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(54) Title: PERFORMING PHARMACODYNAMICS EVALUATIONS USING MICROFLUIDIC DEVICES

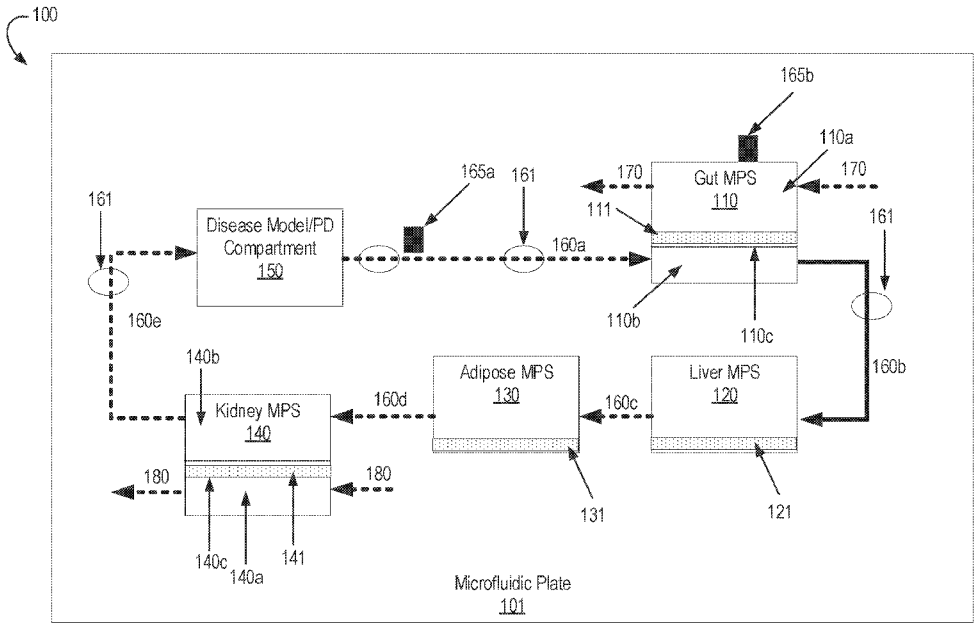

FIG. 1

(57) Abstract: Microfluidic platforms including multiple microphysiological systems. At least one of the platforms include: at least one inlet; a plurality of organ constructs, each organ construct of the plurality of organ constructs being sized relative to other organ constructs of the plurality of organ constructs based on at least one predetermined human pharmacokinetic (PK) parameter; and a plurality of channels, each channel of the plurality of channels causing an organ construct of the plurality of organ constructs to be in fluidic communication with at least one other organ construct of the plurality of organ constructs.

[Continued on next page]

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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

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14 April 2022 (14.04.2022)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/48885

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A01N 1/02 (2022.01)

CPC - G01N 33/5044, G01N 33/5067, C12M 29/10, B01L 3/502715, C12M 21/08, C12M 23/44

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
See Search History document

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 2017/0227525 A1 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 10 August 2017 (10.08.2017); abstract; para [0010], [0023], [0102], [0159], [0165], [0177], [0242]-[0244], [0247]-[0248], [0257], [0261], [0276], [0280], [0281], [0292], [0302], [0305], [0331], [0342]	1-8, 11, 13-15, 17-20 9-10, 12, 16, 21-22
Y	SASSERATH et al., Differential Monocyte Actuation in a Three-Organ Functional Innate Immune System-on-a-Chip. Advanced Science. Published online 02 June 2020, Vol. 7, article 2000323, pages 1-19; pg 14, col 2, para 3	9
Y	WO 2019/222559 A1 (UNIVERSITY OF WASHINGTON) 21 November 2019 (21.11.2019); abstract; para [0144]	10,16
Y	MAASS et al., Multi-functional scaling methodology for translational pharmacokinetic and pharmacodynamic applications using integrated microphysiological systems (MPS). Integrative Biology. 18 April 2017, Vol. 9, No. 4, pages 290-302; abstract; pg 292, col 2, para 2; pg 293, col 1, para 1	12, 21-22

☐ 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
"D" document cited by the applicant in the international application
"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
17 January 2022	FEB 28 2022
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. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/48885

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 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.:
1-22

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 searched, the appropriate additional search fees must be paid.

Group I: Claims 1-22, directed to a method for testing or designing a microphysiological system (MPS), comprising: generating at least one organ construct, the organ construct having a disease type, and selecting a disease-specific pharmacodynamics (PD) biomarker to monitor an interaction between the disease organ construct and a molecular compound, generating at least one PD parameter used to design said MPS (instant application: para [0065] "design parameters (for example, media volume, number of cells by type, surface area, system level flow rate, flow pattern, flow partitioning, and so forth) to maximize the platform's ... ability to ...evaluate PD responses in humans.").

Group II: Claims 23-29, directed to a composition of matter comprising: a system having at least one inlet, a plurality of disease organ constructs, a sensor to monitor a pharmacodynamics (PD) biomarker in one or more organ constructs, and a plurality of channels causing an organ construct of the plurality of organ constructs to be in fluidic communication with at least one other organ construct.

The inventions listed as 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:

Special Technical Features

Group I requires a method for testing or designing a microphysiological system (MPS) by generating PD parameters from the effects of molecular compounds interacting with a disease organ construct, not required by group II.

Group II requires a composition of matter comprising inlets, a plurality of organ constructs, sensors and channels for fluid communication between said organ constructs, not required by group I.

Common Technical Features

The common technical feature shared by Groups I and II is a system (e.g. microphysiological system) comprising at least one organ construct corresponding to an organ type of a plurality of organ types, at least one organ construct of the plurality including a disease, wherein a pharmacodynamics (PD) biomarker in the at least one organ construct is selected based on a disease type.

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is taught by US 2017/0227525 A1 to Massachusetts Institute of Technology (hereinafter 'MIT'). MIT teaches a microphysiological system comprising a plurality of organ types, or constructs (abstract "Fluidic multiwell bioreactors are provided as a microphysiological platform for in vitro investigation of multi-organ crosstalks", para [0157] "constructs can be cultured in isolation, in unique cell media, and then selected for health and viability before they are joined together for a human-on-a-chip experiment", para [0071] "The terms "organ-on-chip (OOC)", "bioreactor", and "microphysiological system (MPS)", used interchangeably, refer to the platform providing for interactions among single or multiple organ or other tissue type") at least one organ construct of the plurality including a disease (para [0256] "The multi-organ apparatus is a useful tool for disease modeling and drug development, especially in identifying and defining the appropriate "minimal set" of interacting organ systems to represent a disease state.") wherein a pharmacodynamics (PD) biomarker in the at least one organ construct is selected based on a disease type (para [0247] "The disclosed apparatus may be applied ... in assessing additional factors such as endogenous growth factor, inflammatory and hormone signals in the prediction of pharmacokinetics and pharmacodynamics (PK and PD).", para [0329] "During media changes, samples were taken from each compartment to assess MPS function throughout the two-week interaction study. Biomarker metrics of healthy cell function were measured during a 2-week co-culture of 4-way MPS: liver, gut, lung, and endometrium").

As the technical feature was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.