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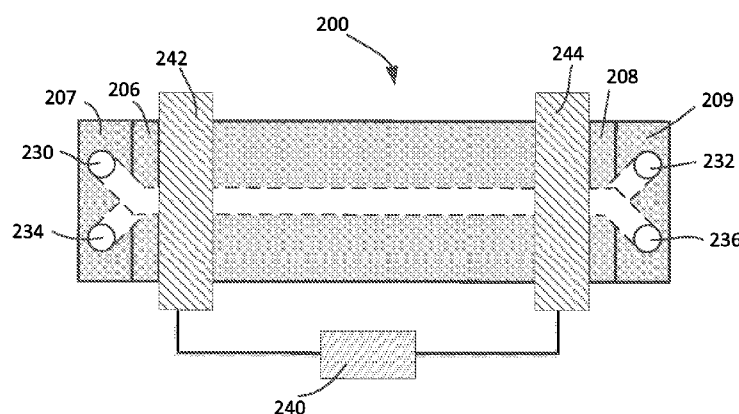
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[Continued on next page]

(54) Title: ORGANOMIMETIC DEVICES AND METHODS OF USE AND MANUFACTURING THEREOF

**FIG. 2B**

(57) Abstract: An organomimetic device includes a microfluidic device that can be used to culture cells in its microfluidic channels. The organomimetic device can be part of dynamic system that can apply mechanical forces to the cells by modulating the microfluidic device and the flow of fluid through the microfluidic channels. The membrane in the organomimetic device can be modulated mechanically via pneumatic means and/or mechanical means. The organomimetic device can be manufactured by the fabrication of individual components separately, for example, as individual layers that can be subsequently laminated together.



SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/071570

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - B01L 3/00; C12M 3/00 (2015.01)

CPC - B01L 3/5027 (2015.09)

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) - B01L 3/00; C12M 1/00, 3/00, 3/06 (2015.01)

CPC - B01L 3/00, 3/50, 3/5027, 3/50273, 2300/0887, 2300/163, 2400/0472, 2400/0481 (2015.09) (keyword delimited)

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

USPC -435/5, 6, 29, 283.1; 977/773, 902

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, Google.

Search terms used: microfluidic, microchannels, laminate, membrane, modulate, pressure, magnetic field, actuator, motor, cells, solenoid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0250585 A1 (INGBER et al) 13 October 2011 (13.10.2011) entire document	1-8, 10-22, 25-45, 46-47, 50-52, 61-78
Y		23-24
Y	US 2002/0166585 A1 (O'CONNOR et al) 14 November 2002 (14.11.2002) entire document	23-24
A	WO 2012/118799 A2 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 07 September 2012 (07.09.2012) entire document	1-78
A	WO 2013/086486 A1 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE et al) 13 June 2013 (13.06.2013) entire document	1-78
A	WO 2013/085909 A1 (RESEARCH TRIANGLE INSTITUTE et al) 13 June 2013 (13.06.2013) entire document	1-78

☐ 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

"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

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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/071570

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.:
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:

See Extra 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 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.:
1-78

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.

Continuation of Box III

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 1-78, are drawn to an organomimetic device.

Group II, claims 79-106, are drawn to a mechanical modulation system for stretch actuation of a microfluidic device.

The inventions listed as Groups I-II 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, an organomimetic device comprising: a first microchannel; a second microchannel; a membrane located at an interface region between the first microchannel and the second microchannel, the membrane including a first side facing toward the first microchannel and a second side facing toward the second microchannel, the membrane separating the first microchannel from the second microchannel, are not present in Group II; and the special technical features of Group II, a microfluidic system for monitoring a behavior of cells, comprising a mechanical actuation device for stretching the microfluidic device, the mechanical actuation system including a plurality of opposing connection elements configured to be fastened to a first location and an opposing second location of a microfluidic device, are not present in Group I.

Groups I and II share the technical feature of a microfluidic device having at least one microchannel in which the cells are disposed, and a first engagement element coupled to a first location of a microfluidic device. However this shared technical feature does not represent a contribution over the prior art. Specifically US 2011/0250585 A1 to Ingber et al. disclose a microfluidic device (organ mimic device 102; FIG. 1; para. [0055] "the organ mimic device can be utilized as multi cell type cellular microarrays, such as microfluidic devices") having at least one microchannel (FIG. 1; para. [0069] "the organ mimic device 102 preferably includes two or more ports which place the microchannels of the device 102 in communication with the external components of the system, such as the fluid and pressure sources") in which the cells are disposed (FIG. 1; para. [0069] "the device 102 is coupled to the one or more fluid sources 104 N in which the fluid source may contain air, blood, water, cells, compounds, particulates, and/or any other media which are to be delivered to the device 102" and para. [0073] "cell injector/remover 108 component is shown in communication with the device 102, whereby the injector/remover 108 is configured to inject, remove and/or manipulate cells, such as but not limited to epithelial and endothelial cells, on one or more surfaces of the interface membrane within the device 102"), and a first engagement element coupled to a first location of a microfluidic device (FIG. 1; para. [0074] pressure source 118 is controlled by the CPU 110 to apply a pressure differential within the device to effectively cause one or more membranes (FIGS. 3A-3B) within the device to expand and/or contract in response to the applied pressure differential" and para. [0096] "In the embodiments shown in FIGS. 3A and 3B, the pressurized fluid is a vacuum or suction force that is applied only through the operating microchannels 252. The difference in pressure caused by the suction force against the microchannel walls 234,244 causes the walls 234, 244 to bend or bulge outward toward the sides of the device 228, 238 (see FIG. 3B)").

Since none of the special technical features of the Group I-II inventions are found in more than one of the inventions, unity of invention is lacking.