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Datasheet for the decision of 21 October 2020

Case Number: T 1636/15 - 3.3.08

Application Number: 06739994.9

Publication Number: 1891208

IPC: C12N5/071

Language of the proceedings: EN

Title of invention:
NOVEL CELLULAR COMPOSITIONS AND METHODS FOR THEIR PREPARATION

Patent Proprietor:
Celsis In Vitro, Inc.

Opponent:
Life Technologies Corporation

Headword:
Hepatocyte preparation/CELSIS

Relevant legal provisions:
EPC Art. 100(c)

Keyword:
Patent as granted - claimed subject-matter extends beyond the content of the application as filed (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1636/15 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 21 October 2020

Appellant: (Patent Proprietor)	Celsis In Vitro, Inc. 1450 South Rolling Road Baltimore, MD 21227 (US)
Representative:	Findeisen, Marco Witte, Weller & Partner Patentanwälte mbB Postfach 10 54 62 70047 Stuttgart (DE)
Respondent: (Opponent)	Life Technologies Corporation 5791 Van Allen Way Carlsbad, CA 92008 (US)
Representative:	Roques, Sarah E. J A Kemp LLP 14 South Square Gray's Inn London WC1R 5JJ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 22 June 2015 revoking European patent No. 1891208 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. R. Vega Laso
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 891 208 with the title "Novel cellular compositions and methods for their preparation" was granted from the European patent application No. 06739994.9 which was filed under the Patent Cooperation Treaty and published as WO 2006/115682 (in the following "the application as filed").

II. Claims 10, 14 and 18 of the application as filed read as follows:

"10. A method of producing a desired preparation of multi-cryopreserved hepatocytes, said hepatocytes being capable of being frozen and thawed at least two times, and in which greater than 50% of the hepatocytes of said preparation are viable, said method comprising:

(A) subjecting hepatocytes that have been frozen and thawed to density gradient fractionation to separate viable hepatocytes from non-viable hepatocytes,

(B) recovering the separated viable hepatocytes, and

(C) cryopreserving the recovered viable hepatocytes to thereby form said desired preparation of hepatocytes.

14. The method of claim 10, wherein said preparation comprises a pooled preparation of hepatocytes of multiple sources.

18. The method of claim 10, wherein greater than 70% of the hepatocytes of said preparation are viable."

III. Claim 1 of the patent as granted reads as follows:

"1. A method of producing a preparation of multi-cryopreserved hepatocytes, comprising:

(A) providing hepatocytes from multiple sources that have been cryopreserved and thawed
(B) pooling such hepatocytes and subjecting them to density gradient fractionation to separate viable hepatocytes from non-viable hepatocytes,
(C) recovering the separated viable hepatocytes, and
(D) cryopreserving the recovered viable hepatocytes to thereby form said preparation of hepatocytes, wherein greater than 70% of the hepatocytes of said preparation are viable."

Dependent claims 2 to 8 are directed to particular embodiments of the method of claim 1.

IV. The patent was opposed on the grounds for opposition of Article 100(a) in conjunction with Articles 54 and 56 EPC, and Article 100(b) and (c) EPC.

V. In a decision posted on 22 June 2015, an opposition division found that the subject-matter of claim 1 of the patent as granted extended beyond the content of the application as filed and that, consequently, Article 100(c) EPC prejudiced the maintenance of the patent as granted. In particular, the opposition division found that there was no basis in the application as filed for a process as defined in the claim, which comprised the step of pooling hepatocytes from multiple donors and isolating the viable cells from the pool (see last sentence of the third paragraph on page 5 of the decision under appeal). Hence, the patent was revoked.

VI. The patent proprietor (appellant) lodged an appeal and submitted a statement setting out the grounds of appeal, to which the opponent (respondent) replied.

VII. Pursuant to their respective subsidiary requests, the parties were summoned to oral proceedings before the board.

VIII. On 2 September 2020, the respondent withdrew its request for oral proceedings and informed the board that it would not attend the scheduled oral proceedings.

IX. In a communication issued in preparation of the oral proceedings, the board expressed a provisional opinion concerning the opposition division's findings on Article 100(c) EPC.

X. Oral proceedings were held on 21 October 2020 by videoconference in the presence of the appellant.

XI. The following document is referred to in the present decision:

(10): M.C. Alexander et al., 25 February 1982, The Journal of Biological Chemistry, Vol. 257, No. 4, pages 2049 to 2055.

XII. The submissions made by the appellant, as far as they are relevant to the present decision, were essentially as follows:

Patent as granted - Article 100(c) EPC

The opposition division had inadmissibly read a feature into claim 1 which was not recited therein. Claim 1 did

not prescribe in step (B) a specific order in the sense of first pooling the hepatocytes and then subjecting the pooled lot to density gradient fractionation. Rather, according to step (B) first the "pooling" could be performed and then the "fractioning" operation, or *vice versa*.

If step (B) were nevertheless construed as prescribing a particular order, i.e. first pooling and then fractioning, the claimed method had a basis in the application as filed, in particular in claims 10, 14 and 18 under further consideration of the description, e.g. paragraphs [0067], [0051]-[0061] and [0025]. Claim 14, directed to a method of producing a pooled preparation of multi-cryopreserved hepatocytes from multiple sources, left open whether the pooling was to be carried out before or after the fractionation step. However, from Example 3, in particular paragraph [0067], in combination with Example 1 of the application as filed, the skilled person could derive a method in which hepatocytes from multiple sources were first pooled and then subjected to fractionation. Hence, the opposition division had erred in finding that the subject-matter of claim 1 extended beyond the content of the application as filed.

XIII. The relevant submissions by the respondent were as follows:

Patent as granted - Article 100(c) EPC

There was no disclosure in the application as filed of a method in which hepatocytes from multiple sources were pooled prior to density gradient fractionation. The application did not describe in general terms the method steps to produce a multi-cryopreserved pooled

preparation of hepatocytes from different sources. The examples were also not clear, but to the extent that pooling was described, this was disclosed after recovery of viable hepatocytes by density gradient fractionation. Hence, Article 100(c) EPC prejudiced the maintenance of the patent as granted.

XIV. The appellant requested that the decision under appeal be set aside and the opposition be rejected. It further requested that the case be remitted to the opposition division for examination of the grounds of opposition of Article 100(b) EPC, and Article 100(a) EPC in conjunction with Articles 54 and 56 EPC.

XV. The respondent requested in writing that the appeal be dismissed.

Reasons for the Decision

Interpretation of claim 1 of the patent as granted

1. In the decision under appeal, the opposition division construed the wording of step (B) in the method of claim 1 as requiring a particular sequence of actions: first the hepatocytes provided in step (A) were to be pooled, and then subjected to density gradient fractionation (see section 3.4 of the decision).

2. The appellant contested the opposition division's interpretation arguing that step (B) does not prescribe a specific order for pooling and fractioning the hepatocytes.

3. This argument is without merit. Like the opposition division, the board holds the wording of claim 1 of the

patent as granted to be clear and unambiguous as regards the sequence of the pooling and fractioning steps referred to in step (B): the cryopreserved and thawed hepatocytes from multiple sources which have been provided in step (A) are first pooled, and the pooled preparation is then subjected to density gradient fractionation to separate viable hepatocytes from non-viable hepatocytes. A different interpretation of the wording of step (B), i.e. first the hepatocyte samples are subjected to density gradient fractionation and then the viable cells pooled, would be inconsistent with the wording of the subsequent step (C) ("*recovering the* ***separated*** *viable hepatocytes*"; emphasis added by the board). The term "recovering" in step (C) can only be understood to mean "recovering from the density gradient", because recovery of the viable hepatocytes from the pooled preparation - after having been pooled in the previous step – does not make any technical sense.

4. If the board were nevertheless to accept that, as the appellant contended, the wording of step (B) does not prescribe a specific sequence for pooling and fractionating, claim 1 would encompass two different embodiments of the method: (i) an embodiment in which the cryopreserved and thawed hepatocytes from different sources are first subjected to density gradient fractionation to separate the viable from the non-viable cells and the separated viable cells are then pooled, and (ii) an embodiment in which the hepatocytes from different sources are first pooled and then fractionated to separate the viable cells. With respect to the subject-matter of embodiment (ii) the objection of added matter (see below) would apply equally.

Article 100(c) EPC

5. As a basis for the method of claim 1, the appellant pointed to claims 10, 18 and 14 and paragraphs [0067], [0051]-[0061] and [0025] of the application as filed.

6. Independent claim 10 of the application as filed (see section II above) is directed to a method of producing a preparation of multi-cryopreserved hepatocytes, which method comprises, *inter alia*, subjecting hepatocytes that have been frozen and thawed to density gradient fractionation to separate viable hepatocytes from non-viable hepatocytes. Claim 10 does not specify that the preparation is a pooled preparation of hepatocytes from different sources, nor recites a pooling step.

7. Claim 14 of the application as filed, which depends on claim 10, characterizes the preparation of multi-cryopreserved hepatocytes as a pooled preparation of hepatocytes from multiple sources. However, claim 14 does not mention a pooling step, let alone specifies at which stage of the method of claim 10 the hepatocytes are pooled. As a matter of fact, pooling of hepatocytes from multiple sources could be done at different stages of the method of claim 10:

(i) The "*hepatocytes that have been frozen and thawed*" mentioned in step (A) of the method of claim 10 of the application as filed could be already a pooled preparation of hepatocytes from multiple sources. In this respect, it should be noted that, according to the application the pooled preparation of hepatocytes is not limited to primary hepatocytes (see second sentence in paragraph [0024] of both the application as filed and the patent), and that the wording "*multiple*

sources" does not necessarily mean numerous sources. Hence, low frequency of receipt of fresh tissue and need to cryopreserve primary hepatocytes immediately after isolation would not be impediments to this approach.

(ii) Frozen aliquots of individual hepatocyte samples from different sources could be pooled in a frozen state (see document (10), page 2052, left-hand column, first sentence in the first full paragraph), subsequently thawed and subjected to a density gradient fractionation, and the recovered viable cells cryopreserved anew, as specified in steps (A) to (C) of the method of claim 10 of the application as filed;

(iii) Individual cryopreserved hepatocyte samples from different sources could be thawed separately, the thawed samples pooled, and the pooled preparation be processed as specified in steps (A) to (C) of the method of claim 10;

(iv) Each of the individual frozen and thawed samples could be first subjected to a density gradient fractionation as in step (A) of the method of claim 10, and then the viable hepatocytes recovered after fractionation could be pooled and subsequently cryopreserved as a pooled preparation in step (C) of the method of claim 10;

(v) Alternatively, the individual samples of viable hepatocytes recovered after fractionation could be cryopreserved separately in step (C) and, upon demand, pooled in a frozen state to obtain a pooled hepatocyte preparation.

8. Claim 1 of the patent as granted specifies only one of these possible approaches, namely pooling the cryopreserved and thawed hepatocytes prior to subjecting them to fractionation (approach (iii) above). Although all these possible approaches, including (iii), might be obvious to a person skilled in the art when reading the application, there is no direct and unambiguous disclosure of the specific method of claim 1 in the application as filed. Thus, a combination of claims 10 and 14 of the application as filed cannot serve as a basis for the subject-matter of claim 1 of the patent as granted.

9. Claim 18 of the application as filed, which specifies that more than 70% of the hepatocytes of the preparation produced according to claim 10 are viable, does not provide any additional information concerning the stage of the method at which pooling of the hepatocyte samples from different sources takes place.

10. As regards paragraphs [0051]-[0061], which are part of the description in Example 1, the appellant argued that, in view of paragraph [0025], it would be "*... evident that Example 1 encompasses instructions for the production of a pooled preparation of hepatocytes of multiple sources*".

11. The board does not share this view. While it is stated in paragraph [0024] – rather than in paragraph [0025] to which the appellant referred – that "hepatocyte preparation" denotes a composition of liver cells from one or more sources, a person skilled in the art reading of the application cannot derive from any of paragraphs [0051]-[0061] a specific indication that the 50 cryovials in step 3 of the method described in

Example 1 ("Refreezing of Thawed Hepatocyte Preparations") contain hepatocytes from multiple sources.

12. As regards the passage in paragraph [0067] to which the appellant referred ("*Six lots of pooled hepatocytes, comprising either five-donor pools or ten-donor pools, are prepared as described above*"), the board cannot accept the appellant's argument that the skilled person would understand from this statement that the hepatocyte preparation obtained in Example 1 is a pooled preparation of hepatocytes from multiple sources.

13. Paragraph [0067], which is part of the disclosure in Example 3 ("Characterization of Pooled Hepatocytes", paragraphs [0066]-[0070]), is followed by a detailed description of how the pooled lots of hepatocytes are prepared. There is no doubt that – as the opposition division found and the appellant did not dispute - in the method described in Example 3 the individual lots are pooled **after** the fractionation step (see paragraph [0068], in particular the last sentence). Hence, it is unclear what the wording "*as stated above*" in the context of Example 3 means, because neither Example 1 nor Example 2 describe fractionating and then pooling individual lots from different donors.

14. For these reasons, the board concludes that the method according to claim 1 of the patent as granted has no basis in the application as filed. Since the claimed subject-matter extends beyond the content of the application as filed and, as found in the decision under appeal, Article 100(c) EPC prejudices the maintenance of the patent as granted, the appellant's request to set aside the decision cannot be granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated