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Datasheet for the decision of 7 April 2021

Case Number: T 0899/18 - 3.3.08

Application Number: 05720113.9

Publication Number: 1726640

IPC: C12N5/0735, A01K67/027, C12Q1/02, C12N15/09

Language of the proceedings: EN

Title of invention:
RAT EMBRYONIC STEM CELL

Patent Proprietor:
Sumitomo Chemical Company, Limited
National Cancer Center

Opponent:
Schlich, George

Headword:
Rat embryonic stem cell/SUMITOMO

Relevant legal provisions:
EPC Art. 100(b)

Keyword:
Sufficient disclosure in the patent - (yes)

Decisions cited:
T 2001/12, T 0206/13

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0899/18 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 7 April 2021

Appellant: (Opponent)	Schlich, George 9 St Catherine's Road Littlehampton Sussex BN17 5HS (GB)
Respondent: (Patent Proprietor 1)	Sumitomo Chemical Company, Limited 27-1, Shinkawa 2-chome Chuo-ku Tokyo 104-8260 (JP)
Respondent: (Patent Proprietor 2)	National Cancer Center 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, (JP)
Representative:	Tuxworth, Pamela M. J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 1 February 2018 rejecting the opposition filed against European patent No. 1726640 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. R. Vega Laso
	R. Winkelhofer

Summary of Facts and Submissions

I. European patent No. 1 726 640 with the title "Rat embryonic stem cell" was granted from the European application No. 05720113.9 which was filed under the Patent Cooperation Treaty and published as WO 2007/087384 in the Japanese language.

II. Independent claims 1, 2, 5 and 13 to 15 of the patent as granted read as follows:

"1. A rat embryonic stem cell characterized by having the following properties (a)-(j):

(a) expressing Oct3/4 gene and Nanog gene,
(b) positive for alkaline phosphatase activity,
(c) having an embryoid body forming ability,
(d) expressing SSEA (Stage-Specific Embryonic Antigen)-1 and SSEA-4,
(e) having the same number of chromosomes as does a normal rat cell,
(f) capable of being subcultured and holding the undifferentiated state,
(g) having in vitro pluripotency,
(h) having the potential to differentiate into cells of the three embryonic germ lineages,
(i) having teratoma formation ability, and
(j) having an ability to produce a chimeric rat.

2. A method of producing a rat embryonic stem cell which comprises the steps (A)-(D), using a culture medium with 2% or less serum concentration:

(A) dissociating an inner cell mass formed by the culture of rat blastocysts in a LIF-free culture

medium so that the cells remain in the state of cell aggregates,
(B) culturing primary embryonic stem cells resulting from the culture of the dissociated inner cell mass until they can be passaged,
(C) dissociating the primary embryonic stem cells, which have become capable of being passaged so that the cells remain in the state of cell aggregates,
(D) passaging and culturing the cells to establish an embryonic stem cell,

wherein an rLIF-containing culture medium is used in steps (B)-(D).

5. A rat embryonic stem cell obtained by the method according to any one of claims 2 to 4.

13. Use of a rat embryonic stem cell of claim 1 or 5 in the production of a genetically modified rat.

14. A method of producing a genetically modified rat, which comprises the following steps (X)-(Z):

(X) introducing a desired gene into the rat embryonic stem cell of claim 1 or 5,
(Y) preparing an oocyte for transplantation comprising the rat embryonic stem cell into which the gene was introduced,
(Z} transferring the oocyte for transplantation into a pseudopregnant female rat to produce an offspring rat.

15. A genetically modified rat produced by the production method of claim 14."

Dependent claims 3 and 4 are directed to embodiments of the method of claim 2. Claims 6 and 7 relate to a culture kit for rat embryonic stem cells, and claims 8 and 9 to a method of inducing differentiation of a rat embryonic stem cell. Claim 10 is directed to a cDNA library of genomic library derived from a rat embryonic stem cell of claim 1 or 5. Claims 11 and 12 relate to a screening method for identifying a differentiation inducer for tissues or cells. Dependent claim 16 is directed to embodiments of the genetically modified rat of claim 15.

