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Datasheet for the decision of 25 November 2021

Case Number: T 0150/18 - 3.3.01

Application Number: 10183361.4

Publication Number: 2266499

IPC: A61K35/12, A61L27/38, C12N5/077

Language of the proceedings: EN

Title of invention:
Three-dimensional tissue structure

Patent Proprietor:
Cellseed Inc.

Opponent:
Oser, Andreas

Headword:
Tissue structure/CELLSEED

Relevant legal provisions:
RPBA 2020 Art. 15(3)
EPC Art. 100(a), 54(2), 56

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It can be changed at any time and without notic

Keyword:
Oral proceedings - held in absence of party
Novelty - (yes)
Inventive step - (no)

Decisions cited:
G 0004/92

Catchword:

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Case Number: T 0150/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 25 November 2021

Appellant: (Opponent)	Oser, Andreas Sohnckestrasse 12 81479 München (DE)
Representative:	Prüfer & Partner mbB Patentanwälte · Rechtsanwälte Sohnckestraße 12 81479 München (DE)
Respondent: (Patent Proprietor)	Cellseed Inc. 3-61, Haramachi Shinjuku-ku Tokyo 162-0053 (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 November 2017 rejecting the opposition filed against European patent No. 2266499 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairman	A. Lindner
Members:	T. Sommerfeld
	L. Bühler

Summary of Facts and Submissions

I. European patent 2266499 is based on application 10183361.4, which is a divisional application of European patent application 04707319.2 (filed as international application published as WO 2005/011524). The patent is entitled "Three-dimensional tissue structure" and was granted with 19 claims.

Claims 1 as granted reads as follows:

"1. A three-dimensional structure for use in a method of implanting into a heart of human to treat dilated cardiomyopathy, dilated phase hypertrophic cardiomyopathy or ischemic heart disease, comprising a cell derived from a part other than myocardium of an adult,
wherein the three-dimensional structure is free from a scaffold, and has at least 6 cm^2 area, and wherein the cell is a myoblast."

II. An opposition was filed against the granted patent, the opponent requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 54(2) and 56 EPC and Article 100(a) EPC), lack of sufficiency of disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

III. During the proceedings before the opposition division, the patent proprietor requested that the opposition be rejected and the patent maintained as granted (main and sole request).

IV. In its decision announced at oral proceedings, the opposition division rejected the opposition on the basis of Article 101(2) EPC.

V. The opponent (appellant) lodged an appeal against this decision. In the statement of the grounds of appeal, the appellant requested that the decision of the opposition division be set aside and the patent be revoked in its entirety. It moreover submitted new documents D43 to D47.

VI. In its reply to the statement of grounds of appeal,the patent proprietor (respondent) requested that the appeal be dismissed and that the patent be maintained as granted (main request). Moreover, the respondent requested that the decision of the opposition division to admit documents D37 to D41 be reversed and these documents be excluded from the proceedings, and that new documents D43 to D47 not be admitted. It also submitted new documents D48 and D49.

VII. By letter dated 1 March 2019, the appellant requested that documents D37 to D41 be taken into consideration in the appeal proceedings and that documents D43 to D47 be admitted. It moreover submitted new documents D50 to D52.

VIII. A summons for oral proceedings before the board was issued, followed by a communication pursuant to Article 15(1) RPBA giving the board's preliminary opinion on some issues.

IX. By letter dated 19 April 2021, the respondent stated that it would not be represented at the oral proceedings and withdrew the request for oral proceedings.

X. Oral proceedings before the board took place as scheduled by videoconference and in the absence of the respondent. At the end of the oral proceedings the chairman announced the board's decision.

XI. The documents cited during the proceedings before the opposition division and the board of appeal include the following:

D1 Memon I A, presentation made at the 27th Annual Science Meeting of the Japanese Circulation Society, 28 March 2003
D1a experimental report (2 pages)
D16 experimental report (2 pages)
D20 experimental report and declaration by Y. Nagano (6 pages)

XII. The appellant's submissions, in so far as they are relevant to the present decision, may be summarised as follows:

Claim 1 did not require that the structure be made of human cells and in fact the patent also contemplated the possibility of using xenografts (paragraphs [0077], [0079] and [0080]). As to the claimed size feature, document D1a, which was an experimental report following as closely as possible the teaching of D1 (in particular on page 10 of D1), showed that myoblast cell sheets having an area of more than 6 cm^2 were obtained by following the teaching of D1. D1 also referred to cardiomyoplasty, a term that could be categorised as the two diseases in the claim, "hypertrophic cardiomyopathy" and "dilated cardiomyopathy".

