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**Datasheet for the decision
of 16 October 2012**

Case Number: T 1176/09 - 3.3.08

Application Number: 02766356.6

Publication Number: 1435779

IPC: A01N 37/18, A01N 43/04,
C12N 5/00, C12N 15/63,
A01N 63/00, C07H 21/04,
C07K 1/00

Language of the proceedings: EN

Title of invention:
Modulation of stem cells using zinc finger proteins

Applicant:
Sangamo BioSciences, Inc.

Headword:
Modulation of stem cells/SANGAMO BIOSCIENCES

Relevant legal provisions:
EPC Art. 53(a), 54, 56, 83, 123(2)
EPC R. 28(c)

Keyword:
"Requirements of the EPC - met"

Decisions cited:
G 0001/03, G 0002/10, T 2464/10

Catchword:
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Case Number: T 1176/09 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 16 October 2012

Appellant: Sangamo BioSciences, Inc.
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 29 December 2008
refusing European patent application
No. 02766356.6 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: M. Wieser
Members: B. Stolz
R. Moufang

Summary of Facts and Submissions

- I. The appeal lies against the decision of the examining division to refuse European patent application EP 02766356.6 pursuant to Article 97(2) EPC.
- II. The examining division found that the main request before it did not comply with the requirements of Article 123(2) and lacked novelty (Article 54 EPC), that auxiliary requests I and II lacked novelty, and that auxiliary requests III to V lacked an inventive step (Article 56 EPC).
- III. With its grounds for appeal, the applicant (appellant) filed a main request and auxiliary requests I to VI.
- IV. The appellant was summoned to oral proceedings. A communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to the summons, informed it of the preliminary non-binding opinion of the board on some of the issues of the appeal proceedings.
- V. With letter dated 14 September 2012, the appellant filed a new main request and auxiliary requests I to XX.
- VI. Oral proceedings were held on 16 October 2012. In the course of the proceedings the appellant filed a new main request and withdrew all its previous requests.
- VII. The only independent claim of the main request, claim 1, reads:
"1. An in vitro method of altering the state of differentiation in an embryonic stem cell or

population of embryonic stem cells, comprising the step of administering one or more zinc finger proteins (ZFPs) wherein each ZFP has three DNA-binding domains

F1: RSDHLAR (SEQ ID NO: 2),

F2: TSGSLTR (SEQ ID NO: 3), and

F3: RSDNLAR (SEQ ID NO: 4),

which are designed and/or selected to bind to a target site in an endogenous gene which is OCT 3/4, wherein the ZFP alters the state of cellular differentiation, with the proviso that the cell or population of cells is no human embryonic stem cell or population of human embryonic stem cells."

Dependent claims 2 to 5 refer to preferred embodiments of the method of claim 1.

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

D2: Kang J. S. and Kim J.-S., 24 March 2000, "Zinc finger proteins as designer transcription factors", JBC, vol. 275, no. 12, 8742-8748,

D3: Beerli R. R. et al., 15 February 2000, "Positive and negative regulation of endogenous genes by designed transcription factors", PNAS vol. 97, no.4, 1495-1500,

D7: Niwa H. et al., April 2000, "Quantitative expression of Oct-3/4 defines differentiation, dedifferentiation or self-renewal of ES cells", Nature vol. 24, 372-376.

D8: Nordhoff V. et al., April 2001, "Comparative analysis of human, bovine, and murine Oct-4 upstream promoter sequences", Mammalian Genome vol. 12, 309-317.

IX. Appellant's arguments as far as relevant for the present decision can be summarized as follows:

The subject matter was novel and involved an inventive step. The examples sufficiently disclosed and supported the claimed subject matter. The disclaimer excluded subject matter which was excluded from patent protection.

X. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request.

Reasons for the decision

Admissibility of the main request

1. Claims 1 to 5 of the main request were filed at the oral proceedings. They are based on claims 1, 2, 4, 8 and 9 of auxiliary request XX, filed one month before oral proceedings, from which they are distinguished only by the deletion of two unclear and redundant repetitions in claim 1 and by adapting the dependencies in claims 4 and 5 (former claims 8 and 9).
2. Former auxiliary request XX has been filed by the appellant in response to the communication expressing the board's preliminary opinion, addressing issues

which were raised for the first time during appeal procedure.

Under these circumstances, the board decided to admit the main request (Article 13(1) RPBA).

Article 123(2) EPC

3. Compared to claim 1 as originally filed, claim 1 of the main request has been restricted to a method of altering the state of differentiation in an embryonic stem cell or population of embryonic stem cells, comprising the step of administering a ZFP characterised by three specific DNA-binding domains which bind to a target site in the oct-3/4 gene, and a disclaimer has been added, excluding human embryonic stem cells.
4. The claimed subject matter is disclosed in Example 1, describing the role of Oct-3/4 in embryonic stem cells, in combination with examples 2 to 4, demonstrating the effect of a ZFP with the claimed specific DNA binding domains in mouse embryonic stem cells.
5. By way of a disclaimer, a method using human embryonic stem cells or a population of human embryonic stem cells is excluded from the subject-matter of claim 1. Under Article 53(a) EPC in conjunction with Rule 28(c) EPC, European patents shall not be granted in respect of biotechnological invention which concern uses of human embryos for industrial or commercial purposes. According to the decision of the Enlarged Board of Appeal G 1/03 (OJ EPO 2004, 413) a disclaimer may be allowable to disclaim subject-matter which, under

Articles 52 to 57 EPC, is excluded from patentability for non-technical reasons.

The subject matter remaining in the claim after the introduction of the disclaimer is an in vitro method of altering the state of differentiation in a non-human embryonic stem cell. The claimed method using mouse embryonic stem cells is disclosed in the application as filed (cf. point 3 above). The exclusion of human embryonic stem cells does not introduce a new technical teaching nor does it lead to the disclosure of any subject matter going beyond the application as filed. Therefore, the disclaimer also satisfies the condition set out in point 1a of the order of decision G 2/10 (OJ EPO 2012,376; cf. decision T 2464/10 of 25 May 2012).

6. The board is therefore satisfied that the requirements of Article 123(2) EPC are met.

Articles 83 and 84 EPC

7. The subject matter of claims 1 to 5 is clear and supported by the description. The invention is sufficiently disclosed in Examples 1 to 4. Thus, the requirements of Articles 83 and 84 EPC are met.

Article 54 EPC

8. A method with all the features of claim 1 is not disclosed in the cited prior art. The claimed subject-matter is therefore novel.

Article 56 EPC

9. Document D7 represents the closest prior art. It discloses the alteration of the state of differentiation in embryonic stem cells by conditional expression and repression of oct-3/4. Expression of the oct-3/4 gene is regulated by a Tetracyclin responsive promoter element.
10. In the light of this disclosure the technical problem underlying the present invention can be seen in the provision of an alternative method for altering the state of differentiation of embryonic stem cells by modulation of the oct-3/4 expression.
11. For the solution of this problem claim 1 proposes a method using a zinc finger protein having three DNA binding domains as specified in claim 1 which are designed to bind to a target site in the oct-3/4 gene.
12. As shown in Examples 3 and 4, expression of the specified zinc finger protein leads to the expected change in the expression pattern of genes regulated by oct-3/4 expression. The board is therefore satisfied that the above mentioned problem is solved.
13. It remains to be established if the claimed solution involves an inventive step.
14. Although the upstream regulatory sequences of the oct-3/4 gene were known from document D8, which provides a comparison of the human, bovine and murine oct-3/4 upstream promoter sequences, neither document D7 nor document D8 contain any pointer or incentive to

regulate oct-3/4 expression in a cell with a modified zinc finger protein.

Even if, for the sake of the argument, the skilled person would have considered to regulate oct-3/4 gene expression with zinc finger proteins, because they were considered broadly useful in the regulation of endogenous genes (document D2, abstract), it would not have been obvious to target the selected DNA sequence. Prior art documents D2 (cf. Figure 1) and D3 (cf. Figure 4) describe zinc finger proteins which were targeted to DNA sequences close to the transcriptional start sites of the respective target genes. Thus, these documents teach away from the method of claim 1, targeting a specific zinc finger protein to the oct-3/4 sequence shown in example 2, which sequence, as can be seen in figure 2 of document D8, is situated about 780 base pairs upstream from the translational start site of the oct-3/4 gene.

15. Therefore, the board is convinced that the skilled person, based on documents D7 and D8, even when additionally considering documents D2 and/or D3, would not have arrived at the method of claim 1 in an obvious way.
16. The subject-matter of claim 1 and of dependent claims 2 to 5 involves an inventive step and meets the requirements of Article 56 EPC.
17. The board decides that the main request meets the requirements of the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of claims 1 to 5 of the new main request filed at the oral proceedings and the description and the figures still to be adapted.

The Registrar:

The Chairman:

A. Wolinski

M. Wieser