III. The patent was opposed on the grounds for opposition of Article 100(a) and (b) EPC.

IV. In a decision posted on 1 February 2018, an opposition division found that the ground for opposition of Article 100(a) EPC had not been substantiated, and that the ground of Article 100(b) EPC did not prejudice the maintenance of the patent as granted. Hence, the opposition was rejected.

V. In its decision, the opposition division found that, in view of the experimental evidence provided in the examples of the patent, the rat embryonic stem cells of claims 1 and 5 were sufficiently disclosed. The same applied with respect to the methods of claims 2 and 14, the use of claim 13 and the genetically modified rat of claim 15. In the view of the opposition division, neither feature (j) in claim 1 nor any of independent claims 13 to 15 required that the rat embryonic stem cells were germline-competent cells.

VI. The opponent (appellant) filed an appeal against the decision.

VII. The patent proprietors (respondents) submitted a reply.

VIII. The parties were summoned to oral proceedings before the board. In a communication sent in preparation of the oral proceedings, the board drew attention to matters which seemed to be of special significance and expressed a provisional opinion on some of the issues raised by the appellant.

IX. Oral proceedings were held on 7 April 2021 by video conference.

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

(1): M. Kawamata and T. Ochiya (2010) Methods in Molecular Biology, Vol. 597, ed. I. Anegon, pages 169 to 177;

(2): Declaration of Takahiro Ochiya, dated 25 June 2013; and

(3) P. Li *et al.* (2008), Cell, Vol. 135, No. 7, pages 1299 to 1310; copy of the NIH-PA Author Manuscript available in PMC.

XI. The submissions made by the appellant were essentially as follows:

The opposition division erred in finding that the patent disclosed the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Contrary to Article 1 of the Protocol on Interpretation of Article 69 EPC, the opposition division had interpreted the claims without any reference to the description or the consistently

stated purpose of the alleged invention. Hence, their conclusions on sufficiency of disclosure were based on an erroneous analysis of the scope of the claims. The claims encompassed germline-competent rat embryonic stem (ES) cells as there was no disclosure in the specification of anything else than a germline-competent rat ES cell and compositions derived therefrom.

Even though the patent did not include any technical evidence therefor, a person skilled in the art reading the patent would have considered it plausible that stem cells as defined in claim 1 could be used to produce a chimeric animal that could pass on the genetic information via the normal processes of selective breeding, thus producing progeny that are heterozygous non-chimeric animals suitable for obtaining homozygous animals by further breeding. However, plausibility was not the same as sufficiency.

The assumption of the inventors that a mitotically competent cell would also be meiotically competent and thus yield a germline-competent rat embryonic stem cell, was false. As evidenced by document (1), the patent was speculative and its disclosure had been later found to be insufficient. Document (1) demonstrated that in 2010 one of the inventors had not been able to work the claimed invention to produce germline-competent rat embryonic stem cells. Since there were significant doubts substantiated by verifiable facts in the form of published documents (1) and (3) that the disclosure in the patent was insufficient, the burden of proof of sufficiency lay with the respondents.

The experimental evidence in document (2) had no probative value and could not cure the lack of sufficiency of disclosure in the patent because, when this evidence had been produced, the state-of-the-art had been that the method of rat cell production described in the patent was not achievable. The patent should not have been interpreted retroactively in the light of document (2), as the opposition division had done.

Feature d) characterizing the rat embryonic stem cell of claim 1 was incompatible with the ability to obtain a genetically modified rat. Contrary to the opposition division's view, SSEA-4 expression was a stable and reliable marker of germline-competency for rat embryonic stem cells – not for rat embryonic stem cells in general. As apparent from document (1), a germline-competent rat embryonic stem cell was necessarily SSEA-4$^-$; hence, feature d) in claim 1 was factually incorrect.

XII. The submissions by the respondents were as follows:

By reproducing the examples of the patent, the skilled person would have been able to make the rat embryonic stem cells of claim 1, in particular by carrying out the method of claim 2, without an undue burden. The skilled person would also have been able to carry out the claimed methods and use. Neither serious doubts had been raised in that respect in appeal proceedings, nor any valid reasoning provided as to why the decision under appeal was incorrect.

The objection of lack of sufficient disclosure was based upon a flawed interpretation of the claims, namely that the rat ES cells of the invention must be

capable of being transmitted through the germline, even though not a specific requirement of the claims. The Protocol on the Interpretation of Article 69 EPC could not be used to justify importing features into a claim from the description. The properties recited in claim 1 corresponded to the properties possessed by the rat ES cells described in the examples of the patent.

