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Datasheet for the decision of 6 February 2007

Case Number: T 1072/04 - 3.3.03

Application Number: 97943460.2

Publication Number: 0927196

IPC: C08B 37/04

Language of the proceedings: EN

Title of invention:
Polymers containing polysaccharides such as alginates or modified alginates

Applicant:
THE REGENTS OF THE UNIVERSITY OF MICHIGAN

Opponent:
-

Headword:
-

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)

Keyword:
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1072/04 **-** 3.3.03

D E C I S I O N
of the Technical Board of Appeal 3.3.03
of 6 February 2007

Appellant: THE REGENTS OF THE UNIVERSITY OF MICHIGAN
Wolverine Tower, Room 2071
3003 S. State Street
Ann Arbor
Michigan 48109-1280 (US)

Representative: Bizley, Richard Edward
HLBBshaw
Merlin House
Falconry Court
Bakers's Lane
Epping
Essex CM16 5DQ (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office dated 23 January 2004 and posted 17 February 2004 refusing European application No. 97943460.2 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: R. Young
Members: C. Idez
E. Dufrasne

Summary of Facts and Submissions

I. European patent application No. 97 943 460.2, based on International application No. PCT/US97/16890, filed on 19 September 1997, claiming the priority of three earlier US-patent applications and published under No. WO-A-98/12228 on 26 March 1998 was refused by a decision of the Examining Division announced orally on 23 January 2004 and issued in writing on 17 February 2004.

II. The decision of the Examining Division was based on a main request consisting of 13 claims, on a first auxiliary request consisting of 12 claims, on a second auxiliary request consisting of 16 claims and on a third auxiliary request consisting of 14 claims, all submitted with the letter of the Applicant dated 22 December 2003.

The Examining Division rejected the main request on the grounds that the subject-matter of Claim 1 thereof lacked novelty over Example 13 of document D1 (EP-A-0 712 635) and over document D3 (WO-A-95/24 429). According to the decision, the subject-matter of Claim 1 of the first auxiliary request lacked inventive step in view of document D3, and the subject-matter of Claims 1 and 9 of the second auxiliary request and the subject-matter of Claims 1 and 8 of the third auxiliary request lacked inventive step in view of the combination of document D3 with document D2 (US-A-5 227 298).

It was further held in the decision that dependent Claims 2 and 10 of the second auxiliary request and dependent Claims 2 and 9 of the third auxiliary request lacked clarity.

III. Notice of Appeal was filed on 26 April 2004 by the Appellant (Applicant) with simultaneous payment of the prescribed fee. With the Statement of Grounds of Appeal filed on 24 June 2004, the Appellant submitted a new main request and three auxiliary requests.

IV. A communication was issued on 30 March 2006 by the Board, in which the Board gave its preliminary view concerning issues under Article 84 EPC, in particular in view of the expression "cell attachment peptide" in the claims of the requests filed with the Statement of Grounds of Appeal, concerning the question of novelty in view of Example 13 of D1, the question of inventive step in view of documents D2 and D3, and the allowability of the requests under Article 123(2) EPC. All these points were addressed by the Appellant in its response dated 28 July 2006, which was accompanied by four sets of claims representing a new main request and its new first, second and third auxiliary requests and by, inter alia, the following documents:

D8: B. Alberts et al. "Molecular Biology of The Cell"; Third Edition, Garland Publishing, Inc, 1994, pages 986-1000;

D9: H. R. Petty, "Molecular Biology of Membranes — Structure and Function", Plenum Press, 1993, pages 273-277;

D10: EP-B1-0-391 928; and

D11: EP-B1-0-929 323.

The following arguments have been ***inter alia*** presented by the Appellant:

(i) Concerning Article 84 EPC:

(i.1) The definition of a molecule useful for cell adhesion had been clarified by stating that it was "a peptide containing a cell attachment ligand".

(i.2) The expression "peptide containing a cell attachment ligand" had a clear meaning to one skilled in the art, as confirmed by documents D8 to D11.

(ii) Concerning novelty and inventive step:

(ii.1) The problem on which the invention focused might be regarded as how to provide a matrix suitable for cell transplantation and tissue engineering in which the use of specific cell attachment ligands in the material provided high control over cell-matrix interactions.

(ii.2) D1 related to medical polymer gels adapted to deliver a drug. The drug was attached to the polymer through a cleavable group that could be cleaved via an enzymatic reaction to release the drug.

(ii.3) Example 13 of D1 disclosed an alginate gel to which the growth factor TGF β (a protein) was releasably bonded. As with many bioactive molecules,

TGF β would interact with receptors on the cell surface.

(ii.4) Growth factors such as TGF β were not regarded as cell adhesion molecules in the art.

(ii.5) Thus, D1 did not disclose a modified alginate comprising a polymer containing at least one alginate chain section to which was covalently bonded at least one molecule useful for cell adhesion wherein the molecule was a peptide containing a cell attachment ligand.

(ii.6) Since a growth factor was not a cell adhesion ligand and since it served a different purpose, Dl was not concerned with the problem on which the present invention was focused and could not provide any guidance to the solution of this problem.

(ii.7) Document D3 was concerned with a method of producing activated esters of carboxy polysaccharides.

(ii.8) D3 did not disclose, clearly and unambiguously, the combination of alginic acid with a polypeptide.

(ii.9) Furthermore, D3 did not address the problem on which the present invention was focused.

(ii.10) Although D3 suggested that modified hyaluronic acid (HA) might be used for coating laboratory equipment and dishes for the cultivation and regeneration of cells and tissues, there was no specific suggestion of the suitability of such materials as scaffolds for cell transplantation.

(ii.11) Concerning document D2, it failed to disclose covalent binding of the alginate to either a molecule for cell adhesion or to cells. D2 disclosed only encapsulation and not covalent bonding.

(ii.12) Inventive step of the claimed subject-matter resided in the alginate material having a molecule useful for cell adhesion covalently bonded thereto.

V. In a communication issued on 17 November 2006 accompanying a summons to oral proceedings, the salient issues were identified by the Board as being the allowability of the requests under Article 123(2) EPC, the problem of clarity linked to the presence in the claims of the expressions "molecule useful for cell adhesion which is a peptide containing a cell attachment ligand" and the question of novelty over documents D1, and D18 (Derwent Abstract Nr 1993-049148[06] referring to the Japanese patent application JP-A-05000081) and the question of inventive step in view of documents D2 and D18.

VI. With its letter dated 5 January 2007, the Appellant filed five further auxiliary requests, and submitted, *inter alia*, the following documents:

D18b: English translation of the JP-A-05000081; and

D19: Copy of an Internet Publication of the University of Colorado entitled "Cell adhesion molecules"; and

D20: Affidavit of Dr David J. Mooney.

It also presented ***inter alia*** the following arguments:

(i) The expression "molecule useful for cell adhesion which is a peptide containing a cell attachment ligand" was clear to the skilled worker. Reference was made to documents D19 and D20.

(ii) As evidenced by the Affidavit of Dr Mooney, TGF β, as disclosed in D1 would in no way be considered by the skilled reader to constitute a "molecule useful for cell adhesion".

(iii) As evidenced by the Affidavit of Dr Mooney and by D18b (particularly Example 1), there was no disclosure or suggestion in the reference that the collagen was covalently bonded to the alginate bead. The "bridge" referred to in the D18 abstract pertained to crosslinks within the collagen.

VII. With its letter dated 10 January 2007 the Appellant submitted the following document:

D25: B. Alberts et al. "Molecular Biology of the Cell", Third Edition, Garland Publishing, Inc. New York & London, 1994; pages 963 to 971.

and with its letter dated 11 January 2007 it filed a signed version of the affidavit of Dr Mooney (D20).

VIII. With its letter dated 1 February 2007, the Appellant submitted a new main request and two new auxiliary requests which replaced all the previous requests. Claim 1 of the main request read as follows:

"An injectable solution or gel for forming cell transplantation matrices comprising a modified alginate which comprises a polymer containing at least one alginate chain section to which is covalently bonded at least one molecule useful for cell adhesion wherein the molecule is a peptide containing a cell attachment ligand."

IX. Oral proceedings took place before the Board on 6 February 2007.

Following preliminary observations from the Board concerning the allowability of the main request submitted with the letter of 1 February 2007 under Articles 123(2) EPC and 84 EPC, and the question as to whether the feature in Claim 1 of the main request that at least one molecule useful for cell adhesion wherein the molecule was a peptide containing a cell attachment ligand was covalently bonded to the alginate chain section could constitute a distinguishing feature over the disclosure of document D1 (Example 13) and of Example 8 of document D6 (WO-A-93/21906) read in the light of documents D19 and D25 filed by the Appellant with its submissions dated 5 January 2007 and 11 January 2007, the Appellant submitted a new main request consisting of twelve claims.

Claims 1 to 12 of the main request read as follows:

"1. An injectable solution or a gel for forming cell transplantation matrices comprising a modified alginate which comprises at least one alginate chain section to which is covalently bonded at least one molecule useful for cell adhesion wherein the molecule is a peptide

containing the amino acid sequence arginine-glycine-aspartic acid (RGD), GREDVY, YIGSR or REDV, and further comprising viable cells for said transplantation.

2. A solution or a gel of claim 1 wherein the molecule useful for cell adhesion wherein the molecule useful for cell adhesion contains the amino acid sequence arginine-glycine-aspartic acid (RGD).

3. A solution or a gel of either claim 1 or 2 wherein the molecule useful for cell adhesion is bonded through a uronic acid residue on the alginate chain section.

4. A solution or a gel of any one of claims 1 to 3, wherein the alginate chain section has a molecular weight of less than 50,000.

5. A solution or a gel of any one of claims 1 to 3 wherein the alginate chain section has a molecular weight of less that 30,000.

6. A solution or a gel of any one of claims 1 to 3 wherein the alginate chain section has a molecular weight of 100,000 or more.

7. A transplantation matrix comprising a hydrogel of a modified alginate which comprises at least one alginate chain section to which is covalently bonded at least one molecule useful for cell adhesion wherein the molecule is a peptide containing the amino acid sequence arginine-glycine-aspartic acid (RGD), GREDVY, YIGSR or REDV, and further comprising viable cells for said transplantation.

8. A matrix of claim 7 wherein the molecule useful for cell adhesion contains the amino acid sequence arginine-glycine-aspartic acid (RGD).

9. A matrix of either of claim 7 or claim 8 wherein the molecule useful for cell adhesion is bonded through a uronic acid residue on the alginate chain section.

10. A matrix of any one of claims 7 to 9, wherein the alginate chain section has a molecular weight of less than about 50,000.

11. A matrix of any one of claims 7 to 9 wherein the alginate chain section has a molecular weight of less that 30,000.

12. A matrix of any one of claims 7 to 9 wherein the alginate chain section has a molecular weight of 100,000 or more."

The Appellant also submitted a document referred to below as D26 (Sheet showing the structural sequences of lectin from Ulex Europaeus) in order to show that lectin from Ulex Europaeus such as the one referred to in Example 8 of D6 did not exhibit any of the specific peptide sequence RGD, GREDVY, YIGSR or REDV.

The discussion then moved to the question of inventive step. In that respect the Appellant submitted arguments starting either from D2 or D18 as the closest state of the art, which may be summarized as follows:

(i) One essential feature of the transplantation matrices according to D2 was that the polylysine would be ionically linked to the alginate polymer.

(ii) There would have been no hint for the skilled person to omit this essential feature and to replace the polylysine by a peptide compound forming a covalent bond with the alginate and having cell attachment properties.

(iii) Furthermore, D2 required that the encapsulation matrices would exhibit a two-layer structure.

(iv) Concerning D18 (D18b), it was not concerned with transplantation matrices but only with cell culture media.

(v) The presence of epoxy compound would also preclude the use of the collagen coated alginate beads for transplantation purposes.

(vi) Furthermore, the collagen was not covalently bound to the alginate.

X. The Appellant requested that the decision of the Examining Division be set aside, and a patent be granted on the basis of the main request (claims 1 to 12) filed at the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Wording of the claims*

2.1 Claim 1 of the main request is supported by original Claims 13, 1, 3 and 4, by lines 1 to 5 on page 3, lines 1 to 5 on page 27 and lines 4 to 5 on page 30 of the application as originally filed (cf. WO-A-98/12228).

2.2 Independent Claim 7 is supported by original Claim 14 read in combination with original Claims 1, 3 and 4, with lines 1 to 5 on page 27 and lines 4 to 5 on page 30 of the application as originally filed.

2.3 Dependent Claims 2, 3, 4, 5 and 6 and dependent Claims 8, 9, 10, 11 and 12 are supported by original Claims 6, 2, 9, 10 and 11.

2.4 Consequently, Claims 1 to 12 meet the requirements of Article 123(2) EPC.

2.5 Since the expression "molecule useful for cell adhesion" has been clarified by indicating that this molecule is a peptide containing a specific amino acid sequence (i.e. RGD, GREDVY, YIGSR or REDV), the Board is satisfied that the requirements of Article 84 EPC are met by the main request.

3. No objection under Article 83 EPC has been raised by the Examining Division in the course of the examining procedure. The Board is also satisfied that the main request meets the requirements of Article 83 EPC.

4. *Novelty*

4.1 According to the decision of the Examining Division, the novelty of the subject-matter of Claim 1 of the main request submitted with letter dated 22 December 2003 has been challenged only in view of document D3 and of Example 13 of document D1.

4.2 In this connection the Board notes, however, that Claim 1 of that main request read as follows:

"A modified alginate which comprises at least one alginate chain section to which is covalently bonded at least one molecule useful for cell adhesion wherein the molecule is a cell attachment peptide, a proteoglycan attachment peptide sequence, a proteoglycan, an RGD peptide, fibronectin, vitronectin, Laminin A, Laminin B1, Laminin B2, Collagen 1 or thrombospondin."

4.3 It is hence clear that the subject-matter of independent Claims 1 and 7 of the present main request has been restricted in comparison to the subject-matter of Claim 1 of the main request on which the decision of the Examining Division was based.

4.4 Since, as indicated in the decision under appeal (cf. points 5.2 and 5.3 thereof) neither D1 nor D3 discloses alginate compositions comprising viable cells, it is evident that, at least for this reason, documents D1 and D3 cannot be novelty destroying for the subject-matter of independent Claims 1 and 7. The same conclusion equally applies for the subject-matter of dependent Claims 2 to 6, and 8 to 12.

4.5 Although document D6 has not been considered in the decision under appeal as being novelty destroying for the subject-matter of Claim 1 of the main request then on file, the Board observes that document D6 in its Example 8 discloses an alginate hydrogel which is covalently bonded to the lectin from Ulex Europaeus, and that in view of document D19 (cf. page 2, paragraph "Selectins") and of document D25 (page 967, lines 35 to 42) the lectin from Ulex Europaeus would fall under the Appellant's own definition of a molecule useful for cell adhesion.

4.6 The Board notes, however, that the hydrogel of Example 8 of D6 does not comprise viable cells, and that, as shown by document D26 submitted by the Appellant in the course of the oral proceedings before the Board, the lectin from Ulex Europaeus does not appear to contain any of the peptide sequence RGD, GREDVY, YIGSR or REDV.

4.7 Consequently, the subject-matter of Claims 1 to 12 must also be considered as novel over document D6.

4.8 Document D18 and document D18b, which is an English translation of the Japanese patent application JP-A-05000081 to which D18 refers, both mention that this Japanese patent application discloses hydrogels of alginates which have been coated by collagen to which viable cells are adhered.

4.9 While it is indicated in D18 (Example) that the collagen coated alginate gel is treated with an epoxy compound for introducing "bridges", according to D18b

(Example 1), the epoxy compound is used to introduce "crosslinks".

4.10 Although in the Board's view it would not be unthinkable that the term "bridge" mentioned in D18 might encompass covalent bonds between the amino group of the collagen and the acid and/or the hydroxy groups present on the alginate polymer generated by the reaction with the epoxy compound, the Board, in view of the affidavit of Dr Mooney (cf. D20; paragraph 4) according to which the epoxy compound only crosslinks the collagen and in the absence of undisputable evidence from its side that a covalent bonding is inevitably created between the collagen and the alginate through the epoxy compound, can only consider that it has not been clearly and unambiguously established that the alginate gel disclosed in the Japanese patent application to which D18 refers is indeed covalently bonded to the collagen.

4.11 Consequently, the novelty of the subject-matter of Claims 1 to 12 is to be acknowledged over the disclosure of D18 (D18b).

5. *Closest state of the art, the technical problem*

5.1 The application in suit is concerned with modified alginate compositions comprising viable cells which can be used for cell transplantation matrices. Such compositions are disclosed in document D2, which the Board considers as the closest state of the art.

5.2 Document D2 deals with a method for encapsulation of viable cells such as pancreatic islets, within microcapsules having a double wall of polylysine alginate layering. The microcapsules are used as transplantation matrices (column 4, lines 11 to 31).

5.3 While it is true, as submitted by the Appellant under point 4.2 of the Statement of Grounds of Appeal, that D2 does not mention that the alginate should be covalently linked to a molecule for cell adhesion, and that the polylysine is ionically bonded to the alginate (cf. D2, column 8, lines 36 to 39), it cannot, however, be excluded in view of lines 24 to 27 on page 24 of the application in suit, that the modified alginate according to D2 would also exhibit some cell adhesion type properties.

5.4 In that context, the Board further notes that that there is no evidence (e.g. experimental data) on file showing that the transplantation matrices obtained from the modified alginate compositions according to the application in suit exhibit improved properties in comparison to those obtained from the modified alginate compositions according to D2.

5.5 Consequently, in the absence of such comparison, the technical problem starting from document D2 is to be seen in the provision of alternative modified alginate compositions useful for the manufacture of cell transplantation matrices.

5.6 According to the application in suit this problem is solved by using an injectable solution or a gel comprising a modified alginate which is covalently

bonded to a molecule containing a specific peptide sequence (i.e. RGD, GREDVY, YIGSR or REDV) and viable cells as defined in Claim 1 of the main request.

6. *Inventive step*

6.1 It remains to be decided whether the proposed solution was obvious having regard to the prior art documents referred to in the decision under appeal (cf. page 2, paragraph 11, i.e. documents D1, D2, D3, D4 (WO-A-93/09176), D5 (WO-A-94/07536), and D6) as well as the document D18 (D18b) cited during the appeal proceedings.

6.2 As indicated above, one essential feature of the modified alginate used in the manufacture of transplantation matrices according to document D2 is that the polylysine is ionically bonded to the alginate. Consequently, D2 cannot offer to the skilled person a hint to the solution of the technical problem proposed by the application in suit, i.e. replacing the polylysine by a molecule which is covalently bonded to the alginate, let alone by a molecule comprising the specific peptide sequence referred above in paragraph 5.6.

6.3 Document D4 relates to crosslinkable polysaccharides, such as alginates, exhibiting a moiety containing a carbon-carbon double bond or triple bond capable of free radical polymerization (Claims 1 and 3). Although D4 further discloses the encapsulation of biologically active materials such as living cells (e.g. islets of Langerhans) by crosslinking alginates exhibiting such unsaturated moiety (cf. Claim 26; Example 28), it is evident that it does not suggest that modified

alginates being covalently bonded to a molecule exhibiting the specific peptide sequence referred in paragraph 5.6 above could be also be used in the manufacture of cell transplantation matrices. D4 cannot therefore provide a hint to the solution proposed in the application in suit.

6.4 Documents D1, D3, D5, D6, and D18 (D18b) are even less relevant since they are not concerned with the use of alginate compositions for cell transplantation matrices. Consequently, these documents cannot be of any help for solving the technical problem.

6.5 In view of the above, the Board comes to the conclusion that the subject-matter of Claim 1, and by the same token that of dependent Claims 2 to 6 does not arise in an obvious manner from the cited prior art (Article 56 EPC). The same conclusion applies ***a fortiori*** to the subject-matter of independent Claim 7 which is directed to a transplantation matrices comprising a hydrogel of a modified alginate in the ambit of Claim 1, and to the subject-matter of dependent Claims 8 to 12.

7. It thus follows that the main request of the Appellant Respondent is allowable, and that the decision under appeal must be set aside.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of the main request (Claims 1 to 12) filed at the oral proceedings and after any necessary consequential amendment of the description and drawings.

The Registrar: The Chairman:

E. Görgmaier R. Young