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Datasheet for the decision of 29 November 2012

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Application Number: 04006510.4

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Language of the proceedings: EN

Title of invention:
Tissue regenerative composition

Patentee:
Acell, Inc.

Opponent:
Popp, Eugen

Headword:

Relevant legal provisions:
EPC Art. 54(2)

Keyword:
Novelty (no, all requests)

Decisions cited:

Catchword:

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Case Number: T1359/09 - 3.3.10

D E C I S I O N
of the Technical Board of Appeal 3.3.10
of 29 November 2012

Appellant: (Patent Proprietor)	Acell, Inc. 6 Old Dee Road Cambridge, MA 02138 (US)
Representative:	Kirkham, Nicholas Andrew Graham Watt & Co. LLP St. Botolph's House 7-9 St. Botolph's Road Sevenoaks Kent TN13 3AJ (GB)
Appellant: (Opponent)	Popp, Eugen Meissner, Bolte & Partner GbR Postfach 86 06 24 81633 München (DE)
Representative:	Atkinson, Peter Birch Marks & Clerk LLP 1 New York Street Manchester M1 4HD (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 30 April 2009 concerning maintenance of the European Patent No. 1428540 in amended form.**

Composition of the Board:

Chairman: P. Gryczka
Members: R. Pérez Carlón
F. Blumer

Summary of Facts and Submissions

I. The present appeal lies from an interlocutory decision of the opposition division to maintain European patent No. 1 428 540 in amended form.

II. An opposition had been filed, on the ground *inter alia* that the subject-matter of the claims was not novel (Article 100(a) EPC).

III. *Inter alia*, the following documents have been cited:

D1: Sutherland *et al. The Journal of Urology* **1996**, vol. 156, pages 571-577,
D3: US 4,801,299,
D12: Brown *et al. Tissue Engineering*, **2006**, vol. 12, pages 519-526 and
D28: Birkholz *et al. EyeRounds.org* **2009**, pages 1-11.

IV. The opposition division decided *inter alia* that the subject-matter of claim 1 of the main request filed during the oral proceedings before it and of the first auxiliary request before it was not novel, but that the second auxiliary request then pending fulfilled the requirements of the EPC.

V. The patent proprietor (appellant 2) and the opponent (appellant 1) appealed the decision.

VI. With the statement setting out the grounds of appeal, appellant 2 filed three set of claims as main request and auxiliary requests 1 and 2.

VII. Claim 1 of the main request, which is the same as in the patent as granted, reads as follows:

"A matrix for restoring, remodeling, replacing or repairing a tissue of the urogenital tract, a tissue of the gastrointestinal tract, skin tissue, nervous tissue or connective tissue, comprising:
a devitalized mammalian epithelial basement membrane and tunica propria immediately subjacent to the basement membrane".

Claim 1 of the first and of the second auxiliary requests is identical to claim 1 of the second auxiliary request maintained by the opposition division, and differs from claim 1 of the main request in that it contains, additionally, the following feature:

"wherein the devitalized mammalian basement membrane is decellularized, delaminated or deepithelialized basement membrane".

VIII. Oral proceedings before the board took place on 29 November 2012.

IX. Appellant 1 argued that the subject-matter of claim 1 of all the requests on file was not novel over D1, which disclosed an acellular matrix for replacing bladder tissue, obtained from rat bladder, and which was lined by the original epithelial basement membrane and by the original matrix of the detrusor.

X. Appellant 2 argued that D1 failed to disclose the following features of claim 1:

- an intact epithelial basement membrane,
- a devitalized, decellularized, delaminated or deepithelialized epithelial basement membrane,

- a matrix comprising tunica propria, and
- a matrix suitable for restoring, remodeling, replacing or repairing a tissue.

The chemicals used in D1 were too harsh for obtaining an intact, functional basement membrane, which was proven by the poor performance of the matrix of D1 in terms of mortality and calculi formation.

As D1 disclosed a "full thickness" matrix (see abstract and page 574, "discussion", line 12), it must include the epithelium. The matrix of D1 contained "ghost cells" and rests of cellular membranes, as was apparent from figure 1 of D1. The word "acellular" in document D1 could not mean that no cells were present, since in that case no matrix would be left. For these reasons, appellant 2 concluded that the matrix of D1 did not have a devitalized, decellularized or deepithelialized epithelial basement membrane.

Alternatively, if the board would take the view that the tissue of D1 was completely decellularized, no tunica propria would be present, since this layer contained a non-negligible amount of cells.

The matrix of D1 was not biodegradable and the authors of D1 reported high mortality and calculi formation. For these reasons, appellant 2 concluded that it was not suitable for the intended use.

XI. Appellant 1 requested that the decision under appeal be set aside and that the European patent No. 1 428 540 be revoked.

XII. Appellant 2 requested that the decision under appeal be set aside and the patent be maintained on the basis of

any one of the main request, the auxiliary request 1 and the auxiliary request 2, all requests as filed with the statement setting out the grounds of appeal dated 4 September 2009.

XIII. At the end of the oral proceedings, the chairman announced the decision.

Reasons for the Decision

1. The appeal is admissible.

Main request:

2. Novelty, Article 54(2) EPC:

2.1 Document D1 describes a matrix obtained from rat bladder (see materials and methods) and its use for surgical augmentation cytoplasty of the bladder of Sprague-Dawley rats which had previously underwent partial cystectomy. The matrix of D1 is, therefore, suitable for restoring, remodelling, replacing or repairing a tissue of the urogenital tract, as required by claim 1 of the main request.

2.2 Both parties agreed on interpreting the term "devitalised" in claim 1 of the main request as "acellular or substantially acellular", according to paragraph [7] of the contested patent, and the board sees no reason to depart from this view.

The matrix of D1 is "acellular" (see the first paragraph of the abstract, the penultimate line on the left column of page 571; the heading of the section "materials and methods"; the third line under the heading "animal preparation" on page 572; the second

full paragraph on the right column of page 573; or the 6th line of the section "discussion" on page 574). According to D1, rat bladder is treated with distilled water to lyse the cells, with a detergent and, finally, with a deoxyribonuclease on 1 M NaCl solution "to extract all cells from the tissue". After these steps, the authors of D1 reported that:

"*absence of stromal and epithelial cellular elements was confirmed histologically*" (see materials and methods).

D1 discloses, therefore, an acellular matrix and, hence, a matrix whose epithelial basement membrane is devitalized, as required by claim 1 of the main request.

2.3 It remains to be examined whether the matrix of D1 contains tunica propria immediately subjacent to the epithelium basement membrane.

On the section "discussion", starting on line 12, D1 discloses:

"the inner surface of our extracellular matrix preparation is lined by the original epithelial basement membrane and the outer zone of the matrix represents the original matrix of the detrusor".

It is common ground between the parties that the tunica propria of native bladder lays immediately underneath the epithelial basement membrane, and above the tunica muscularis which, in the bladder, is the detrusor. The board sees no reason to depart from this view.

Since the authors of D1 had neither removed nor added

any intermediate layer between the epithelial basement membrane and the detrusor, it can only be concluded that the matrix of D1 also contains tunica propria immediately subjacent to the basement membrane, as in the native tissue.

2.4 D1 discloses, therefore, all the features of claim 1 of the main request, and renders the subject-matter of said claim not novel in the sense of Article 54(2) EPC.

3. Appellant 2 argued that paragraph [7] of the patent in suit defined that "for the purpose of the present invention, epithelial basement membrane means at least a portion of the *intact* epithelial basement membrane". According to appellant 2, the product of D1 could not contain at least a portion of the intact epithelial basement membrane for the following reasons:

3.1 The matrix of D1 could not have an intact, functional epithelial basement membrane after the harsh detergent treatment used.

Appellant 2 has not provided experimental evidence in support of this allegation. The authors of D1 disclose the presence of the epithelial basement membrane. The experimental evidence provided in D1 is consistent with the conclusions drawn therein, and with the scientific explanations contained in said document. In the view of the board, the contents of D1 cannot be rebutted by merely alleging that the results might have been different from those published.

3.2 Appellant 2 relied on D3 for proving that the treatment of D1 should have altered the epithelial basement membrane.

D3 discloses that deoxycholate is a denaturalising detergent, capable of dissolving the nuclear envelope and nuclear contents. However, D3 does not disclose the effect of this detergent, or the effect of denaturalising detergents in general on epithelial basement membranes, or on any other extracellular fibre.

3.3 Appellant 2 has also relied on D12 for proving that the process of the invention could not leave the epithelial basement membrane intact. The conditions used in D12 were comparable to those of D1; however, the matrix of D12 did not have collagen VI and, hence, lacked an epithelial basement membrane.

The process of D12 has been carried out over a different tissue (liver), and the alleged absence of collagen VI does not prove that this should have been also the case in D1, in particular taking into account that at least some parts of the liver do not have an epithelial basement membrane.

3.4 The passage on page 573, right column of D1, reads:

"initially the preponderance of cellular infiltrate occurred along the luminal surface with gradual migration into the entire matrix graft".

From this passage, appellant 2 concluded that D1 disclosed cell migration from the luminal surface into the matrix, which would not have been possible through an intact, functional epithelial basement membrane.

The board considers, on the contrary, that the first part of the sentence describes in fact the effect of an intact epithelial basement membrane according to

paragraph [49] of the contested patent and to the oral submissions of appellant 2, namely the fast formation of a cellular layer over said membrane.

The second part of the sentence mentions "gradual migration". The board does not share the interpretation of appellant 2 that it indicates migration from the upper epithelial layer through the epithelial basement membrane, but considers that it merely discloses a faster infiltration on the luminal surface than into the inner part of the matrix. This passage does not disclose which path these cells followed, and does not prove, therefore, that an intact epithelial basement membrane was not present.

3.5 The argument of appellant 2 that the matrix of D1 does not contain an intact epithelial basement membrane must, hence, be rejected.

4. In an alternative line of argument, appellant 2 maintained that the epithelial basement membrane of D1 was not devitalized in the sense required by present claim 1:

4.1 Appellant 2 relied on the wording "full thickness" for concluding that the matrix of D1 contained epithelial cells.

The expression "full thickness" appears twice in D1: on the abstract, and on page 574, under the heading "discussion", line 12. In this last appearance, it reads:

"*our extracellular matrix scaffold represents the full thickness of the tissue*".

This sentence, however, needs to be read in its context. The authors of D1 disclosed a known matrix with less layers, in contrast to which their matrix "*represents*" the full thickness of the tissue. This passage discloses that the matrix of D1 provides an scaffold for every histological layer of the tissue, and not, as maintained by appellant 2, that the matrix "is" a full thickness matrix. The next sentence under the heading "discusion" closer explains its structure:

"*the inner surface of our extracellular matrix preparation is lined by the original epithelial basement membrane and the outer zone of the matrix represents the original matrix of the detrusor*".

If the epithelial basement membrane lines the inner surface of the matrix, the epithelial cells of the bladder tissue used as starting material must necessarily have been removed. The interpretation of appellant 2 that the epithelium was a part of the matrix is in contradiction with the disclosure in document D1 of an acellular matrix lined by the epithelial basement membrane.

This argument must, therefore, be rejected.

4.2 Appellant 2 argued that D1 disclosed that distilled water was used "*to lyse cells and release intracellular contents*". In the view of appellant 2, D1 disclosed that only intracellular contents had been released; other parts such as the cell membrane were still present, in agreement with the disclosure of a "full thickness" matrix in D1. For this reason, appellant 2 concluded that the matrix of D1 was not "devitalized" in the sense of claim 1 of the main request.

However, document D1 explicitly discloses that the absence of cellular elements had been confirmed (see "materials and methods", page 572, lines 8-10).

This argument of appellant 2 must be rejected.

4.3 Appellant 2 argued that the passage of D1 under the heading "materials and methods", which reads:

"*absence of stromal and epithelial cellular elements was confirmed histologically in the bladder and gastric segments*"

was not consistent with the disclosure of D1 as a whole: if the whole stroma was absent, there would be no matrix left. The skilled person would then conclude that the epithelial basement membrane of D1 could not be completely acellular.

However, this sentence discloses the absence of cells in the stroma, not the absence of stroma. This argument should, therefore, fail.

4.4 Appellant 2 relied on the disclosure in figure 1 of D1 for proving that cells would still be present in the matrix disclosed. Figures A and B were labeled "mucosa" and "serosa". As the mucosa layer was present, appellant 2 concluded that the matrix of D1 contained the epithelium.

The board, however, agrees with the interpretation of appellant 1 that the labeling of figure 1 is only intended to show the direction of the tissue. This interpretation is consistent with the footnote in said figure "*...demostrating absence of cellular elements*" and with the colour obtained in the Masson trichrome

stain.

The board concludes that the labelling in figure 1 does not prove the presence of epithelium in the matrix of D1. This argument of appellant 2 is, therefore, rejected.

4.5 Appellant 2 has challenged the results of the Masson trichrome stain in D1, since they had been obtained over a non-fresh tissue. Appellant 2 has relied on document D28 for proving that the same sample could lead to different staining colours.

Appellant 2 has not provided evidence on the influence of the ageing of a tissue on a Masson trichrome stain. It could be concluded from D28 that the final colour of a sample can vary. However, the authors of D1 deduced from their protocol that the samples obtained contained no cells under the conditions chosen. This disclosure of D1 cannot be challenged only on the basis of allegations without sound evidence.

4.6 The board concludes, thus, that D1 discloses an acellular matrix, and therefore that its epithelial basement membrane is devitalized in the sense of claim 1 of the main request.

5. Appellant 2 argued that if the matrix of D1 would be decellularised, no tunica propria could be present, since this layer contained *per se* a non negligible amount of cells.

However, the wording of claim 1 does not require a fully functional tunica propria. Furthermore, claim 1 can be interpreted as having a devitalized epithelial basement membrane and a devitalized tunica propria; a

matrix comprising the extracellular elements of both layers falls within the subject-matter of claim 1.

This argument of appellant 2 must, thus, be rejected.

6. Finally, appellant 2 alleged that the matrix of D1 was not suitable for the intended use in the light of the high mortality reported, and of the high incidence of calculi. In the view of appellant 2, the matrix of D1 was not sufficiently biodegradable, and lead for this reason to ineffective healing.

Document D1 discloses the use of its matrix for regenerating bladder tissue, and the degree of success is not a feature of claim 1. The board concludes, thus, that the matrix of D1 is suitable for the intended use defined in claim 1 of the main request.

7. Appellant 2 further argued that it was the task of appellant 1 to prove the correctness of the disclosure of D1.

The board considers, however, that appellant 1 had discharged its onus of proof by providing document D1 and a full, sound argumentation relying on the disclosure of this document. Thus, in the absence of experimental evidence, the arguments of appellant 2 contradicting the disclosure of D1 must be rejected.

8. For these reasons, the board concludes that there is no inconsistency in the disclosure of D1, which describes all the features of claim 1 of the main request for the reasons explained in point 2. above. Said request must thus be refused for lack of novelty.

First and second auxiliary requests:

9. Novelty, Article 54(2) EPC:

Claim 1 of the first and second auxiliary requests further requires that the devitalized epithelial basement membrane is decellularized, delaminated or deepithelialized basement membrane.

Since the board has considered when examining the main request (see point 2.2) that the feature "devitalized" meant "acellular" and the embodiments "decellularized" and "deepithelized" in claim 1 of these auxiliary requests fall within the definition "acellular", the subject-matter of claim 1 of the first and second auxiliary requests is not novel over the matrix disclosed in D1 for the same reasons as the main request.

These requests must therefore also be refused.

10. Since the board arrived to the conclusion that the subject-matter of none of the requests on file was novel, it is not necessary to decide whether the claimed subject-matter is clear and finds a basis in the application as filed.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent in revoked.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated