. As observed in point 4.2.3 of G 1/07 (*supra*), following  
decisions G 1/03 (*supra*) and G 2/03 (OJ EPO 2004,  
page 448) which dealt with the issue of the so-called  
"undisclosed" disclaimers, different opinions have been  
expressed in the jurisprudence of the Boards of Appeal  
on whether the findings of said decisions relate also  
to the disclaiming of embodiments which are disclosed  
in the application as filed as part of the invention.  
Indeed, on the one hand, a series of decisions, by  
applying the notion of "undisclosed disclaimers", did  
not allow disclaimers based on such embodiments (cf.  
e.g. T 1050/99 (*supra*) and T 795/05 of 13 December  
2007). This approach has been adopted in the Guidelines  
for Examination (cf. Part C- Chapter III-16, point 4.20,  
April 2010). On the other hand, the decisions T 1107/06  
(*supra*) and T 1139/00 (*supra*) have adopted the approach  
whereby the criteria established in the decisions  
G 1/03 and G 2/03 (*supra*) do not apply and,  
consequently, a disclaimer can be allowed based on such  
"disclosed" embodiments.
16. In the present case, whether the first approach is  
followed rather than the second makes a decisive  
difference, as in the first case auxiliary requests II  
and III would have to be rejected under Article 123(2)  
EPC with the consequent dismissal of the appeal, while  
in the second case these requests would be considered

not to offend against Article 123(2) EPC and the decision under appeal could be set aside.

17. In view of the above, in the light also of Article 112(1)(a) EPC and Article 22 RPBA and in consideration of the express request of the appellant, this board considers it to be appropriate to refer a question to the Enlarged Board of Appeal.
18. A question in this respect has been put forward by the appellant (cf. point X, last paragraph, *supra*). However, the board prefers for reasons of the simplicity of its formulation, to refer *ex officio* the question of law as set out in the Order.
19. As the pending issue has already been abundantly treated from the legal point of view in the case law of the Boards of Appeal, the present board sees no need to carry out any further analysis for consideration by the Enlarged Board of Appeal.

**Order**

**For these reasons it is decided that:**

To refer ex officio the following question to the Enlarged Board of Appeal:

"Does a disclaimer infringe Article 123(2) EPC if its subject-matter was disclosed as an embodiment of the invention in the application as filed?"

The Registrar:

The Chairman:

A. Wolinski

L. Galligani