If not novelty destroying, document D1 was the closest prior art and showed that myoblast sheets derived from rat myoblasts could be produced using a three-dimensional cell sheet construct on a temperature-responsive gel (slide "cell sheet constructs", lower slide on page 6, labeled page 4, of D1); this corresponded to the only technical teaching of the patent (Examples 7 and 8). Since the same rat myoblast sheet size was obtained as in Examples 7 and 8 of the patent, this indicated that the use of ascorbic acid was not essential. Document D20 provided further evidence for this observation, showing that it was instead the presence of serum that was important (Figures 1 and 2 and point 4.2 of D20). Thus, when applying the teaching of D1 to human myoblast cells and using common general knowledge, the skilled person would arrive at the claimed subject-matter without being inventive.

XIII. The respondent's arguments, in so far as they are relevant to the present decision, may be summarised as follows.

Treatment of humans was not disclosed in D1 apart from it being D1's long-term goal. Moreover, the fact that xenotransplantation was possible did not mean that any non-human cells, let alone the rat cell sheets of D1, would be suitable for successful xenotransplantation into humans. Paragraphs [0077] and [0080] of the patent did not allow the conclusion that the rat myoblast sheets of D1 or myoblast sheets from any other species could be suitable for implantation into the human heart. In addition, D1 did not disclose a sheet with the claimed size, nor did D1a show that such a size would inevitably result from the teaching of D1. Finally, D1 did not disclose the diseases recited in

the claim, namely dilated cardiomyopathy and dilated phase hypertrophic cardiomyopathy.

One distinguishing feature between claim 1 and D1 was the size of the cell structure which made the implant particularly suitable for therapeutic transplantation into diseased human hearts and allowed the treatment of even large affected areas. The objective technical problem could be formulated as the provision of an improved cell implant (in particular with respect to its area size) for the treatment of humans with dilated cardiomyopathy, dilated phase hypertrophic cardiomyopathy or ischemic heart disease. The problem was solved by the claimed subject-matter, as confirmed by the examples in the patent (Examples 7 and 9) and by the additional data provided in D16. The solution was not obvious because D1 was in no way concerned with the size of rat cell sheets, nor did it discuss which sheet sizes would be particularly useful. Moreover, as emphasised in the patent, it was not possible to use conventional techniques to provide implantable prosthetic tissue of a large size and excellent strength (e.g. paragraph [0017]). D1 explicitly specified that the thickness and size of myoblast sheets for clinical application were a limitation (page 14 labelled as page 12 - upper slide) and did not provide any pointer as to how the skilled person could obtain such large myoblast structures, let alone any motivation for including ascorbic acid in the culture medium in order to solve the technical problem. The post-published data provided by the appellant did not provide any further help. D1a related to porcine myoblast cells, which had not been shown to be suitable for transplantation into the human heart, and did not show that sheets with the desired size could be obtained without ascorbic acid; in fact most sheets

obtained in D1a had a smaller size. D20, on the other hand, did not include any size measurement and therefore no conclusions at all could be drawn. Hence, the skilled person would not arrive at the claimed subject-matter from the disclosure of D1, alone or in combination, in an obvious way.

XIV. The appellant requested that the decision under appeal be set aside and that European patent No. 2266499 be revoked. He further requested that documents D37 to D41 be taken into consideration in the appeal proceedings and that documents D43 to D47 be admitted.

The respondent requested in writing that the appeal be dismissed and that the patent be maintained as granted. The respondent moreover requested that the decision of the opposition division to admit documents D37 to D41 be reversed and that these documents be excluded from the proceedings, and that documents D43 to D47 not be admitted.

Reasons for the Decision

1. The appeal is admissible.

2. The oral proceedings before the board took place in the absence of the respondent, which had been duly summoned but decided not to attend.

The present decision is based on facts and evidence put forward during the written proceedings and on which the respondent has had an opportunity to comment. Therefore the conditions set forth in Enlarged Board of Appeal opinion G 4/92, OJ EPO 1994, 149, are met.

Moreover, as stipulated by Article 15(3) RPBA the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case.

3. Article 100(a) EPC / Articles 54(2) and 56 EPC

3.1 In the appealed decision, the opposition division came to the conclusion that granted claim 1 was novel over D1 because D1 did not disclose that the structure was made of human cells (which was implicit in granted claim 1) and did not disclose a cell sheet with a size of at least 6 cm^2.

3.2 The board disagrees that granted claim 1 implies that the cells used in the cell sheet have to be of human origin. Moreover, the board considers that D1, while presenting results for an animal model of cardiac ischemic disease, nevertheless suggests treatment of humans: D1 concludes in particular that the results obtained suggest "a promising strategy for myocardial regeneration clinically" (page 4, labeled as page 2, last sentence). However, D1 does not disclose a structure with the size of 6 cm^2. Hence claim 1 is novel over D1.

3.3 Document D1 is the closest prior art for the subject-matter of granted claim 1. The differences from the claimed subject-matter are as listed above under novelty, namely that the treatment of humans is not explicitly disclosed in D1 and that no size of the structure to be implanted is indicated in D1. As regards this latter feature, the board notes that the size of the structure is linked to the target of the

implant, as is stated in the patent application e.g. on page 96, first full paragraph and on page 28, third paragraph: "The term 'large size' in relation to a prosthetic tissue typically means that the prosthetic tissue has an area sufficient to cover a site to which the prosthetic tissue is implanted"; "The sufficient size of an implantable prosthetic tissue varies depending on a part targeted by implantation, but can be determined as appropriate by those skilled in the art". Hence the board considers that this feature is directly linked to the medical application, which is the treatment of myocardial conditions in humans, i.e. larger animals. The technical problem can thus be formulated as the provision of a treatment for the listed conditions in humans, and the solution is the use of a three-dimensional structure for heart implantation as claimed. Although there is no data in the application demonstrating that the effect was achieved in human patients, let alone for the specifically listed conditions, the board is convinced that the available data on rats, hamsters and pigs (Examples 2, 3, 4 and 9) can readily be taken as supporting evidence that the corresponding therapeutic effect would be attained in humans.

3.4 It then has to be determined whether the claimed solution is inventive. As regards the treatment of the listed conditions in humans, the board notes that the same basic evidence is presented in the patent and in D1. Like Example 2 of the patent, D1 teaches that autologous myoblast cell sheets regenerate myocardium in a rat model of cardiac disease caused by ischemia; the cell sheets were produced using exactly the same method as disclosed in Example 2 of the patent, namely by culturing autologous skeletal myoblasts isolated from leg muscle onto dishes coated with a temperature-

responsive macromolecule, and then detaching them as single monolayers and implanting two of these monolayers into the rat heart. Example 2 arrives at essentially the same conclusion as document D1: "Skeletal myoblast implantation attenuated heart remodeling and regenerated impaired myocardium to ameliorate global cardiac function as compared with cell implantation. This finding suggests a promising strategy for regenerative therapy for myocardium." (paragraph [0323] of the application as published; page 135, lines 20 to 25, of the application as filed). The board considers that, just as the teaching of Example 2 enables the use of skeletal myoblast cell structures in treating the conditions listed in the claim (all related to cardiac structural impairment due to ischemia), the same teaching of D1 would also render the use of this treatment for the same conditions obvious. It is true that the patent contains more data and in particular also presents data regarding a hamster model for dilated cardiomyopathy (Example 3) and a myocardial infarct pig model (Example 4), always using autologous skeletal myoblast cell sheets produced in the same way as in Example 2. The board nevertheless considers that these data merely back up what had been already enablingly disclosed in Example 2 of the patent (and in the prior art D1).

3.5 It would thus be obvious for the skilled person to apply the same method of treatment taught in D1 to the listed human conditions of the claim. In view of the much larger size of a human heart in comparison to a rat heart, it would also be apparent to the skilled person that larger implants might be needed. As mentioned above, there is no teaching in the patent that the specifically defined size of 6 cm^2 has any particular effect other than being adapted to the

targeted cardiac defect to be repaired. The board thus considers that the issue is whether the skilled person, based on the teaching of the prior art, would be able to routinely produce an implant structure with a size, such as 6 cm^2, which is large enough for it to be suitable for therapy of the human heart.