Even though germline transmission was not a specific feature of the claims, document (2) demonstrated that rat ES cells produced according to the method of the invention could nevertheless be transmitted through the germline. Sections 1 to 4 of document (2) described the production of rat ES cells and corresponded to the method of Example 3 of the patent. Sections 5 to 7 described the introduction of a marker gene into the rat ES cells and the production of a chimeric rat containing the marker gene, using the same method of the invention. Section 8 then described the additional crossing of the chimeric rat to produce offspring and showed that those offspring expressed the same marker gene present in the rat ES cells. No counter-evidence had been provided against the experimental evidence in document (2). It was permissible to take the post-filed evidence of document (2) into account because the application made it plausible that the claimed rat ES cells were germline-competent.

The argument that SSEA-4 is a stable and reliable marker of germline-competent rat ES cells was irrelevant and not supported by any evidence. In any case, the conflicting SSEA-4 expression data might cast doubt on the reliability of SSEA-4 as a marker of rat ES cells, but not on the functional properties of the claimed rat ES cells.

XIII. The appellant requests that the decision under appeal be set aside and that the patent be revoked.

XIV. The respondents request that the appeal be dismissed.

Reasons for the Decision

Main request (patent as granted) – Article 100(b) EPC

1. In the decision under appeal, the opposition division found that, in view of the experimental evidence provided in the examples of the patent, the rat embryonic stem cells of claims 1 and 5 were sufficiently disclosed. The same applied with respect to the methods of claims 2 and 14, the use of claim 13 and the genetically modified rat of claim 15. Neither feature (j) in claim 1 nor any of independent claims 13 to 15 required that the rat embryonic stem cells were germline-competent cells. While the further ability to mate a chimeric rat and obtain transgenic breeds as described in the patent was considered to be desirable, in the opposition division's view this ability was not required by the claims (see item 9, in particular page 5, lines 1 to 5 of the decision).

2. The board shares the opposition division's view that none of claims 1, 2 and 5 requires the rat embryonic stem cells of the invention to be germline-competent. According to feature (j) in claim 1, the claimed rat embryonic stem cell must have "*the ability to produce a chimeric rat*". The detailed technical teachings in the examples of the patent enable the skilled person to obtain rat embryonic stem cells from which a chimeric rat can be produced (see, in particular, paragraphs [0126], [0127] and [0134] to [0140], as well as Figures 24 and 25 of the patent). The appellant did

not submit any experimental counter-evidence which might cast doubts on the experimental data provided in the examples of the patent.

3. The methods and results disclosed in the patent are confirmed by the experimental evidence in document (2), which was produced and submitted by the respondents after the publication date of the application on which the present patent was granted. While the appellant argued that the probative value of document (2) was highly suspect, he did not put forward any persuasive arguments to support his allegation.

4. The appellant also sought to support his objection of lack of sufficient disclosure by referring to Article 69 EPC and pointing to passages of the patent specification in which crossing or breeding are mentioned in connection with methods for producing various types of genetically modified rats (see, e.g., paragraphs [0002] and [0080] of the patent). In the appellant's view, those statements implied that germline-competency, i.e. the ability of an embryonic stem cell line to contribute to germ cell formation and transmit genetic modifications to progeny, was an essential feature of the rat embryonic stem cells according to the invention. Since the rat embryonic stem cells as defined in claim 1 or obtained by the method of claim 2 allegedly lacked such a competency, the disclosure in the patent was insufficient.

5. The board disagrees. It is the consistent position of the Boards of Appeal (see, *inter alia*, decisions T 2001/12 of 29 January 2015, and T 0206/13 of 28 September 2015) that an objection of insufficient disclosure under Article 83 EPC cannot legitimately be based on the argument that the application would not

enable a person skilled in the art to achieve a non-claimed technical effect. As stated in decision T 0206/13 (*supra*):

> "*..., the requirement of sufficiency of disclosure set forth in Article 83 EPC relates to the invention defined in the claims, and in particular to the combination of structural and functional features of the claimed invention, and there is no legal basis for extending such a requirement to also encompass other technical aspects possibly associated with the invention (in particular,* ***technical features or effects mentioned in the description****) but not required by the claimed subject-matter. Thus, such technical aspects might be pertinent in the assessment of other requirements of the EPC (in particular, the requirements of Article 84 and 56 EPC, see for instance decision T 2001/12, point 4.4 of the reasons), but the question of whether the disclosure of the application would enable the skilled person to achieve such non-claimed technical aspects cannot legitimately be raised under Article 83 EPC ...*" (see second paragraph in point 3.4 of the Reasons; emphasis added by the board).

6. The same applies with respect to the objection that the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC).

7. Like claims 1, 2 and 5, the claims which relate to the use of rat embryonic stem cells according to the invention for producing a genetically modified rat

(claims 13 and 14), and the produced genetically modified rat (claim 15), do not require that the embryonic stem cells are germline-competent. In the light of the experimental results provided in the examples of the patent, there is no doubt that chimeric rats produced by the methods taught in the patent are genetically modified, in particular by insertion of the GFP gene into the cell genome in most tissues, including testis (see Figure 24 of the patent). No experimental evidence to the contrary has been submitted by the appellant.

8. Alone for these reasons, the appellant's objection of lack of sufficient disclosure in the patent is not considered to be justified. Additionally, the documentary evidence on file does not cast doubts on the sufficiency of the disclosure in the patent.

9. Document (1) is a chapter of a book including methods and protocols for rat genomics published in 2010, i.e. well after the filing date of the patent in suit. The appellant relied on various passages of this document, but in particular on a passage in which the authors - one of whom is named as an inventor in the patent at issue - state: "*Although we established new lines of rat cells with chimeric contribution, they could not complete germline transmission (8)*" (see page 170, lines 7 to 9).

10. The culture medium for rat embryonic stem cells used in the method under the reference "(8)" is described in document (1) as containing 3% fetal bovine serum (see page 171, first paragraph under the heading "Establishment of Rat ES Cells by Reduction of Fetal Bovine Serum (FBS)"). In contrast, the method of claim 2 of the patent requires a culture medium with 2%

or less serum concentration, and in the examples of the patent serum replacement reagent (KSR) is used, as the inventors found it to be superior to FBS in establishing rat embryonic stem cells (see column 27, lines 38 and 39 of the patent).

11. It follows from the above that the statements in document (1) on which the appellant relied, relate to a method for producing rat ES cells that differs from the claimed method. Apart from the fact that one of the inventors named in the patent in suit is also an author of both document (1) and the scientific publication referred therein under "(8)", there is no link between those statements and the method of the invention. Hence, document (1) cannot serve to discharge the burden of proof lying on the appellant.

12. Further, the appellant referred to documents (1) and (3) to support his argument that, contrary to feature (d) of the embryonic stem cell of claim 1, an "authentic" rat embryonic stem cell needs to be SSEA-4$^-$ ("*... the rat ES cells expressed SSEA-1, but not SSEA-4 ...*", see document (1), last paragraph on page 174 referring to the publication under "(10)", which is document (3) in the present proceedings).

13. Document (3) describes a method in which rat embryonic stem cells are derived, propagated and genetically manipulated in the presence of small molecules that specifically inhibit the GSK3, MEK, and FGF receptor tyrosine kinases (see Abstract). The board is not persuaded that the fact that rat ES cells obtained applying the method described in document (3) do not express SSEA-4 necessarily means that an essential feature of rat embryonic stem cells is the lack of SSEA-4 expression. Since the method for preparing rat

ES cells described in document (3) differs substantially from the method of the invention, it cannot be excluded that the expression pattern of cell surface markers in the obtained cells may differ at least to a certain extent. In the absence of further evidence showing that, independently of the method used for the preparation of rat embryonic stem cells, lack of SSEA-4 expression in fact characterizes the undifferentiated state, the appellant's argument that the rat embryonic stem cells claimed in the patent are not "authentic" embryonic stem cells, is not persuasive.

14. Summarising the above: the evidence in documents (1) and (3) does not discharge the appellant's burden of proof, nor supports his objection of lack of sufficient disclosure of the claimed rat embryonic stem cells.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

C. Vodz B. Stolz

Decision electronically authenticated