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Datasheet for the decision of 1 February 2022

Case Number: T 0527/17 - 3.3.01

Application Number: 07862321.2

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Language of the proceedings: EN

Title of invention:
MUSCLE DERIVED CELLS FOR THE TREATMENT OF CARDIAC PATHOLOGIES AND METHODS OF MAKING AND USING THE SAME

Patent Proprietor:
UNIVERSITY OF PITTSBURGH

Opponent:
Innovacell AG

Headword:
Muscle Derived Cells/PITTSBURGH

Relevant legal provisions:
EPC Art. 123(2), 56, 83
RPBA 2020 Art. 13(2)

Keyword:

Admittance - main request (yes) - first auxiliary request (no) - second auxiliary request (yes)
Inventive step - main request (no) - second auxiliary request (yes)
Amendments - allowable (yes)
Sufficiency of disclosure (yes)

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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 0527/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 1 February 2022

Appellant: (Patent Proprietor)	UNIVERSITY OF PITTSBURGH 200 Gardner Steel Conference Center Thackeray & O'Hara Streets Pittsburgh, PA 15260 (US)
Representative:	Haseltine Lake Kempner LLP Cheapside House 138 Cheapside London EC2V 6BJ (GB)
Appellant: (Opponent)	Innovacell AG Mitterweg 24 6020 Innsbruck (AT)
Representative:	Drexl, Janna Dehmel & Bettenhausen Patentanwälte PartmbB Herzogspitalstraße 11 80331 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 13 January 2017 concerning maintenance of the European Patent No. 2097088 in amended form**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	L. Bühler

Summary of Facts and Submissions

I. The patent proprietor and the opponent each filed an appeal against the opposition division's interlocutory decision concerning the maintenance of European patent No. 2 097 088 in amended form.

As both parties are appellants and thus also respondents, in the following they will be referred to as the patent proprietor and the opponent.

II. The following documents are referred to in the present decision:

D5 D. Yaffe, Zoology, 1968, 61, 477-83
D8 WO 99/56785
D9 WO 01/78754

III. The patent had been opposed on the grounds of Article 100(a) (for lack of novelty and inventive step), 100(b) and 100(c) EPC.

IV. In the decision under appeal, the opposition division concluded that:

- the main request added subject-matter
- the subject-matter of the first auxiliary request was not sufficiently disclosed
- the subject-matter of the second auxiliary request was sufficiently disclosed and inventive starting from D9

V. In its statement of grounds of appeal, the opponent requested that the decision be set aside and that the patent be revoked in its entirety.

VI. With its statement of grounds of appeal, the patent proprietor filed the claims of a main request and auxiliary requests 0, 1 to 16 and 1A to 16A.

Auxiliary request 9A contained nine claims. Independent claims 1 and 6 read as follows.

"*1. A pharmaceutical composition comprising human muscle-derived progenitor cells (MDCs) for use in improving left ventricular contractility of the heart wherein said improving comprises administering the MDCs to the heart of a human subject in need thereof wherein the MDCs are isolated according to the method comprising:*

(a) suspending human skeletal muscle cells isolated from the human subject in a medium in a first cell culture container for between 30 and 120 minutes thereby producing a cell population of adherent cells and a population of non-adherent cells;
(b) decanting the medium and population of non-adherent cells from the first cell culture container to a second cell culture container;
(c) culturing in the second cell culture container for 1-3 days to allow the population of decanted, non-adherent cells in the medium to attach to the walls of the second cell culture container; and
(d) isolating the population of cells adhered to the walls of the second cell culture container, wherein the isolated population of cells are human MDCs and are used for treatment."

"*6. A method of isolating an autologous end population of human skeletal muscle-derived progenitor cells (MDCs) comprising*

(a) suspending human skeletal muscle cells from the human of interest in a medium in a first cell culture container for between 30 and 120 minutes thereby producing a cell population of adherent and a population of non-adherent cells;
(b) decanting the medium and the population of non-adherent cells from the first cell culture container to a second cell culture container;
(c) allowing the population of the decanted, non-adherent cells in the medium from the first cell culture container to attach to the walls of the second cell culture container; and
(d) isolating the population of cells adhered to the walls of the second cell culture container,

thereby, isolating said end population of MDCs."

