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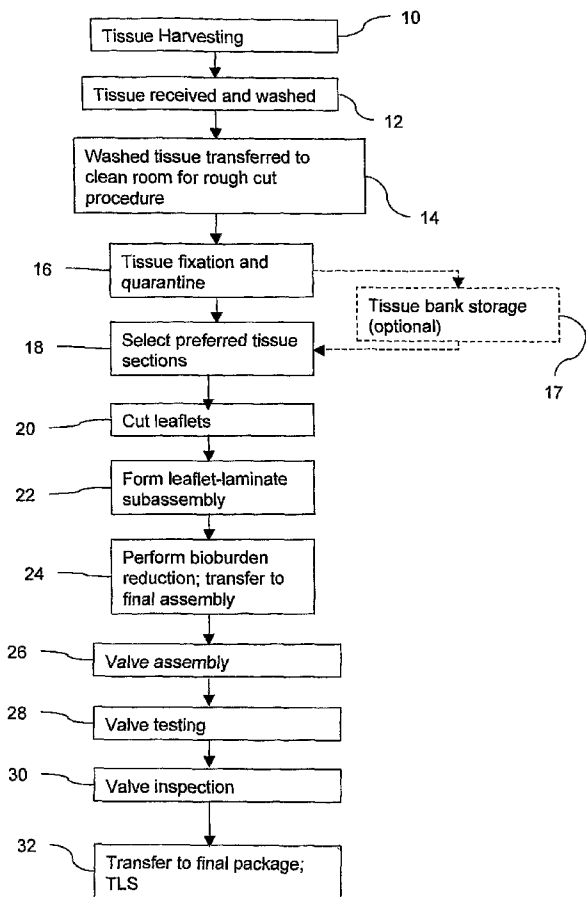
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11/032,923 11 January 2005 (11.01.2005) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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[Continued on next page]

(54) Title: METHODS FOR PROCESSING BIOLOGICAL TISSUE



(57) Abstract: A method for processing biological tissue used in biological prostheses includes providing a tissue procurement solution formed from a phosphate buffered saline (PBS) solution and a chelating agent. The tissue is transferred from the tissue procurement solution and undergoes chemical fixation. The fixed tissue is then immersed in a series of fresh bioburden reduction process (BRP) solutions to extract phospholipids. The tissue procurement solution reduces the bioburden on the stored tissue and preserves tissue architecture by minimizing tissue swelling. The tissue procurement solution further reduces calcium from the incoming water and/or tissue, and inhibits enzymes that digest the collagen matrix. The serial immersion of the tissue in the fresh bioburden solutions ensures optimal extraction of phospholipids thereby mitigating subsequent calcification of the tissue.

WO 2006/076316 A3



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INTERNATIONAL SEARCH REPORT

International application No  
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**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. A01N1/02

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
Minimum documentation searched (classification system followed by classification symbols)  
A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  
EPO-Internal, WPI Data, CHEM ABS Data

| C. DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
|--|--|-----------------------|
| Category*                              | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X                                      | US 2003/035843 A1 (LIVESEY STEPHEN A [AU] ET AL) 20 February 2003 (2003-02-20)     | 1-8, 11, 12           |
| Y                                      | paragraphs [0176], [0211]  | 19, 20                |
| X                                      | US 4 994 237 A (LOGIN GARY R [US] ET AL) 19 February 1991 (1991-02-19)             | 1-8, 11, 12           |
| Y                                      | table 1<br>claim 1   | 19, 20                |
| X                                      | US 2003/125813 A1 (CARPENTIER SOPHIE M [FR] ET AL) 3 July 2003 (2003-07-03)        | 13-18                 |
| Y                                      | paragraphs [0043] - [0082]   | 19, 20                |
| X                                      | US 2003/226208 A1 (CARPENTIER ALAIN F [FR] ET AL) 11 December 2003 (2003-12-11)    | 13-18                 |
| Y                                      | paragraph [0013] - paragraph [0057]  | 19, 20                |
|  | -/--   |                       |

Further documents are listed in the continuation of Box C.  See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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| Date of the actual completion of the international search<br><b>1 June 2007</b> | Date of mailing of the international search report<br><b>12/06/2007</b> |
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| Name and mailing address of the ISA/<br>European Patent-Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Authorized officer<br><b>Fort, Marianne</b> |
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## INTERNATIONAL SEARCH REPORT

International application No  
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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
|--|---|-----------------------|
| Category*  | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
| X  | WO 2004/006974 A (EDWARDS LIFESCIENCES<br>CORP [US]) 22 January 2004 (2004-01-22)   | 13-18                 |
| Y  | paragraph [0082] - paragraph [0092]<br>-----  | 19,20                 |
| A  | US 4 885 005 A (NASHEF AWS S [US] ET AL)<br>5 December 1989 (1989-12-05)<br>cited in the application<br>the whole document<br>----- | 13-20                 |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2006/000732

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  
  
1-8, 11-12(part.), 13-20
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8, 11-12(part.)

A solution for storing biological tissue used in a biological prostheses comprising a mixture of PBS solution having a concentration of at least 50 mM and a chelating agent and a method for storing harvested tissue using the same

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2. claims: 9-10, 11-12 (part.)

A solution for storing biological tissue used in a biological prostheses comprising a mixture of a chelating agent and a buffer selected from the group consisting of a phosphate-based buffer, a citrate-based buffer, and a borate buffer, the buffer having a concentration of at least 100mM and a method for storing harvested tissue using the same

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3. claims: 13-20

A method for processing fixed biological tissue comprising the steps of:

- (a) immersing the fixed biological tissue in a first fresh bioburden reduction process (BRP) solution
- (b) heating the first fresh BRP solution to a temperature of about 37°C
- (c) removing the fixed biological tissue from the fresh BRP solution
- (d) immersing the fixed biological tissue in a next fresh BRP solution; and
- (e) heating the next fresh BRP solution to a temperature of about 37°C

or

immersing tissue in a mixture of PBS solution having a concentration of at least 50mM and a chelating agent; transferring the tissue to a phosphate buffered fixation solution; cutting a portion of the tissue into a desired shape; transferring the cut tissue portion into a serie of fresh bioburden reduction process solutions, wherein each fresh BRP solution is heated for a period of time.

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date   |
|--|------------------|-------------------------|--|
| US 2003035843                          | A1               | 20-02-2003              | NONE   |
| US 4994237                             | A                | 19-02-1991              | NONE   |
| US 2003125813                          | A1               | 03-07-2003              | AU 2003214801 A1 24-07-2003<br>BR 0306744 A 28-12-2004<br>CA 2471197 A1 17-07-2003<br>EP 1478413 A2 24-11-2004<br>JP 2005514113 T 19-05-2005<br>WO 03057269 A2 17-07-2003<br>US 2005071926 A1 07-04-2005 |
| US 2003226208                          | A1               | 11-12-2003              | NONE   |
| WO 2004006974                          | A                | 22-01-2004              | AU 2003249272 A1 02-02-2004<br>BR 0305562 A 28-09-2004<br>CA 2490060 A1 22-01-2004<br>EP 1531878 A1 25-05-2005<br>JP 2005532877 T 04-11-2005   |
| US 4885005                             | A                | 05-12-1989              | NONE   |