3.6 There is no indication either in the patent or in document D1 on how to attain such a large size, let alone the specific size of at least 6 cm^2. Example 7 of the patent application teaches the preparation of prosthetic tissue using ascorbic acid and concludes that "tissue was not cultured to a size of several millimeters in the culture system without ascorbic acids. If the tissue exceeded such a size, cracks occurred and the growth stopped" and "Thus, implantable prosthetic tissue could not be provided. In contrast, a prosthetic tissue of the present invention, which was cultured in a medium supplemented with an ascorbic acid, grown into an implantable size, and was easy to detach" (paragraph [0348] of the application as published; page 143, lines 7 to 15, of the application as filed). It is not apparent from this example (nor is it apparent from Example 8, which teaches the use of a specific type of ascorbic acid) what animal was used as the source for the myoblasts and whether they were cultured in the same way as in Example 2 (e.g. at the same cell confluence). From Example 9 it appears that the myoblasts were derived from hamsters, since it is stated that "The prosthetic tissue produced in the presence of ascorbic acids in Examples 7 and 8 was implanted into dilated cardiomyopathy hamsters. All the implanted mice were cured, and survived as long as ordinary hamsters do" (paragraph [0357] of the application as published; page 145, lines 29 to 32, of the application as filed). However, it is not apparent

how they were cultured in order to produce the cell sheet structures.

3.7 It is thus considered that culturing with ascorbic acid leads to the production of myoblast cell structures of "implantable size" but that culturing under the conditions described in Example 2 (and in document D1) also achieves this, since there it is also disclosed that the cell sheets could be successfully implanted and were therapeutically effective. Additionally, in the slides of D1 it is indicated that a size of 1.11 +/- 0.05 cm^2 was obtained (page 6, labelled as page 4, lower slide with the title "Cell Sheet Constructs") which appears similar to the size shown in Figure 38 of the patent, displaying the results of Example 7 when using ascorbic acid. There is no teaching in the prior art that an implant size of 6 cm^2 could not be reached when using the method of D1. D1 itself lists the thickness and size of myoblast sheets for clinical application among the limitations of the method (page 14, labelled as page 12, slide "Limitations"), but does not in any way teach that the desired properties could not be arrived at. Even if there was such a teaching away, this prejudice would not have been overcome by the patent since it is not taught there how to reach the desired size.

3.8 Post-published evidence has been filed by both parties in order to demonstrate that a 6 cm^2 implant size could be attained by following the teaching of D1 (D1a) or by using the method taught in Example 7 of the patent (D16 and D20). D1a discloses that the culture of swine skeletal myoblasts according to the teaching of D1 (or Example 2 of the patent, for that matter) leads to the production of myoblast cell sheets with measurements between 24 mm and 32 mm (for the shorter axis) and

between 24 mm and 34 mm for the longer axis (Table 2). Even if, as argued by the respondent, not all of these sheets have an area of at least 6 cm^2, still quite a number of them do, thus conclusively demonstrating that the culture method as disclosed in D1 allows implants with the size as claimed to be obtained. In this respect, the board disagrees with the conclusions of the opposition division that, because D1a used swine cells, it could not provide definitive evidence that cell sheets of at least 6 cm^2 could be obtained using human cells and the teaching of D1: it is noted that the same would then also be true for the patent, which, in the setting making use of culture with ascorbic acid, only used hamster myoblasts (as appears implicit from Example 9), and for the post-published document D16, submitted by the patent proprietor as evidence for the attainment of the claimed size when culturing with ascorbic acid, wherein it is not even disclosed what the animal source of the myoblasts is. Moreover, the cell culture protocol in Examples 7 and 8 of the patent and in D16 makes use of the coating with a temperature-responsive macromolecule too, just as is the case in D1, so that it cannot be concluded that the size obtained is a result only of the conditions of D1 or only of the addition of ascorbic acid.

3.9 Hence, the board considers that, contrary to the conclusions of the opposition division, the skilled person would arrive at an implant having the size as claimed in an obvious way. The board thus comes to the conclusion that granted claim 1 does not involve an inventive step and that therefore the ground for opposition under Article 100(a) EPC prejudices the maintenance of the patent as granted.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated