Microphysiological Systems Development at NIST

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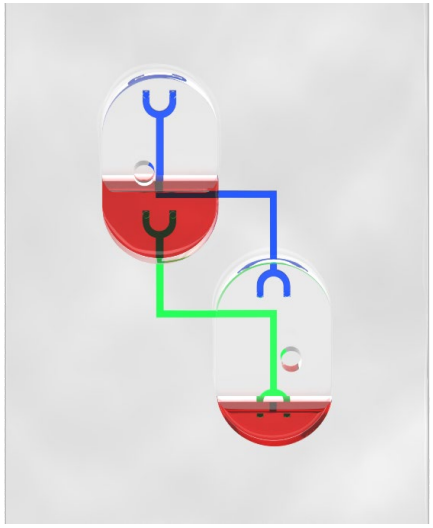
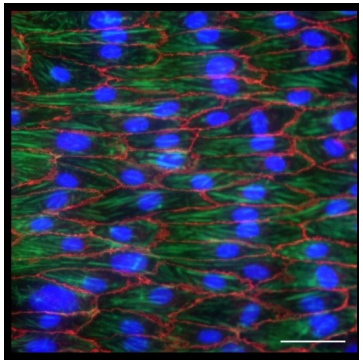
ICCVAM - Public Forum

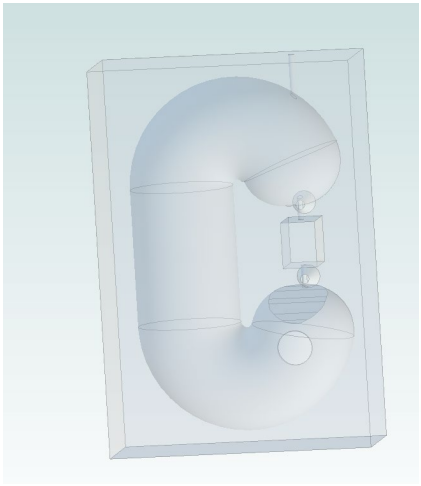
May 20, 2024

Organ-on-a-Chip: barrier tissues

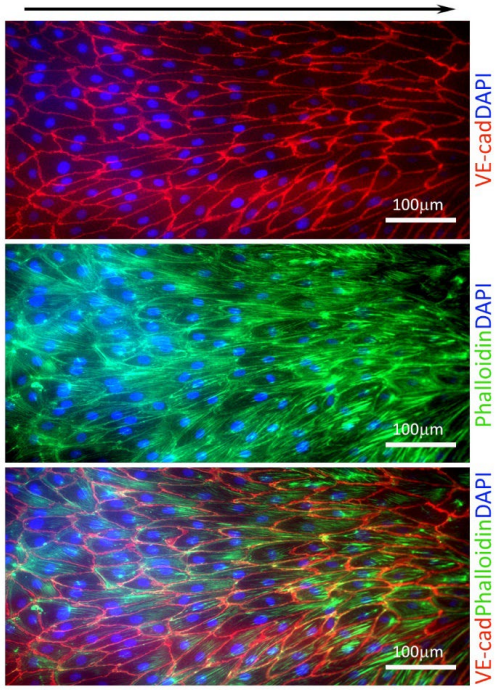




Yang et al., **Lab on a Chip**, 19/19, 3212-3219, **2019**



Lee et al. manuscript in preparation

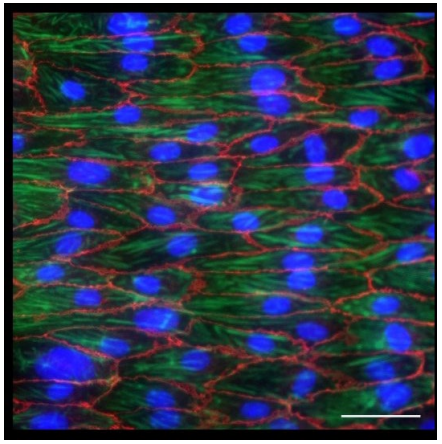


Advantages of microenvironment:

- presence of shear
- transport experiments in the presence of flow
- interactions with endothelium in the presence of flow

Endothelial cells (HUVEC) align under unidirectional flow

unidirectional flow

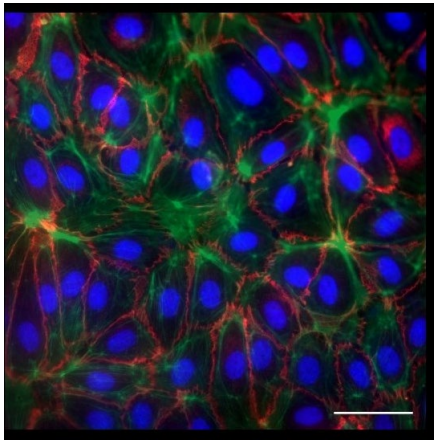


green: actin

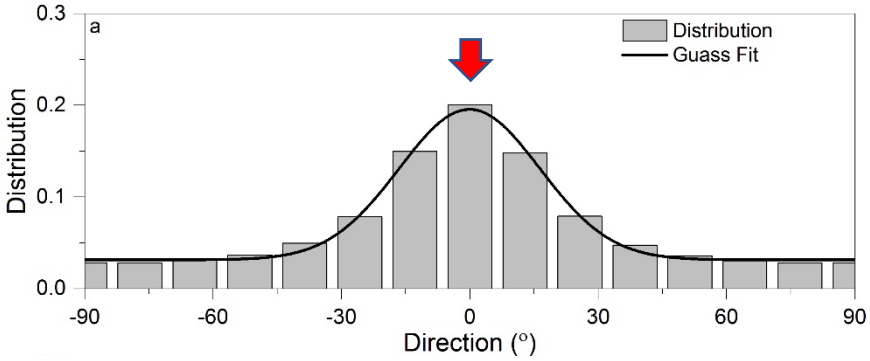
blue: nuclei

red: VE-cadherin

bidirectional flow

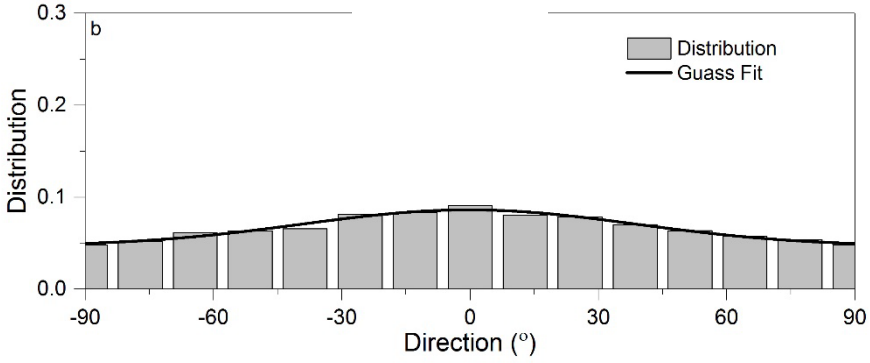


angles of actin fibers



Actin fibers are aligned with the direction of flow.

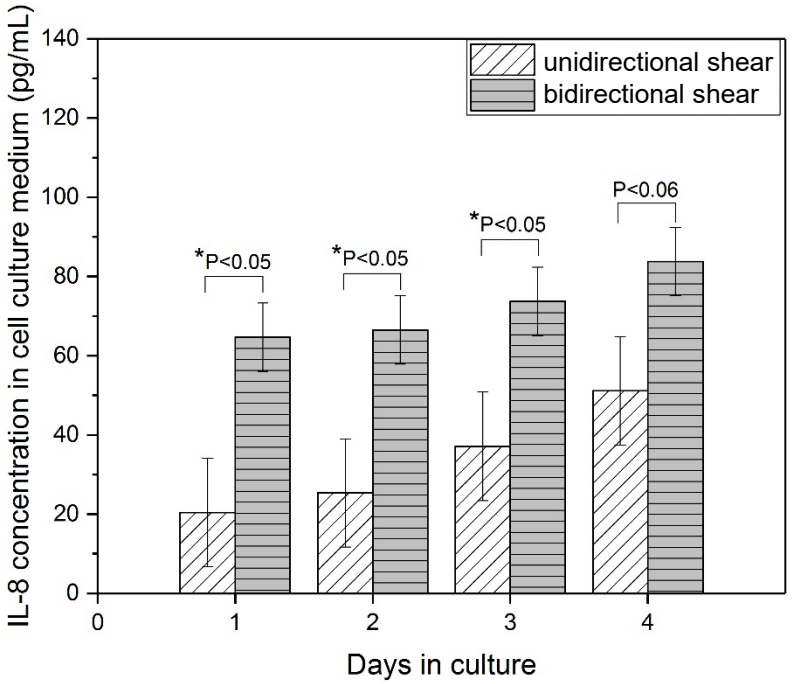
angles of actin fibers



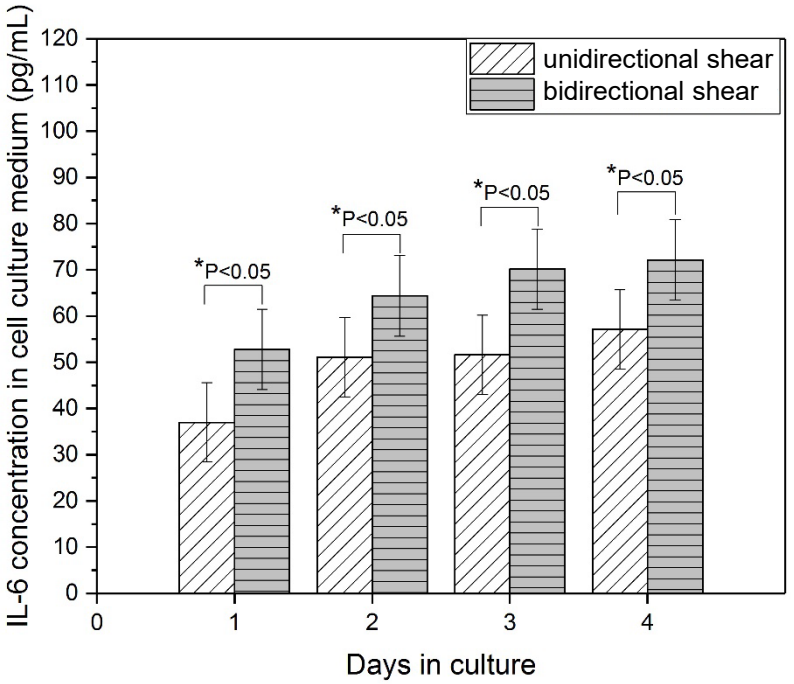
Most actin fibers are not aligned with the direction of flow.

Unidirectional flow causes less inflammation

IL-8 expression



IL-6 expression

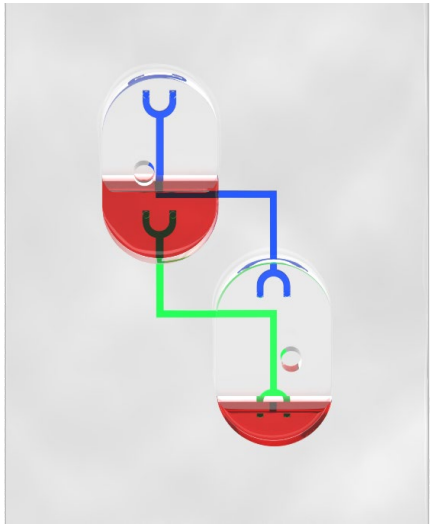


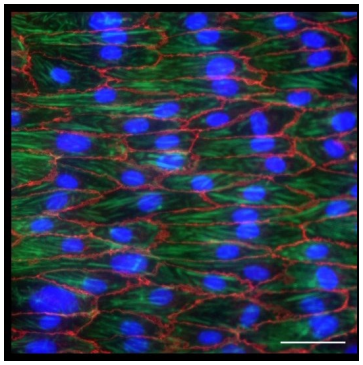
IL-6- and IL-8 proteins indicate inflammation.

➡ Unidirectional flow causes less inflammation than bidirectional flow.

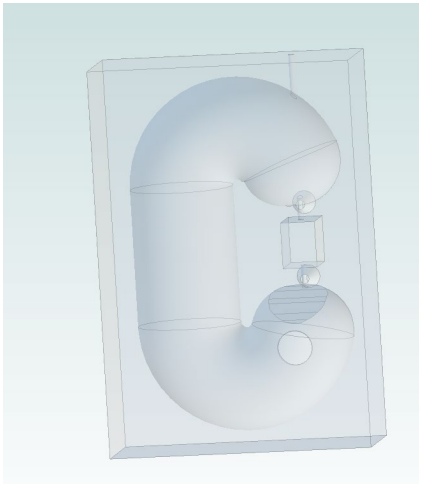
Yang et al., **Lab on a Chip**, 19/19, 3212-3219, **2019**

Organ-on-a-Chip: blood vessels and kidney





Yang et al., **Lab on a Chip**, 19/19, 3212-3219, **2019**



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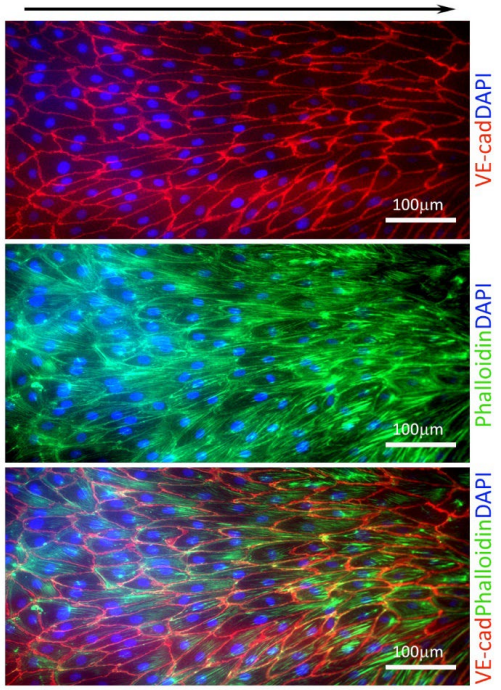


Worcester University: infection-on-a-chip (collaboration with Dr. Stewart)

Binghamton University: kidney on a chip (glomerulus and proximal tubule, collaboration with Dr. Mahler and a GMSE student)

Multi-organ microphysiological systems

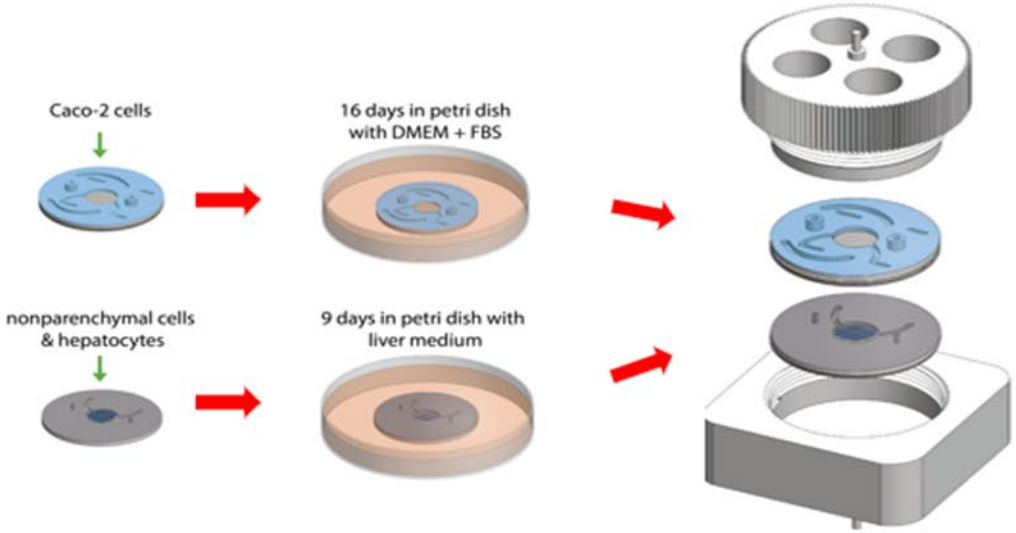
Motivation:

1) Estimating the bioavailability of drugs

2) Measuring primary and secondary toxicity

Bioavailability of orally taken drugs

Simulating the first pass metabolism with GI tract and liver tissues



Mahler et al.,Biotech. & Bioeng., **2009**, 104/1, 193-205

Esch et al., Lab on a Chip, 14/16, **2014,** 3081-3092

Esch et al., Lab on a Chip, **2016**, 16/14, 2719-2729

- drug concentrations
- PBPK models
- in vitro to in vivo conversion

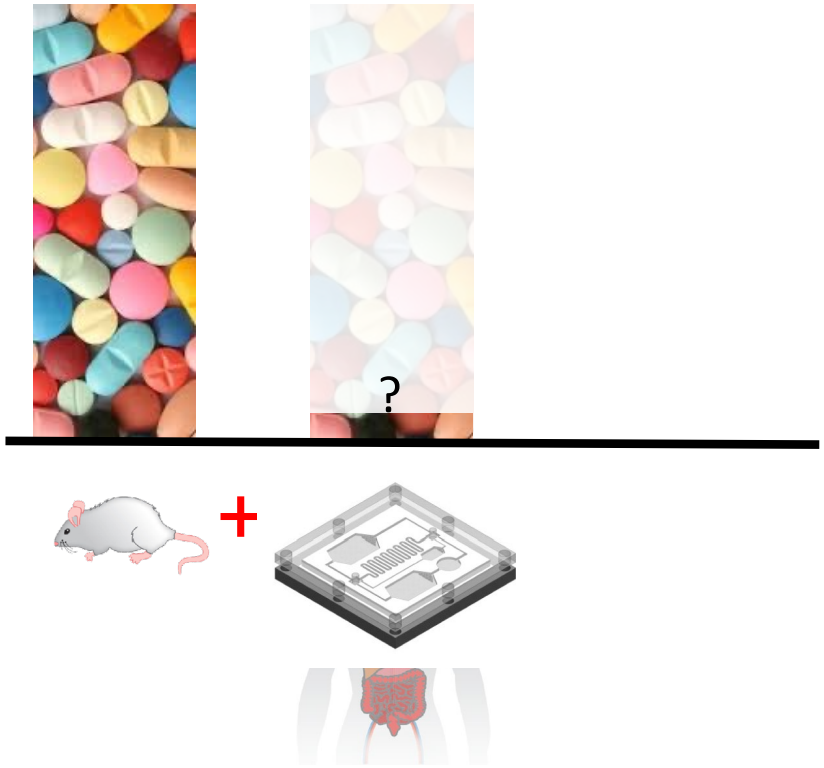
Multi-organ microphysiological systems

Motivation:

1) Estimating the bioavailability of drugs

2) Measuring primary and secondary drug toxicity

Long-term goal: human-centered drug development



For every 50 drugs that cure disease in animals,
there are only a few that also do that in patients.

Can MPS be better models of the human body than animals?

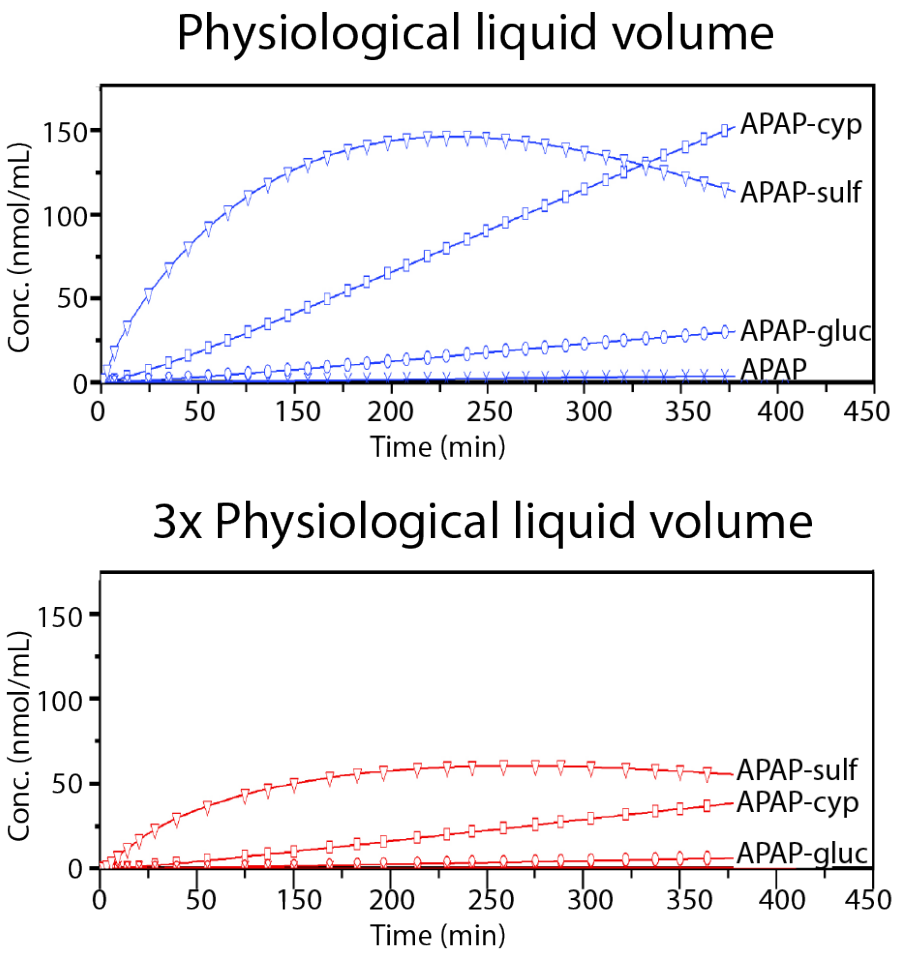
Multi-organ microphysiological systems

➡ understanding parameters that affect experimental outcomes

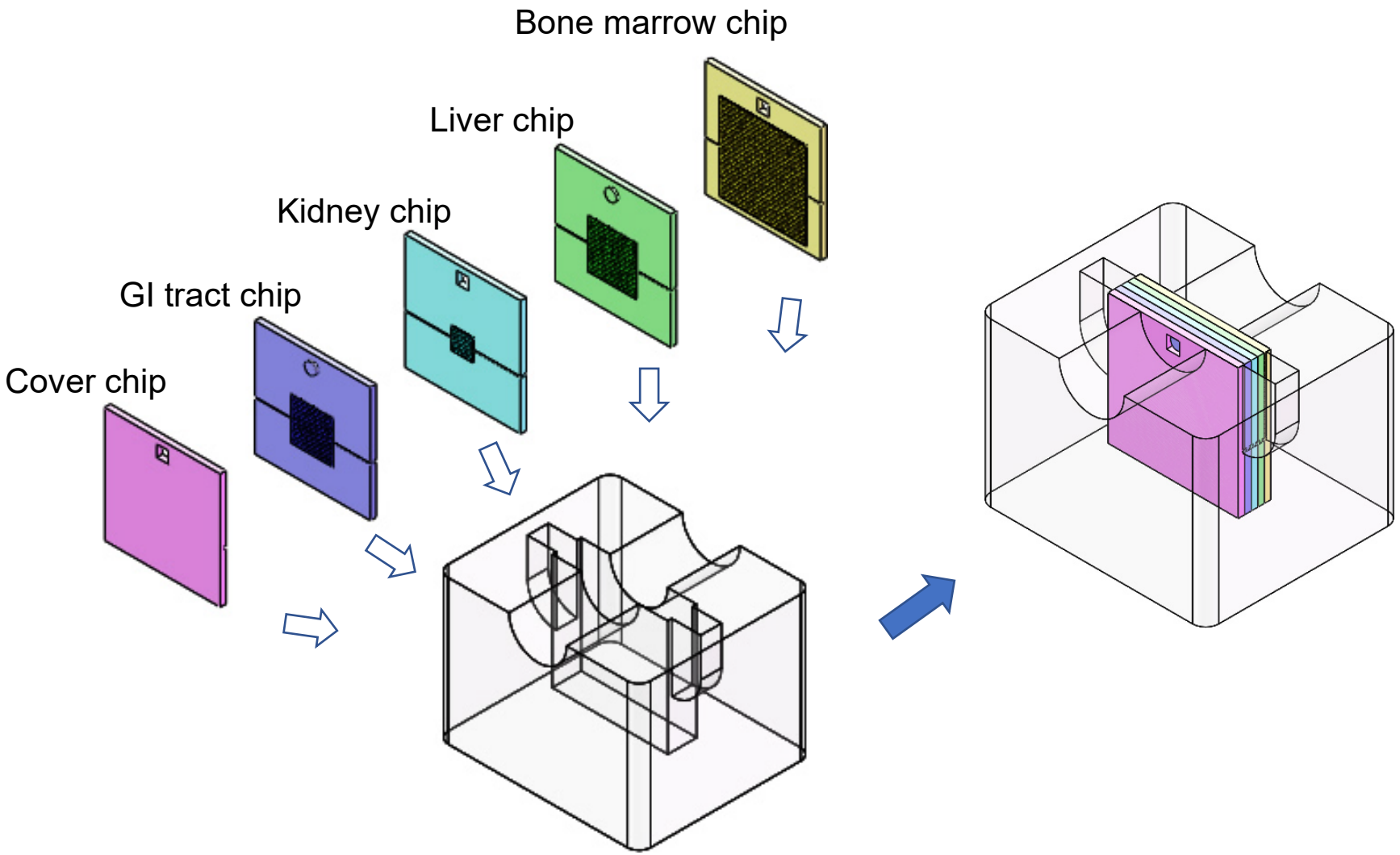
Devices:
- scaling
- tissue volumes
- perfusion rates
- liquid volume

Tissues:
- cells
- density
- enzyme activity
- medium composition

Operational:
- medium change
- days in co-culture

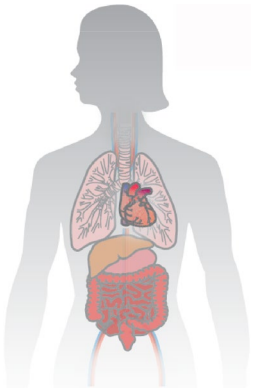


The Body Cube was designed with very short fluidic connections

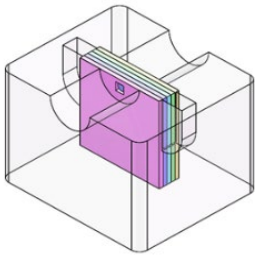


Chen & Esch, Microphysiological Systems, **2020**, 4, 1-13

The Cube contains physiological amounts of blood surrogate



	Organ volumes ± stdev. (L)	Functional organ volumes ± stdev. (L)	Organ volume ratios
GI tract	1.23 ± 0.22	0.70 ± 0.13	0.75* *as 3D tissue
liver	1.57 ± 0.26	0.94 ± 0.16	1.00
kidney	0.32 ± 0.07	0.19 ± 0.04	0.20
bone marrow	5.1 ± 0.89	2.98 ± 0.52	3.17
blood	5.82 ± 0.73	5.82 ± 0.73	6.19

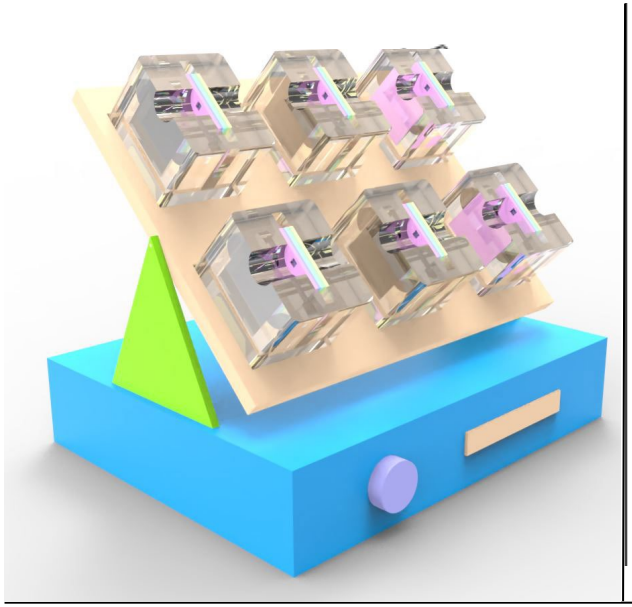


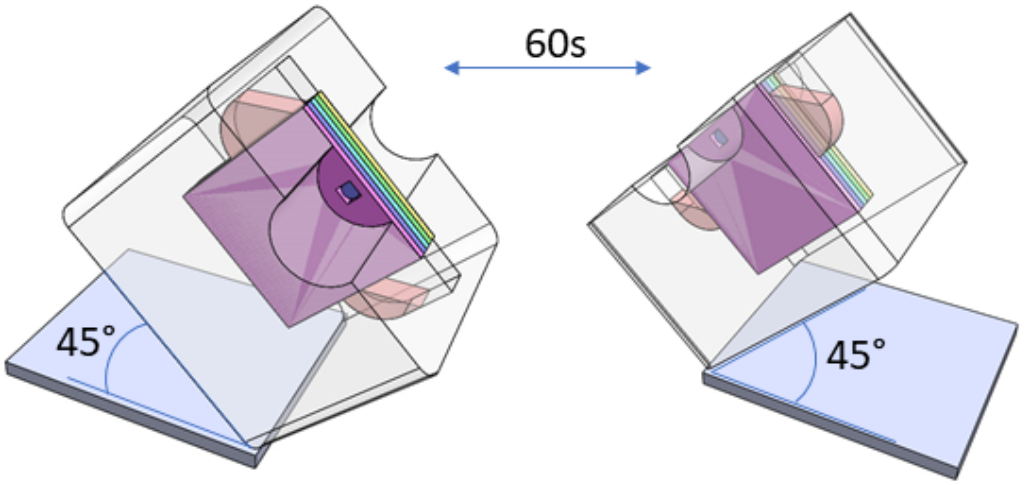
$$V_{(MPS)} = \frac{V_{(human)}}{73{,}000}$$

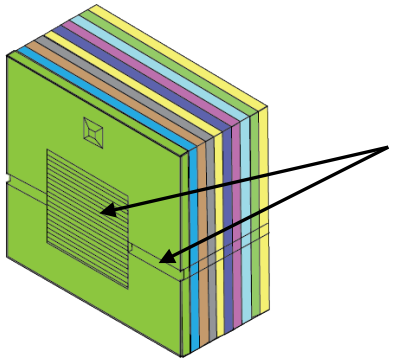
	MPS organ volume ± stdev. (µL)	Organ volume ratios
GI tract	9.6 ± 1.7	0.75* *as 3D tissue
liver	12.8 ± 2.1	1.00
kidney	2.5 ± 0.5	0.20
bone marrow	40.8 ± 7.1	3.18
blood	79.7 ± 10.0	6.20

Chen & Esch, Microphysiological Systems, **2020**, 4, 1-13

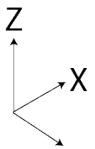
Fluidic flow is driven by gravity and regulated by hydraulic resistances





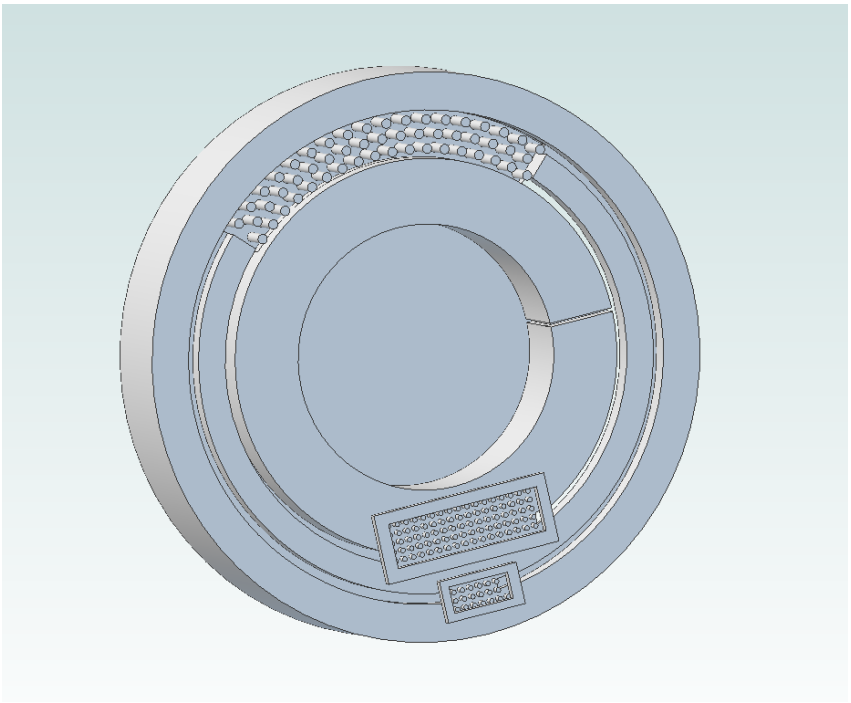


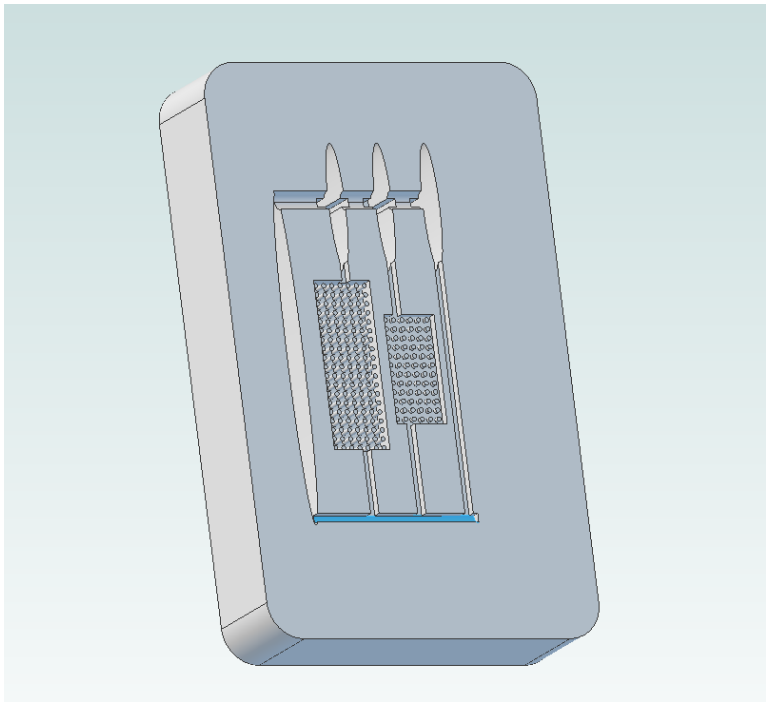
microfluidic channels provide hydraulic resistance to the flow



Chen et al., Microphysiological Systems, **2020**, 4, 1-13
Chen L. & Esch M.B., **US Patent Appl.** #17/234,298

A new design enables concurrent microscopy and metabolic monitoring





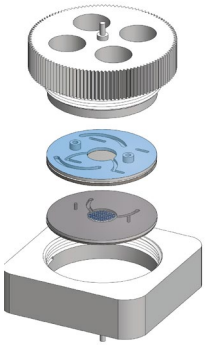
The design provides:

- physiological tissue volume ratios
- physiological blood surrogate residence times
- physiologically scaled blood surrogate volumes
- access to tissues during the experiment
- Can be operated with 100 µL of cell culture medium

Esch M.B., **US Patent Appl. #** 17/513,942 (10/29/2021)

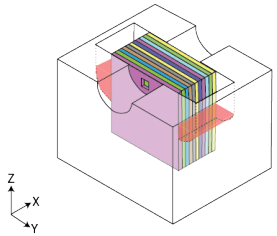
Multi-organ microphysiological systems

1) Technology development

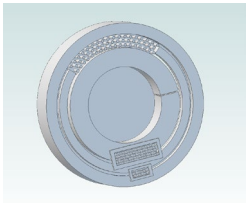


US Patent
#10,927,335

US Patent App.
in preparation



US Patent
#11,905,504

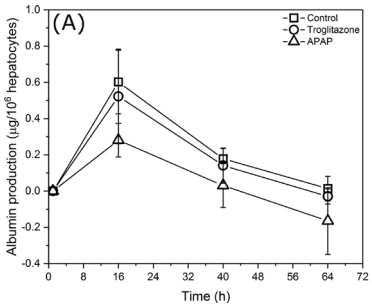


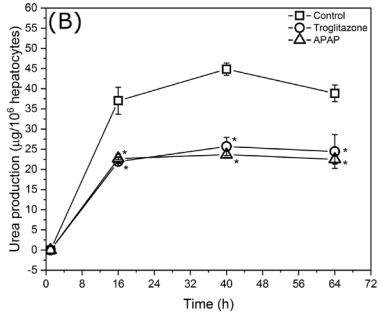
US Patent App.
#17/513,942

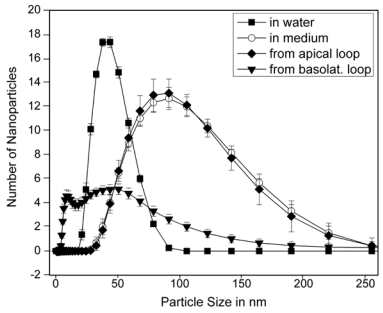
➡ Tech transfer

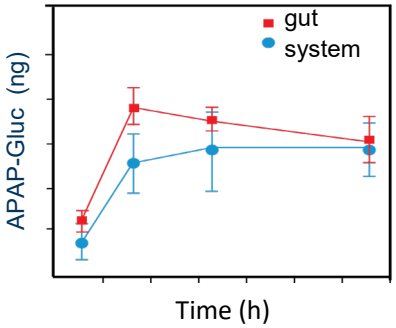
2) Experimentation:

- Metabolite concentrations
- Toxicity measurements
- Functional measurements





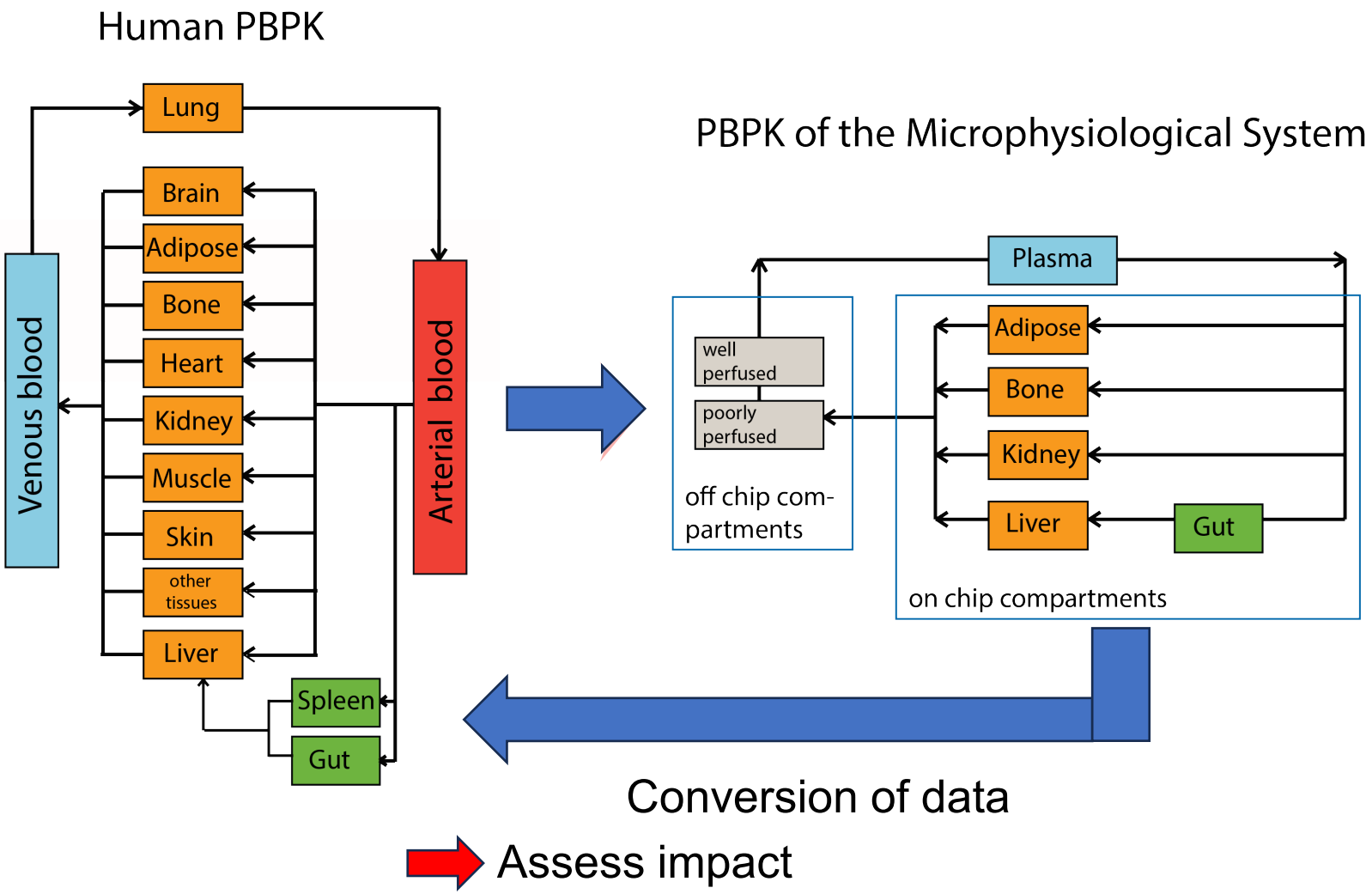




➡ Standards development

Multi-organ microphysiological systems

3) In vitro to in vivo conversion



Thank you!

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