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[Continued on next page]

(54) Title: TISSUE-ENGINEERED PUMPS AND VALVES AND USES THEREOF

(57) Abstract: The present invention provides tissue-engineered pumps and valves, methods of fabricating such pumps and valves, and methods of use of such pumps and valves.

FIG. 1A

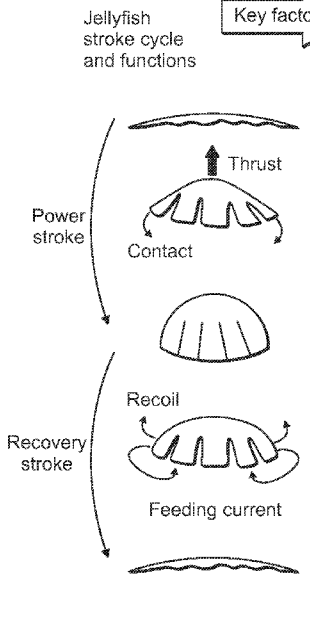
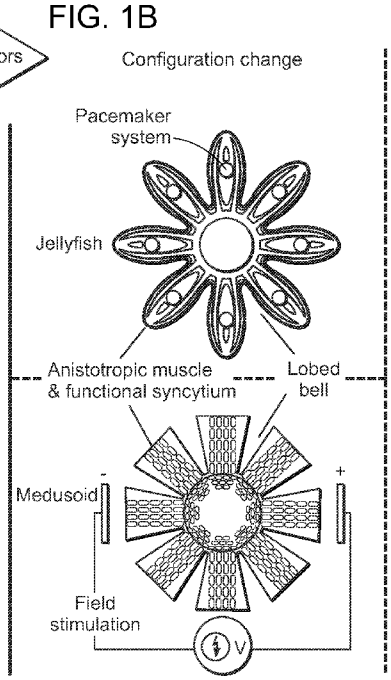


FIG. 1B



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/51267

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61F 2/07; A61K 35/34; F04B 9/00 (2013.01)
USPC - 417/441, 443; 424/93.21
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)
IPC(8): A61F 2/07; A61K 35/34; F04B 7/00, 9/00 (2013.01)
USPC: 417/441, 443; 424/93.1, 93.2, 93.21, 93.7

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 practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google Scholar; DialogPro; IP.com; tissue, pump, anisotropic, muscle, tube, check, valve, housing

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	PILAREK, M et al. 'Biological cardio-micro-pumps for microbioreactors and analytical micro-systems.' Sensors and Actuators B: Chemical, Vol. 156, No. 2, Elsevier, 15 February 2011, pp. 517-526 [online], [retrieved on 2013-10-01]. Retrieved from the Internet <URL: http://www.sciencedirect.com/science/article/pii/S0925400511001122>; figures 5-6; page 521, column 2, paragraph 4; page 522, column 1, paragraph 1; page 522, column 2, paragraph 3-4; page 524, column 1, paragraph 2; page 525, column 1, paragraph 1	1-3, 7, 9, 11-12, 15, 35-36 --- 4-6, 8, 10, 13-14, 30/1, 30/12, 31/1, 30/12, 37-40
Y	US 2012/0135448 A1 (PARKER, KK et al.) 31 May 2012; figure 2c; paragraphs [0007]-[0008], [0043], [0085], [0184]	4-6, 13-14
Y	US 2007/0164641 A1 (PELRINE, RE et al.) 19 July 2007; figures 3G-3J; paragraphs [0019], [0139], [0157]-[0159], [0167]	8, 10, 40
Y	US 2009/0317852 A1 (PARKER, KK et al.) 24 December 2009; paragraphs [0084]-[0088]	30/1, 30/12, 31/1, 31/12
Y	WO 2012/006320 A1 (PARKER, KK) 12 January 2012; page 5, lines 10-20; page 6, lines 9-34	37-38
Y	US 2011/0041935 A1 (ZHOU, P et al.) 24 February 2011; figures 5a-5b, 6a-b, 8-9; paragraphs [0004], [0012]-[0013], [0061], [0077]-[0078], [0083]-[0084]	39

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 December 2013 (23.12.2013)	16 JAN 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/51267

Box No. 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.: 32-34
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. 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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-15, 30/1, 30/12, 31/1, 31/12, 35-40 are directed toward a tissue-engineered pump and method for forming the tissue-engineered pump.

Group II: Claims 16-29, 30/16, 30/27, 31/16, and 31/27 are directed toward another tissue-engineered pump and method for forming the tissue-engineered pump.

Group III: Claims 41-44 are directed toward a tissue-engineered cardiac valve and a method of forming a tissue-engineered cardiac valve.

-***-Continued Within the Next Supplemental Box-***-

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 additional fees, this Authority did not invite payment of additional fees.

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.:

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.:
1-15, 30/1, 30/12, 31/1, 31/12, 35-40

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/51267

-***-Continued from Box No. III: Observations where unity of invention is lacking-***-

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include a tissue-engineered pump, comprising: a housing; a tubular member comprising an engineered anisotropic muscle tissue and accommodated within the housing, the tubular member comprising an inlet portion, an outlet portion and a cavity disposed between the inlet portion and the outlet portion; a first valve disposed at the inlet portion of the tubular member, the first valve configured to enable a fluid flow into the cavity of the tubular member through the inlet portion; a second valve disposed at the outlet portion of the tubular member, the second valve configured to enable a fluid flow out of the cavity of the tubular member through the outlet portion; and an energy source for electrically stimulating a collection of cells within the engineered tissue to cause contraction of a volume of the cavity, which are not present in Group III; a tubular member comprising an engineered anisotropic muscle tissue and accommodated within the housing a housing; a conical member accommodated within the housing, the conical member comprising a rounded tip and a side wall cooperatively enclosing a cavity, wherein the rounded tip comprises an engineered circumferential muscle tissue, and wherein the side wall comprises an engineered anisotropic muscle tissue, which are not present in Group II; the special technical features of Group II include a tissue-engineered pump, comprising: a housing; a conical member accommodated within the housing, the conical member comprising a rounded tip and a side wall cooperatively enclosing a cavity, wherein the rounded tip comprises an engineered circumferential muscle tissue, and wherein the side wall comprises an engineered anisotropic muscle tissue; a first valve coupled to the conical member for enabling a fluid flow into the cavity of the conical member; and a second valve coupled to the conical member for enabling a fluid flow out of the cavity of the conical member, which are not present in Group III; and a conical member accommodated within the housing, the conical member comprising a rounded tip and a side wall cooperatively enclosing a cavity, wherein the rounded tip comprises an engineered circumferential muscle tissue, and wherein the side wall comprises an engineered anisotropic muscle tissue; and an energy source for electrically stimulating a collection of cells within the engineered tissue to cause contraction of a volume of the cavity, which are not present in Group II; the special technical features of Group III include a tissue-engineered cardiac valve, comprising: a polymeric fiber scaffold configured as a hollow tubular member including a plurality of leaflets; and a collection of umbilical endothelial cells seeded onto the leaflets of the polymeric fiber scaffold; a method of forming a tissue-engineered cardiac valve, comprising: providing a cylindrical mandrel including sinuses for valve constructs; rotating a reservoir containing a polymer in proximity to the mandrel, wherein rotation of the reservoir ejects the polymer from the reservoir to form micron, submicron or nanometer dimension polymeric fibers; and depositing the polymeric fibers on a surface of the mandrel, thereby forming apolymeric fiber scaffold, the polymeric fiber scaffold configured as a hollow tubular member including a plurality of valve constructs, which are not present in Groups I and II.

The common technical features of Groups I-III are a tissue-engineered pump, comprising: a housing; a hollow member comprising an engineered anisotropic muscle tissue and accommodated within the housing, the hollow member comprising an inlet portion, an outlet portion and a cavity disposed between the inlet portion and the outlet portion; a first valve disposed at the inlet portion of the hollow member, the first valve configured to enable a fluid flow into the cavity of the hollow member through the inlet portion; a second valve disposed at the outlet portion of the hollow member, the second valve configured to enable a fluid flow out of the cavity of the hollow member through the outlet portion; an energy source for stimulating a collection of cells within the engineered tissue to cause contraction of a volume of the cavity; tissue-engineered device and a hollow tubular member including a plurality of valves.

These common technical features are disclosed by the article 'Biological cardio-micro-pumps for microbioreactors and analytical micro-systems' by Pilarek, et al. (hereinafter 'Pilarek'). Pilarek discloses a tissue-engineered pump (hybrid micro-pump actuating by cardiomyocytes attached to dome-shaped diaphragm; page 522, column 2, paragraph 2; figure 6) comprising: a housing (top layer of this micro-device was a PDMS-based microchannel layer; page 522, column 2, paragraph 3; figure 6); a hollow member (microchannel chamber; page 522, column 2, paragraph 3; figure 6) comprising an engineered anisotropic muscle tissue (hybrid diaphragm with a confluent monolayer of cardiac cells, cardiomyocytes which are anisotropic (anisotropic muscle tissue); page 522, column 2, paragraph 3; figure 6; page 525, column 1, paragraph 1) and accommodated within the housing (diaphragm was situated at the centre of the bottom side of chamber within the PDMS base; page 522, column 2, paragraph 3; figure 6), the hollow member comprising an inlet portion (inlet into the nozzle; figure 6), an outlet portion (diffuser to outlet; figure 6) and a cavity disposed between the inlet portion and the outlet portion (microchannel chamber; page 522, column 2, paragraph 3; figure 6); a first valve disposed at the inlet portion of the hollow member (the nozzle is a passive micro valve; page 522, column 2, paragraph 3; figure 6), the first valve configured to enable a fluid flow into the cavity of the hollow member through the inlet portion (the fluid flow goes into the inlet through the nozzle into the chamber; page 522, column 2, paragraph 3; figure 6); a second valve disposed at the outlet portion of the hollow member (the diffuser is a passive micro valve; page 522, column 2, paragraph 3; figure 6), the second valve configured to enable a fluid flow out of the cavity of the hollow member through the outlet portion (the fluid flow goes through the chamber through the diffuser and out the outlet; page 522, column 2, paragraph 3; figure 6); an energy source for stimulating a collection of cells within the engineered tissue to cause contraction of a volume of the cavity (the hybrid diaphragm has cardiomyocytes which when used in micro-bio-pumps are autonomously actuated with glucose as the energy source; page 518, column 2, paragraph 2; page 522, column 2, paragraph 3); a tissue-engineered device (hybrid micro-pump (engineered device) actuating by cardiomyocytes (muscle tissue) attached to dome-shaped diaphragm; page 522, column 2, paragraph 2; figure 6) and a hollow tubular member (microchannel chamber; page 522, column 2, paragraph 3; figure 6) including a plurality of valves (top layer of this micro-device was a PDMS-based microchannel layer supported with nozzle and diffuser as passive micro-valves; page 522, column 2, paragraph 3; figure 6).

Since the common technical features are previously disclosed by Pilarek, these common features are not special and so Groups I-III lack unity.