Dependent claims 7 to 9 read as follows.

"*7. The pharmaceutical composition for use of claim 1 or the method of claim 6, wherein the MDCs are subsequently frozen.*"

"*8. The pharmaceutical composition for use of claim 1 or the method of claim 7, wherein the MDCs are frozen at a temperature below -30 °C, and preferably at a temperature below -70 °C.*"

"*9. The pharmaceutical composition for use of claim 1 or method of claim 7, wherein the MDCs are frozen on dry ice.*"

VII. The board scheduled oral proceedings in line with the parties' requests. In preparation for the oral proceedings, the board issued a preliminary opinion. It considered, among other things, that:

- at least the main request and auxiliary requests 0, 1 to 8, 10 to 16, 1A to 8A and 10A to 16A added subject-matter
- the subject-matter of auxiliary request 9A did not involve an inventive step due to the absence of the feature "1-3 days" in step (c) of claim 6

VIII. In response to the board's preliminary opinion, the patent proprietor filed four additional claim requests.

IX. Oral proceedings before the board were held by videoconference on 1 February 2022. During the oral proceedings, the patent proprietor withdrew all claim requests then on file and filed three sets of claims as its main request and first and second auxiliary requests.

The main request derives from auxiliary request 9A filed with the patent proprietor's statement of grounds of appeal by deleting claims 7 to 9.

The first auxiliary request derives from the main request by inserting the feature "1-3 days" into step (c) of claim 6.

The second auxiliary request derives from the main request by deleting claim 6.

X. At the end of the oral proceedings, the board announced its decision.

XI. The opponent's arguments relevant to the present decision can be summarised as follows.

The main request and the first and second auxiliary requests filed by the patent proprietor at the oral proceedings before the board should not be admitted. The patent proprietor had already filed a high number of claim requests, and there had been no change in the proceedings justifying the filing of additional requests. Contrary to the patent proprietor's contention, the board had not raised any new objection in its preliminary opinion. Moreover, the combination of features "autologous" and "1-3 days" in claim 6 of the first auxiliary request raised new added subject-matter issues.

Claim 1 of the main request added subject-matter for two reasons. First, the application as filed did not disclose the combination of features "pharmaceutical composition" and "improving left ventricular contractility". The passage on page 16, lines 16-19 was not a valid basis because it was not generally applicable. The passage was in a section relating to Example 1 only. Second, the application as filed did not provide a basis for the terms "adherent" and "non-adherent" cells. On page 6, lines 9-15, the application referred to "rapidly adhering" and "slowly adhering" cells, which had a different meaning. Furthermore, the embodiment disclosed in the latter passage contained essential steps missing from claim 1.

The subject-matter of claim 1 of the main request was not sufficiently disclosed. Example 1 of D9 showed that only MDCs isolated after five or six sequential plating steps could be suitable for improving left ventricular

contractility. Cells as in claim 1, i.e. obtained after only two plating steps, could not augment muscle tissue so they were unsuitable for improving left ventricular contractility.

The subject-matter of claim 1 of the main request was not inventive over the combination of D9 with D8 or D5. It differed from D9 in that its MDCs were human MDCs obtained by a method comprising two consecutive plating steps of 30 to 120 minutes and one to three days. The therapeutic indication in claim 1 was not a difference. Although D9 did not explicitly mention left ventricular contractility, it was concerned with improving ventricular function (Example 7; page 10, lines 26-31; and Figures 7A and 7B), which was the same thing. This could be derived from Example 10 of the patent (title, paragraphs [0131] and [0138], and Table 5), which equated left ventricular contractility with ventricular function. The differences with D9 did not produce any effect. Therefore, if the requirement of sufficiency of disclosure was met, the objective technical problem was providing a simpler process for isolating MDCs suitable for treating cardiac conditions in humans.

The solution proposed in claim 1 was obvious. Starting from the six-step isolation method in Example 1 of D9, the skilled person would have turned to the simplified (two-step) method in Example 9 of D8. This method included all steps (a) to (d) defined in claim 1: primary muscle cells were plated for one hour followed by a second plating of three days. In the first plating, most fibroblasts were removed. The cells attached to the culture container wall in the second plating were mostly myoblasts and constituted the MDC population. Despite not being explicitly mentioned, these MDCs had to be detached from the container wall

and isolated for their subsequent application in therapy. The MDCs from Example 9 of D8 were used for treating joint injury in an animal (rabbit) different from the one in D9 (rat). Nevertheless, like D9 (page 16, lines 26-27), D8 (page 24, lines 17-20) suggested the use of MDCs in humans. In the same vein, D5 disclosed a simplified method for isolating myogenic cells comprising the two plating steps of claim 1. At the end of the second step, cells had to be detached from the container wall and isolated for their subsequent analysis.

The method of claim 6 of the main request was not inventive either. Compared with claim 1, claim 6 did not relate to a therapeutic application and contained no time limitation in step (c). The method in Example 9 of D8 was a suitable starting point. The method of claim 6 differed from it in that the isolated cell population consisted of autologous human MDCs. Step (c) of claim 6 did not contain the feature "1-3 days", which was essential for obtaining an MDC population suitable for improving left ventricular contractility. Therefore, the objective technical problem was providing a method for isolating MDCs from a human skeletal muscle explant. The method of claim 6 was an obvious solution because the methods in D8 (page 24, lines 17-20) were intended for use in humans.

XII. The patent proprietor's arguments relevant to the present decision can be summarised as follows.

The main request and the first and second auxiliary requests filed at the oral proceedings before the board should be admitted. The requests derived from auxiliary request 9A filed with the patent proprietor's statement of grounds of appeal. In its preliminary opinion, the

board considered that auxiliary request 9A was a suitable starting point for discussion. The main request and the second auxiliary request resulted from deleting contentious claims. They did not change the patent proprietor's case and reduced the number of issues to be discussed. Regarding the first auxiliary request, it resulted from deleting dependent claims and bringing independent claim 6 in line with claim 1. This amendment was responsive to the board's preliminary opinion (point 12.5) that the method of claim 6 was not inventive because the feature "1-3 days" was missing from step (c).

The main basis in the application as filed for claim 1 of the main request was in claims 11 and 12 and on page 6, lines 12-13 and page 14, lines 24-28. Regarding the feature "pharmaceutical composition", the application taught in a general manner on page 16, lines 16-19 that for therapeutic purposes, the MDCs of the invention could be administered as such or in the form of a pharmaceutical composition. With respect to the terms "adherent" and "non-adherent" cells, it was apparent that they had the same meaning as "rapidly adhering" and "slowly adhering" cells on page 6, lines 9-15 of the application as filed.

The subject-matter of claim 1 of the main request was sufficiently disclosed. The patent showed in Example 10 that the method of claim 1 isolated highly myogenic human MDCs that were suitable for improving left ventricular contractility. The method in Example 1 of D9 could not raise doubts in this respect because it was not according to claim 1: it involved rodent cells and a different isolation method.

The subject-matter of claim 1 of the main request was inventive starting from D9. The isolation method of claim 1 differed from the one in D9 in the nature of the MDCs (human vs rodent) and in the number and duration of the plating steps. An additional difference was the use for improving left ventricular contractility. D9 did not mention this use. Its Example 7 did not even show an improvement in ventricular function. It only showed that three days after administration into the ventricular wall, viable MDCs were still present at the location. These differences had the effect that human MDCs could be isolated by a simplified method involving less manipulation and better preservation of the native characteristics of the cells. The obtained MDCs were suitable for improving left ventricular contractility. Therefore, the objective technical problem was providing a simple and efficient method for obtaining human MDCs suitable for improving contractility of the heart. Example 10 of the patent showed that this problem was solved by the claimed subject-matter.

The solution proposed in claim 1 was not obvious. D9, D8 and D5 dealt with non-human cells, and none of them related to improving left ventricular contractility. The methods for isolating MDCs in Example 1 of each of D9 and D8 comprised six plating steps. The short method in Example 9 of D8 did not contain any operation equivalent to step (d) of claim 1: the myoblast population obtained after three days was not isolated. As to D5, it did not disclose a final separation step either, and it did not aim at any therapeutic indication. It merely investigated how long myogenic cells could be cultured *in vitro* before undergoing differentiation. Hence, the isolation of an end population of myogenic cells was taught only by

performing a six-step process, as in Examples 1 of D9 and D8. When translating a method tested in a rodent model to humans, the skilled person would have applied the same multiple-step method and would have expected a higher degree of complexity due to the higher complexity of the human organism. So the skilled person was taught away from the simplified method of claim 1.

The method of claim 6 of the main request was inventive, too. It differed from the one in Example 9 of D8 not only in that the MDCs were human and autologous, but also in that they were isolated from the culture container walls at the end of the second plating step (step (d) of claim 6). The MDCs of claim 6 were not necessarily suitable for the therapeutic indication of claim 1. The objective technical problem was providing an alternative method for isolating MDCs. The skilled person found no motivation in the prior art to modify the method of D8 to arrive at the one proposed in claim 6.

XIII. The parties' final requests were as follows.

- The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request or, alternatively, the first or the second auxiliary requests, all filed at the oral proceedings on 1 February 2022.

- The appellant-opponent requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Reasons for the Decision

1. The appeal is admissible. It meets the requirements of Articles 106 to 108 and Rule 99(2) EPC.

2. The patent proprietor had expressed its disagreement with holding the oral proceedings by videoconference. The board nevertheless considered that the videoconference format was appropriate for the case. Therefore, oral proceedings were held by videoconference in accordance with Article 15a RPBA 2020 (see also G 1/21, Headnote).

3. Admittance of the claim requests filed at the oral proceedings before the board (Article 13(2) RPBA 2020)

In accordance with Article 13(2) RPBA 2020, any amendment to a party's appeal case made after notification of a summons to oral proceedings must, as a rule, not be taken into account unless there are exceptional circumstances which have been justified with cogent reasons by the party concerned.

3.1 The main request and the second auxiliary request, both filed at the oral proceedings before the board, result from the deletion of claims 7 to 9 (main request) and 6 to 9 (second auxiliary request) from auxiliary request 9A filed with the statement of grounds of appeal. The board holds that these amendments do not change the patent proprietor's case as put forward in its statement of grounds of appeal: they do not raise any new issue and stay within the legal and factual framework established at the outset of the appeal proceedings for the claims remaining on file.

Therefore, Article 13(2) RPBA 2020 is not applicable to these requests.

3.2 By contrast, the insertion of the feature from the description "1-3 days" into claim 6 of the first auxiliary request raises new issues. For instance, it requires assessing whether the combination of features "1-3 days" and "autologous" was disclosed in the application as filed. Hence, the first auxiliary request changes the patent proprietor's case.

The patent proprietor contended that the first auxiliary request was a reaction to the board's preliminary opinion (point 12.5) that the method of claim 6 of auxiliary request 9A was not inventive because the feature "1-3 days" was missing from step (c).

This argument is not convincing. The objection relating to the absence of the feature "1-3 days" in step (c) of claim 6 was already in the decision under appeal (points 9.1.3, 9.2 and 10) and in the opponent's statement of grounds of appeal (point 4.1). It had been raised in relation to the issue of sufficiency. In its preliminary opinion (point 11, last paragraph), the board simply noted that because claim 6 was not directed to a therapeutic method but to a method of obtaining MDCs, the issue had to be discussed under inventive step rather than sufficiency. Hence, there were no exceptional reasons within the meaning of Article 13(2) RPBA 2020 justifying the filing of the first auxiliary request at oral proceedings.

3.3 Consequently, the board admitted the main request and the second auxiliary request but not the first auxiliary request.

Main request - claim 1

4. Amendments - Article 123(2) EPC

It was common ground between the parties that the main basis for claim 1 in the application as filed is claims 11 and 12, which have the following wording.

"*11. A method of improving cardiac function in a mammalian subject in need thereof comprising;*

(a) isolating skeletal muscle cells from the human subject,

(b) suspending human skeletal muscle cells in a first cell culture container for between 30 and 120 minutes;

(c) decanting the media from the first cell culture container to a second cell culture container;

(d) allowing the remaining cells in the media to attach to the walls of the second cell culture container;

(e) isolating the cells from the walls of the second cell culture container, wherein the isolated cells are MDCs; and

(f) administering the MDCs to the heart of the human subject;

thereby, improving cardiac function in a mammalian subject in need thereof."

"*12. The method of claim 11, wherein the cardiac function improvement is improved left ventricular contractility*."

In addition, the feature in step (c) of claim 1 that the cells are cultured in the second container for one

to three days may be found on page 6, lines 12-13 and page 14, lines 24-28 of the application as filed.

4.1 The opponent raised two added subject-matter objections.

(a) The feature "pharmaceutical composition" in the preamble of claim 1 added subject-matter because improving left ventricular contractility had been disclosed in connection with the administration of MDCs but not a composition containing MDCs. The passage on page 16, lines 16-19 was not generally applicable because it related to Example 1 in which cells were obtained by a method other than the one in claim 11 as filed.

(b) The terms "adherent" and "non-adherent" cells had no basis in the application as filed. The application referred to "rapidly adhering" and "slowly adhering" cells, which had a different meaning. Moreover, the methods disclosed on page 6, lines 9-15 contained essential features that were missing from claim 1.

4.2 Regarding objection (a), the board agrees with the patent proprietor that the application as filed discloses in a general manner the administration of not only MDCs but also pharmaceutical compositions containing them. The repeated reference to MDCs or their compositions throughout the application already teaches that MDCs can be administered as a composition. But, in particular, the general statement on page 16, lines 16-19 that "*[t]he described cells can be administered as a pharmaceutical or physiologically acceptable preparation or composition*" makes it clear

that the MDCs of the invention can be generally used in the form of a pharmaceutical composition.

The opponent argued that the passage on page 16, lines 16-19 was within the section "*Muscle-Derived Cell-Based Treatments*" starting on page 15, line 16, which related to Example 1 (page 15, line 24). As the method of isolation of MDCs in Example 1 was different to that of claim 11 as filed, the teaching of that section could not be combined with claim 11.

The board disagrees. The section "*Muscle-Derived Cell-Based Treatments*" refers in general terms to the MDCs and compositions comprising the MDCs of the invention. Although the section on page 15, line 24 refers to Example 1, it does so merely to indicate the markers that characterise the cells of the invention, which were studied in that example. It cannot be derived from this reference that the cells of the invention generally referred to in the section "*Muscle-Derived Cell-Based Treatments*" are confined to those illustrated in Example 1. Otherwise, it should also be understood that the teaching of the section is limited to e.g. mouse and rat cells, which are the MDCs studied in Example 1. This is clearly not the case since the section refers (page 16, line 4) to humans as a preferred source of cells.

4.3 Regarding objection (b), the board also agrees with the patent proprietor that the designation "adherent" and "non-adherent" cells has a proper, albeit non-literal, basis on page 6, lines 9-15 of the application as filed. This passage reads:

"*the cells are cultured in a flask in culture medium for between about 30 and about 120 minutes. During this*

period of time, the 'rapidly adhering cells' stick to the walls of the flask or container, while the 'slowly adhering cells' or MDCs remain in suspension. The 'slowly adhering cells' are transferred to a second flask or container and cultured therein for a period of 1-3 days. During this second period of time the 'slowly adhering cells' or MDCs stick to the walls of the second flask or container."

According to this passage, in a first step, cells are cultured for 30 to 120 minutes. During this period, some cells stick to the wall of the flask container and others remain in suspension. This operation corresponds exactly to step (a) of claim 1 at issue. Whether the cells that stick to the wall are called "rapidly adhering" cells or "adherent" cells does not make the cells different, both terms refer to the same reality. This applies equally to the cells that remain in suspension with regard to the designation "slowly adhering" or "non-adherent" cells. The cell populations behind the terms used in claim 1 and in the application as filed are identical; employing different labels does not add subject-matter.

The opponent also argued that the passage on page 6, lines 9-15 disclosed a specific embodiment which contained features missing from claim 1, e.g. that before plating, the cells from the skeletal muscle explant were stored, minced and digested with enzymes. Hence, claim 1 constituted an unallowable generalisation of that embodiment.

This argument is not convincing. Claim 1 describes a method starting from human skeletal muscle cells already isolated from the human subject. The prior operations to which the opponent refers (e.g. storing,

mincing and digesting) are customary steps for isolating cells from a muscle explant and not part of the method according to claim 1. Therefore, their absence in claim 1 does not add subject-matter.

4.4 Hence, claim 1 of the main request complies with Article 123(2) EPC.

5. Sufficiency of disclosure - Article 83 EPC

The opponent called into question that the MDC population obtained by the method of claim 1 was suitable for improving left ventricular contractility of the human heart. It argued that Example 1 of D9 showed that cells isolated after only two plating steps were not sufficiently myogenic for augmenting muscle tissue, a precondition for improving left ventricular contractility: at least five or six serial plating steps were necessary for this purpose.

The board agrees with the patent proprietor that the isolation method in Example 1 of D9 does not represent that of claim 1. It was carried out on rodent rather than human cells and, more importantly, it involved a different number and duration of plating steps. In contrast, Example 10 of the patent illustrates the invention as defined in claim 1. It showed (paragraphs [0125] and [0126]); paragraph [0127], last sentence; paragraph [0133], last sentence; and Table 4) that a human MDC population isolated in two subsequent plating steps of 30 to 120 minutes and two days was highly myogenic and potent in terms of muscle generation. When the cells were injected into the heart of an animal model (immunodepressed mice), they induced considerable improvement in left ventricular contractility after myocardial infarction (Table 5 and paragraph [0138]).

Thus, Example 10 of the patent proves that the cells isolated according to the method of claim 1 are suitable for the claimed purpose, and Example 1 of D9 does not raise serious doubts in this respect. The board therefore concludes that the invention is sufficiently disclosed for the skilled person to carry it out without undue burden and that claim 1 meets the requirements of Article 83 EPC.

6. Inventive step - Article 56 EPC

Claim 1 relates to the use of a pharmaceutical composition comprising an MDC population isolated from a human subject for improving the left ventricular contractility of that human subject.

The MDC population of claim 1 is isolated from cells extracted from a human skeletal muscle explant using two plating steps (see patent, page 12, line 54). In the first plating step, cells are allowed to attach to the culture container wall for 30 to 120 minutes. The attached cells, which are mostly fibroblasts, are discarded. The cells remaining in suspension are transferred to a second culture container. In this second plating step, cells are allowed to attach to the container wall during one to three days. The attached cells are the MDCs according to claim 1. They are highly myogenic and consist mostly of myoblasts showing long-term survival after administration into a soft tissue (patent, paragraphs [0014] and [0015]; paragraph [0127], last sentence; paragraph [0133], last sentence; and Tables 4 and 5). They are suitable for improving left ventricular contractility of the human heart (patent, Example 10).

6.1 The parties agreed that D9 is a suitable starting point for the assessment of inventive step in relation to claim 1.

Like the patent, D9 discloses (page 1, lines 8-20; page 6, lines 9-26 and page 24, lines 27-30) the isolation of human or animal MDCs showing long-term survival after transplantation into soft tissues. The MDCs can be used for treating conditions such as injury or weakness associated with myocardial infarction. Examples 1 and 7 of D9 are identical to those in the patent. Example 1 illustrates the isolation of mouse or rat MDCs using multiple plating steps. Most fibroblasts are separated in the first plating, which has a duration of one hour. The supernatant is then replated serially after 30-40% of the cells have adhered to each flask. The pool of cells isolated in the first four plating steps is designated as PP1-4 cells. They do not express the CD34 cell marker characteristic of MDCs (page 6, lines 11-15 and Table 2). MDCs according to the invention of D9, also called PP6 cells, are obtained in the fifth and sixth plating steps. When transplanted into a host animal, they survive more than ten times longer than the cells isolated in previous plating steps (page 31, lines 21-24). In Example 7, MDCs were injected into the ventricular wall of rats. The conclusion was that they could be used for treating conditions secondary to heart failure or myocardial infarction.

6.2 The parties agreed that the subject-matter of claim 1 differs from the teaching of D9 in at least two respects: the origin of the MDCs (human vs rodent) and the method for obtaining them (number and duration of plating steps). As the method of isolation determines the composition of the end cell population, ultimately

the distinguishing feature between the subject-matter of claim 1 and D9 is the composition of their MDC populations.

It was a matter of dispute whether the therapeutic indication in claim 1 constitutes an additional difference.

The board notes that, as argued by the opponent, the title of Example 10 of the patent refers to "improving left ventricular function", while the effect shown in it is an improvement in left ventricular contractility. Thus, the example equates left ventricular contractility with left ventricular function.

The patent proprietor is right that D9 does not explicitly refer to improving left ventricular contractility. However, like the patent, D9 (Example 7; page 10, lines 26-31; and Figures 7A and 7B) is concerned with improving ventricular function after myocardial infarction. As noted by the opponent (letter of 20 July 2021, point 5.2, first paragraph, penultimate sentence), myocardial infarction mostly happens in the left ventricle, which has a greater workload. Thus, the therapeutic indications in D9 and claim 1, if not identical, substantially overlap. Therefore, in the following, the board will consider that the therapeutic indication of claim 1 does not constitute a difference over D9. In any case, this consideration has no bearing on the outcome of the assessment of inventive step (see point 6.6 below).

6.3 The effect brought about by the differences agreed by the parties is that the MDCs of claim 1 are suitable for improving the left ventricular contractility of the human subject from which they have been obtained.

6.4 The objective technical problem to be solved may thus be formulated as providing a product suitable for improving left ventricular contractility in a human subject needing it.

The pharmaceutical composition of claim 1 solves this problem (see point 5 above).

6.5 On the issue of obviousness, the parties cited documents D8 and D5.

D8 (abstract; page 1, lines 8-18 and 23-29; and examples) relates to the isolation and use of myogenic cells, focusing on their orthopedic and urologic applications. Example 9 (page 88, line 27 to page 89, line 8), which is directed to orthopedic treatments, discloses the isolation of myogenic cells using a method as in claim 1 at hand, except that the cells are not human. Cells from a rabbit muscle explant were plated for one hour to remove fibroblasts. The supernatant was then replated for three days to obtain an end cell population enriched in myoblasts. Contrary to the patent proprietor's contention, this end cell population had to be detached from the culture container wall and isolated for its subsequent use in therapy.

D5 (title) is a study on the retention of differentiation potentialities of myogenic cells in *in vitro* cultures. It discloses (page 478, paragraphs 2-4) the isolation of myoblasts from a rat muscle explant using the steps defined in claim 1 at issue: primary cells were plated for 40 minutes to remove fibroblasts and epithelial cells; the supernatant was then replated

for three to four days to obtain an end cell population highly enriched in myoblasts.

6.6 Starting from D9, the board shares the patent proprietor's view that the skilled person would not have turned to the methods of D8 or D5 to improve left ventricular contractility in a human subject.

D9, D8 and D5 rely on the same general principle for isolating myogenic cells, namely that fibroblasts attach to the culture container wall much more rapidly than myoblasts. Thus, each plating step removes fibroblasts and enriches the end population in myoblasts. In the three documents, the primary cell culture was submitted to an initial plating step of no more than one hour in which fibroblasts were removed. D5 and Example 9 of D8 did not contain any additional purification step. At the end of the second plating, myoblasts were collected. In contrast, the method of Example 1 of D9 involved three additional plating steps in which remaining fibroblasts were separated. Thus, the MDC population collected at the end of the method of D9 (PP6 cells) was certainly more enriched in myogenic cells than that of D5 or Example 9 of D8. In fact, the method of D9 (Table 2) managed to completely exclude the cells that do not express the marker CD34, which is characteristic of MDCs. This was not the case when fewer plating steps (PP1-4 cells) were performed. Hence, the skilled person would have considered the end cell populations of D5 and Example 9 of D8 to be less myogenic than those of D9.

The skilled person wishing to translate the therapeutic effect on the myocardium shown in Example 7 of D9 from rodents to humans would therefore be prompted to use human myogenic cells isolated according to the method

of D9 and disregard the methods of D5 or Example 9 of D8.

Hence, the board holds that the subject-matter of claim 1 is inventive.

Main request - claims 2 to 5

7. The subject-matter of claims 2 and 3 is essentially the same as that of claim 1 except that claims 2 and 3 are directed to the use of MDCs as such rather than to a pharmaceutical composition containing them. Claims 4 and 5 are dependent on claims 2 and 3.

The opponent did not raise any objection directed specifically against any of claims 2 to 5.

Regarding the issue of added subject-matter (Article 123(2) EPC), the objection relating to the features "adherent" and "non-adherent" cells, also present in claim 2 and 3, was dealt with in point 4.4 above.

Regarding the issues of sufficiency of disclosure and inventive step, for the reasons put forward in relation to claim 1 (see points 5 and 6), the subject-matter of claims 2 to 5 also meets the requirements of Articles 83 and 56 EPC.

Main request - claim 6

8. Inventive step - Article 56 EPC

Claim 6 is directed to a method of isolating human MDCs which comprises steps (a) to (d) defined in claim 1. However, in claim 6, the duration of step (c) is not limited to one to three days.

8.1 The parties agreed that D8, in particular the two-step method disclosed in Example 9, is a suitable starting point for the assessment of inventive step in relation to claim 6. The board sees no reason to differ.

8.2 The method of claim 6 differs from the one in Example 9 of D8 in that the MDCs are of human origin.

The patent proprietor argued that there were two additional differences. First, the method of D8 does not disclose a second plating step because it does not indicate that the end cell population was detached from the container wall at the end of the process. Second, the cells of claim 6 are autologous.

These arguments must fail. First, D8 (page 89, lines 6-8) discloses that the supernatant of the first plating step was replated for three days to obtain a myoblast population. Obviously, the myoblast population had adhered to the culture container wall during those three days and had to be detached and isolated for its use in the subsequent therapeutic treatment. Second, the feature "autologous" in the method of claim 6 is void since the method does not encompass any step in which the isolated MDCs are administered to a subject.

8.3 The only effect that can be associated to the fact that the MDCs of claim 6 are human rather than rodent is that they can be administered to a human.

As claim 6 does not specify the duration of step (c), its end MDC population is not necessarily suitable for improving left ventricular contractility. This was conceded by the patent proprietor when asked by the board at the oral proceedings. It is apparent that if

step (c) is too short, the MDC population will not be sufficiently enriched in myogenic cells; if too long, MDCs would start differentiating and lose their myogenic character.

8.4 Thus, the objective technical problem to be solved by claim 6 is providing a method for isolating human MDCs.

8.5 The MDCs isolated in D8 (page 24, lines 17-20 and page 102, lines 17-19) were intended for therapeutic purposes in humans. Hence, isolating human MDCs by the method in Example 9 of D8 was an obvious solution to skilled person.

8.6 Therefore, the subject-matter of claim 6 is not inventive.

Second auxiliary request

9. The five claims of the second auxiliary request are identical to claims 1 to 5 of the main request. It has been shown above (points 4 to 7) that these claims meet the requirements of Articles 123(2), 83 and 56 EPC. Consequently, none of the grounds for opposition raised in these proceedings prejudice the maintenance of the patent on the basis of the second auxiliary request.

10. Remittal - Article 111 EPC

At the end of the oral proceedings before the board, the parties agreed that the case be remitted to the opposition division for adapting the description.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted:

   - Claims 1 to 5 of the second auxiliary request filed during the oral proceedings on 1 February 2022

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated