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**Datasheet for the decision  
of 11 September 2007**

**Case Number:** T 1697/06 - 3.3.08

**Application Number:** 94909629.1

**Publication Number:** 0804561

**IPC:** C12N 15/00

**Language of the proceedings:** EN

**Title of invention:**

Regulated transcription of targeted genes and other biological events

**Applicant:**

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,  
et al

**Opponent:**

-

**Headword:**

Transcription/STANFORD

**Relevant legal provisions:**

EPC Art. 83, 84

**Keyword:**

"Clarity and support in the description (yes)"  
"Sufficiency of disclosure (yes)"

**Decisions cited:**

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**Catchword:**

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Case Number: T 1697/06 - 3.3.08

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.08  
of 11 September 2007

**Appellant:** THE BOARD OF TRUSTEES OF  
THE LELAND STANFORD JUNIOR UNIVERSITY et al.  
Stanford  
California 94305 (US)

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**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 7 April 2006  
refusing European application No. 94909629.1  
pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairman:** F. Davison-Brunel  
**Members:** T. J. H. Mennessier  
C. Heath

## Summary of Facts and Submissions

- I. The applicant (appellant) lodged an appeal against the decision of the examining division of 7 April 2006 refusing the European patent application No. 94 909 629.1 with publication number 0 804 561. The application entitled "Regulated Transcription of Targeted Genes and Other Biological Events" originated from the international patent application published as WO 94/18317.
- II. In preparation for oral proceedings before the examining division, the appellant had filed on 13 June 2005 a main request and seven auxiliary requests. At the onset of these proceedings, the auxiliary requests were rejected by the examining division using its discretion under Rule 86(3) EPC because prima facie examination revealed that they contained the same defects as had been objected to during the written procedure. The decision under appeal is, thus, based on the sole main request filed with the letter of 13 June 2005. Reason for the refusal was non-compliance with the requirements of Articles 83 and 84 EPC in relation to claim 1.
- III. The main request of 13 June 2005 consisted of 30 claims.

Claims 1, 9, 10, 18 and 20 read as follows:

"1. A method for initiating a biological process in cells which comprises  
(a) providing cells containing and capable of expressing

(i) at least one DNA construct encoding a chimeric protein comprising

- (ia) at least one ligand-binding domain, capable of binding to a selected ligand, and
- (ib) a heterologous additional protein domain capable of initiating a biological process upon exposure to the ligand, said ligand being capable of binding to two or more chimeric protein molecules; and,

(b) exposing the cells to a non-protein, membrane permeable multivalent ligand which is capable of binding to the chimeric protein encoded by the DNA construct in an amount effective to result in oligomerization of two or more chimeric protein molecules, thereby initiating the biological process."

"9. The method of any one of claims 1 to 8 wherein the heterologous additional protein domain comprises:

- (a) a protein domain capable, upon exposure to the ligand, of initiating a detectable intracellular signal;
- (b) a DNA-binding protein; or
- (c) a transcriptional activation domain."

"10. The method of claim 9 wherein the intracellular signal is capable of activating transcription of a gene under the transcriptional control of transcriptional control element responsive to said oligomerization."

"18. A kit containing a first DNA construct encoding a chimeric protein containing at least one ligand-binding domain (capable of binding to a selected ligand) and a transcriptional activator domain; and a second DNA construct encoding a second chimeric protein containing

at least one ligand-binding domain (capable of binding to a selected ligand) and a DNA binding domain."

"20. The kit of claim 18 or 19, which further comprises a third DNA construct encoding a target gene under the control of a transcriptional control element containing a DNA sequence to which the DNA binding domain binds and which is transcriptionally activated by exposure to the ligand in the presence of the first and second chimeric protein."

Claim 2 was directed to "the method of claim 1 wherein the biological process is transcription of a target gene..."

- IV. The refusal was based on the finding that both the "ligand-binding domain" and the "ligand" as referred to in claim 1 were structurally undefined with the result that it would be an undue burden to isolate and characterise all binding partners, without any effective pointer to their identity. As regards the assessment of novelty, the decision contained only a mere statement which did not amount to a conclusive reasoning.
  
- V. On 14 June 2006, the appellant lodged an appeal against this refusal which was accompanied by the same main and seven auxiliary requests as filed with the petition dated 13 June 2005. The statement setting out the grounds of appeal was submitted on 17 August 2006.
  
- VI. The examining division did not rectify its decision and referred the appeal to the Board of Appeal (Article 109 EPC).

- VII. A communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal presenting some preliminary and non-binding views of the Board was sent to the appellant.
- VIII. In reply to the Board's communication the appellant filed further observations with a letter dated 10 August 2007 which were accompanied by a new main request and three new auxiliary requests.
- IX. At the oral proceedings which were held on 11 September 2007, the appellant filed a further request (claims 1 to 17) and withdrew all its previous requests.

Claims 1, 7, 13 and 15 read as follows:

- "1. A method for **activating the transcription of a target gene** in cells which comprises
- (a) providing cells containing and capable of expressing
    - (i) at least one DNA construct encoding a chimeric protein comprising
      - (ia) at least one ligand-binding domain, capable of binding to a selected ligand, and
      - (ib) a heterologous additional protein domain capable of initiating a biological process upon exposure to the ligand, said ligand being capable of binding to two chimeric protein molecules; and,
    - (ii) a target gene under the expression control of a transcription control element responsive to the oligomerization of said chimeric protein encoded by said DNA construct; and,

(b) exposing the cells to a ligand capable of binding to the chimeric protein encoded by the DNA construct in an amount effective to result in expression of the target gene,

**wherein said ligand has the formula:**

**linker-(rbm<sub>1</sub>,rbm<sub>2</sub>)**

**wherein rbm<sub>(1)</sub>-rbm<sub>(2)</sub> are receptor binding moieties which may be the same or different and which are capable of binding to the chimeric protein(s), said rbm moieties being covalently attached to a linker moiety which is a bi-functional molecule capable of being covalently linked ("-") to two rbm moieties, and wherein said ligand is a non-protein and is membrane permeable, and has a molecular weight of less than about 5 kDa."**

(the differences between this claim and claim 1 refused by the examining division are emphasized by the Board)

"7. The method of any one of claims 1 to 6 wherein the heterologous additional protein domain comprises:  
(a) a protein domain capable, upon exposure to the ligand, of initiating a detectable intracellular signal, **wherein the intracellular signal is capable of activating transcription of a gene under the transcriptional control of transcriptional control element responsive to said oligomerization;**  
(b) a DNA-binding protein; or  
(c) a transcriptional activation domain."

(emphasis added by the Board)

"13. A kit which comprises at least one DNA construct as defined in any one of claims 1 to 9 and which further comprises a ligand as defined in any one of claims 1 to 4."

"15. A kit containing a first DNA construct encoding a chimeric protein containing at least one ligand-binding domain (capable of binding to a selected ligand), and a transcriptional activator domain; a second DNA construct encoding a second chimeric protein containing at least one ligand-binding domain (capable of binding to **said** selected ligand), and a DNA binding domain; and a third DNA construct encoding a target gene under the control of a transcriptional control element containing a DNA sequence to which the DNA binding domain binds and which is transcriptionally activated by exposure to the ligand in the presence of the first and second chimeric protein, **wherein said ligand is a ligand as defined in any one of claims 1 to 4**"

(emphasis added by the Board)

Claims 2 to 6 were dependent on claim 1 and had essentially the same wording as claims 4 to 8 of the main request of 13 June 2005 (previous request).

Claims 8 to 12 were dependent on claim 1 and had the same wording as claims 11 to 15 of the previous request.

Claim 13 had the same wording as claim 16 of the previous request.

Claim 14 was dependent on claim 13 and had the same wording as claim 17 of the previous request.



Claims 16 and 17 were both dependent on claim 13 or 15 and had the same wording as claims 21 and 22 of the previous request.

- X. The submissions made by the appellant, insofar as they are relevant to the present decision, may be summarised as follows:

The present claims were clear and supported by the description. In particular, the ligand was unambiguously defined as a non-protein, membrane permeable compound of less than 5 kDa consisting of two receptor binding moieties covalently attached to a linker. The description including numerous examples and the figures, in particular Figure 15, provided a clear and complete disclosure enabling a skilled person to carry out the claimed method for activating the transcription of a target gene using a ligand and DNA constructs which could be part of the claimed kits.

- XI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the sole request as filed during oral proceedings.

### **Reasons for the decision**

1. The present request differs from the request on which the decision under appeal was based essentially in that (i) claims 1, 7 and 15 are amended versions of previous claims 1, 9 and 18 (compare sections III and IX, *supra*) and (ii) previous claims 23 to 30 have been deleted.

2. Compared to previous claim 1 as considered by the examining division, present claim 1 is no longer directed to a method for initiating a biological process in cells but to a method for activating the transcription of a target gene in cells and, furthermore, (ii) the ligand has been more precisely defined by the introduction of a formula and the indication that it has a molecular weight of less than about 5 kDa (as specified in previous claim 3).
3. Compared to previous claim 9, present claim 7 contains the additional technical feature found in previous claim 10 regarding the intracellular signal.
4. Compared with previous claim 18, present claim 15 has been limited by specifying that the ligand is as defined in any one of present claims 1 to 4 and that the kit contains a third DNA construct as referred to in previous claim 20.

*Article 123(2) EPC; added subject-matter*

5. The subject-matter of claims 1 to 17 finds a basis in the application as filed in the following way:
  - claim 1 is based on originally filed claim 30 in combination with originally filed claims 1 and 25 (depending on claim 24).
  - The subject-matter of claims 2 to 14 and 17 is found in, respectively, originally filed claims 26 to 28, 2, 3, 7 to 9, 11, 13, 31, 37, 38 and 41. The subject-matter of claims 15 and 16 is found in the two originally filed claims numbered 40.

6. The remark should be made that the above mentioned originally filed claims are not necessarily in the same category as the present claims, nor do they enjoy the same dependency. In the Board's judgement, however, the overall teaching of the application leaves no doubt as to the then claimed features being directly applicable to the now claimed methods and kits.
  
7. Therefore, the requirements of Article 123(2) EPC are met.

*Articles 84 and 83 EPC; clarity; support in the description, reproducibility*

8. As already above mentioned, the examining division refused claim 1 - and, consequently, the only request on file - for the reason that it failed to provide a clear definition of the term ligand. Present claim 1 differs from this previous claim in that the ligand has been further defined by specifying that it is a compound with a molecular weight of less than about 5 kDa consisting of two receptor binding moieties covalently attached to a linker moiety. The Board is, thus, satisfied that the matter for which protection is sought is clearly defined without the need of any additional characterisation of the ligand-binding domain of the chimeric proteins (Article 84 EPC, clarity).

9. The subject-matter of claim 1 is appropriately supported by the description which discloses in a generic manner different methods for activating transcription (e.g. page 14, line 20 to page 16) as well as examples illustrating said methods (Examples 4A and 4C) and also teaches in detail how to chemically synthesize suitable ligands (see pages 62 to 71) (Article 84 EPC, support in the description).
  
10. In other words, in the absence of any evidence to the contrary, the Board sees no reason to question the reproducibility of the method of claim 1 on the basis of the information contained in the description, including its numerous examples, and the figures, in particular Figure 15 (Article 83 EPC).
  
11. For these reasons, the Board comes to the conclusion that claim 1 satisfies the requirements of both Articles 84 and 83 EPC. This conclusion extends to claims 2 to 12 which are dependent on claim 1. It also applies to product claims 13 to 17 (kits of parts) in which the ligand is defined with reference to claim 1 and claims dependent thereon.
  
12. Therefore, the request as a whole meets the requirements of Articles 84 and 83 EPC.

**Order**

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

1. The appeal is dismissed.
  
2. The case is remitted back to the first instance for further examination on the basis of the sole request as filed in oral proceedings.

The Registrar:

The Chairman:

A. Wolinski

F. Davison-Brunel