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- 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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(54) Title: MICROFLUIDIC DIFFUSION DEVICES AND SYSTEMS, AND METHODS OF MANUFACTURING AND USING SAME

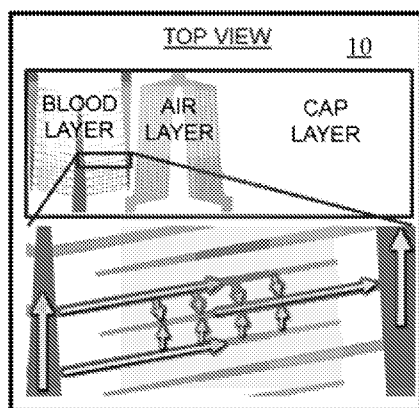


FIG. 5A

(57) Abstract: Disclosed herein are rolled-membrane microfluidic diffusion devices and corresponding methods of manufacture. Also disclosed herein are three-dimensionally printed microfluidic devices and corresponding methods of manufacture. Optionally, the disclosed microfluidic devices can function as artificial lung devices.



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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/025952

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61M 1/00; A61M 1/14; A61M 1/16; A61M 1/36 (2018.01)

CPC - A61M 1/365; A61M 1/16; A61M 1/1698; A61M 1/3652 (2018.08)

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)

See Search History document

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

USPC - 95/45; 95/54; 264/1.6; 435/2 (keyword delimited)

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

See Search History document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2014/0193799 A1 (THE CHARLES START DRAPER LABORATORY INC) 10 July 2014 (10.07.2014) entire document	58, 59 --- 1-9, 16-31, 35-39, 46-57
Y	US 2014/0306371 A1 (THE GOVERNING COUNCIL OF THE UNIVERSITY OF TORONTO) 16 October 2014 (16.10.2014) entire document	1-9, 16-31, 35-39, 46-48
Y	US 5,192,320 A (ANAZAWA et al) 09 March 1993 (09.03.1993) entire document	16-18, 46-57
Y	US 2002/0098124 A1 (BENTSEN et al) 25 July 2002 (25.07.2002) entire document	30
Y	US 2010/0326914 A1 (DROST et al) 30 December 2010 (30.12.2010) entire document	31
A	US 8,449,772 B2 (DIRAC et al) 28 May 2013 (28.05.2013) entire document	1-59
A	US 7,727,399 B2 (LEONARD et al) 01 June 2010 (01.06.2010) entire document	1-59
A	US 8,147,562 B2 (VACANTI et al) 03 April 2012 (03.04.2012) entire document	1-59

 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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/025952

**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(s).

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.:

**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.

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

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 need to be paid.

Group I, claims 1-48, 58-59 are drawn to a microfluidic diffusion device comprising a patterned membrane.

Group II, claims 49-57 are drawn to a microfluidic diffusion device comprising a capillary bed.

The inventions listed in Groups I and 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, a cylindrical substrate having a central axis and an outer surface; a patterned membrane rolled circumferentially over the outer surface of the cylindrical substrate to define a plurality of concentric membrane layers extending radially outwardly from the central axis of the cylindrical substrate, wherein at least one membrane layer of the plurality of concentric membrane layers is patterned to define a plurality of gas flow channels that are configured to receive a gas, wherein at least one membrane layer of the plurality of concentric membrane layers is patterned to define a plurality of liquid flow channels that are configured to receive a liquid, and wherein the at least one membrane layer permits diffusion of: liquid from the plurality of liquid flow channels into the gas within the plurality of gas flow channels, wherein the gas flow pathway and the liquid flow pathway are separated by a membrane that permits diffusion of gas from the gas flow pathway into the liquid flow pathway, and wherein at least one of the gas flow pathway and the liquid flow pathway has a smallest dimension of less than 250 nm, are not present in Group II; and the special technical features of Group II, at least one liquid inlet; at least one liquid outlet; and a capillary bed positioned between the at least one liquid inlet and the at least one liquid outlet relative to the liquid flow axis, the capillary bed comprising a plurality of capillary elements defining respective lumens that are in fluid communication with the at least one liquid inlet and the at least one liquid outlet; and a gas flow pathway extending along a gas flow axis that is perpendicular or substantially perpendicular to the liquid flow axis, wherein the gas flow pathway intersects at least a portion of the capillary bed to define a gas exchange region, are not present in Group I.

Groups I and II share the technical features of a three-dimensionally printed microfluidic diffusion device comprising a liquid distribution pathway extending along a liquid flow axis, a gas flow pathway extending along a gas flow axis, and a material that permits diffusion of gas from the gas flow pathway into liquid within a plurality of flow channels, wherein the microfluidic diffusion device is formed by three-dimensional (3D) printing. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2014/0193799 A1 to The Charles Start Draper Laboratory, Inc. teaches of a three-dimensionally printed microfluidic diffusion device (Abstract, para. [0051]) comprising a liquid distribution pathway extending along a liquid flow axis (Fig. 9B, an artificial lung device (not numbered) comprising vascular channels, para. [0028], wherein the vascular channels contain blood therein as per para. [0035]), a gas flow pathway extending along a gas flow axis (Fig. 9B, wherein the lung device includes oxygen channels containing gaseous oxygen therein, para. [0035] & [0028]), and a material that permits diffusion of gas from the gas flow pathway into liquid within a plurality of flow channels (Fig. 9B, a diffusion membrane therebetween to allow gas diffusion from the oxygen channels to the vascular channels, para. [0035] & [0028]), wherein the microfluidic diffusion device is formed by three-dimensional (3D) printing (Para. [0086], wherein the device is formed via three dimensional printing).

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