

PhysioMimetics: *Humanizing Models of Systemic Inflammatory Diseases with Multi-Organ Platforms and Systems Biology*

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Human Physiome on a Chip

*Gut organoid budding from a human iPS-derived hindgut culture
With Jim Wells (Arora et al Development 2017)*



Systems Biology of Endometriosis (+ Adenomyosis)

Molecular communication networks

Miller et al, *Integrative Biology* (2011)

***Miller et al *PNAS* (2012)**

***Beste et al *Science Translational Medicine* (2014)**

Jørgensen et al, *Fertility & Sterility* (2016, 2018)

Cook et al, *Integrative Biol*, (2017)

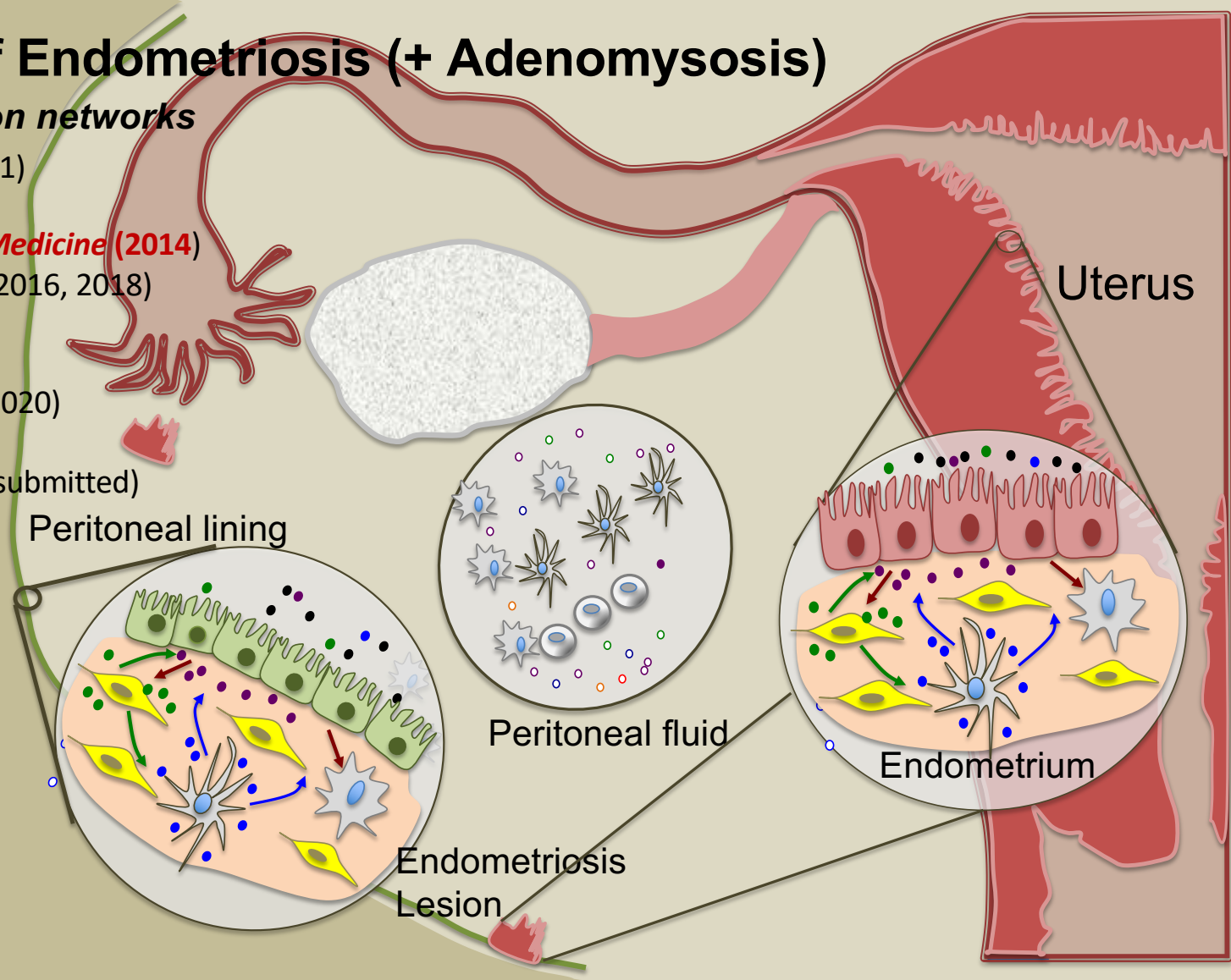
Valdez et al, *Biomaterials* (2017)

Bailey et al, *Repro Biomed Online* (2020)

Perotta et al, *Repro Sci* (2020)

Jørgensen et al, *Fertility & Sterility* (submitted)

***first publications in the field
describing molecular classification
schemes**



JNK inhibitors have cured diverse patient
populations of endometriosis!
(unfortunately, none are human)



Palmer et al., Reprod Sci. 2016

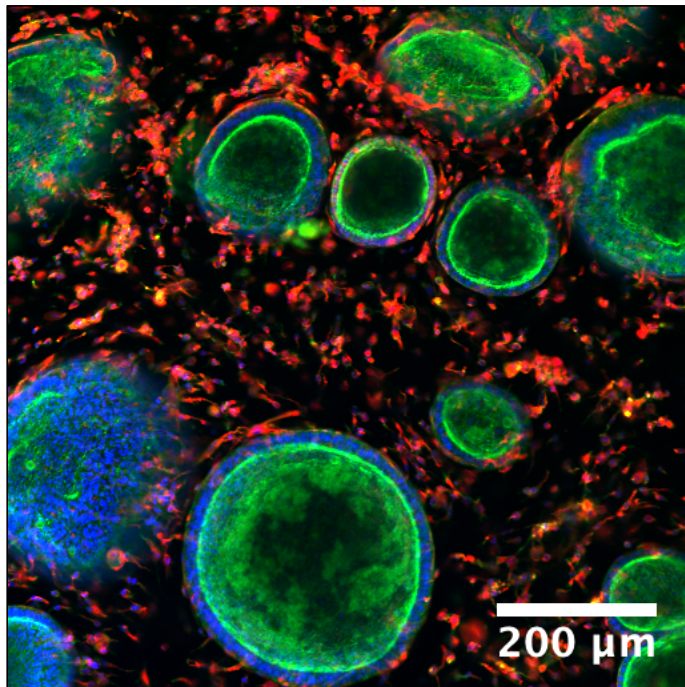


Hussein et al., Fertil Steril. 2016

Clinical trial of JNKi (Preglem) unsuccessful – Patient stratification issue?
Pharma: “we need efficacy models”

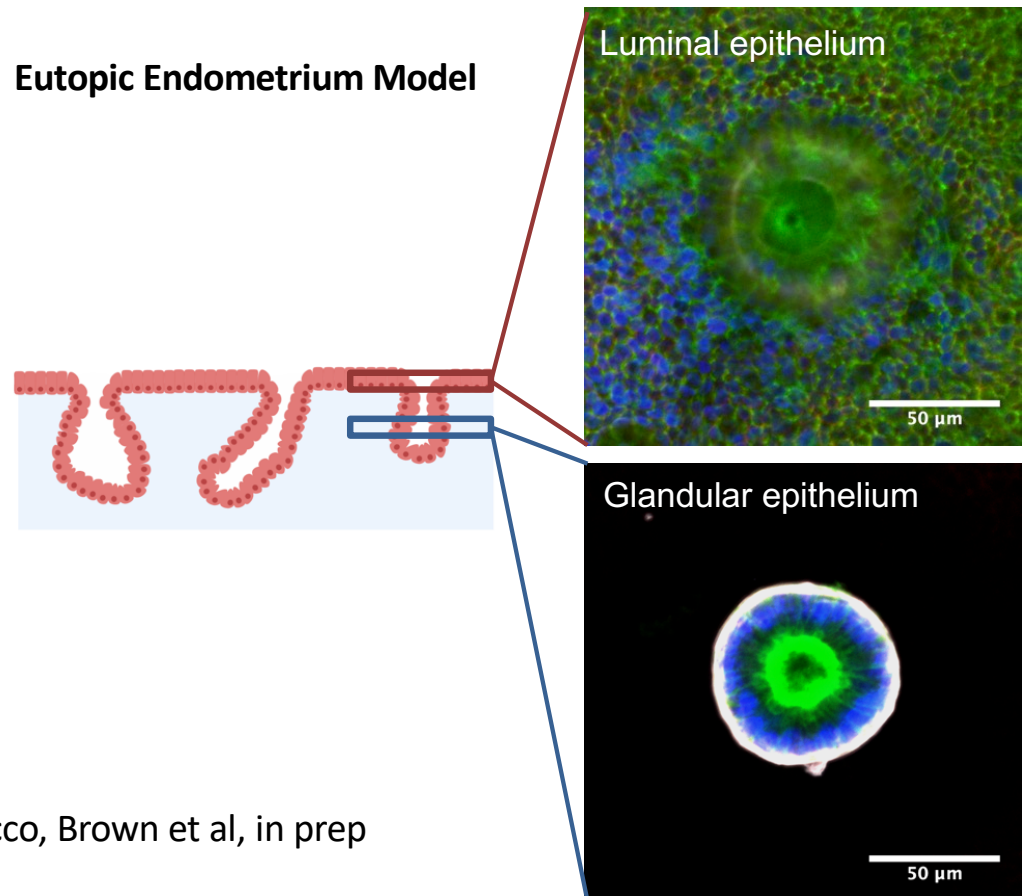
Patient Avatars, part 1: Cocultures of patient-derived human endometrial epithelial organoids and endometrial stromal cells in **synthetic ECM**

Lesion model



Vimentin F-actin Nuclei

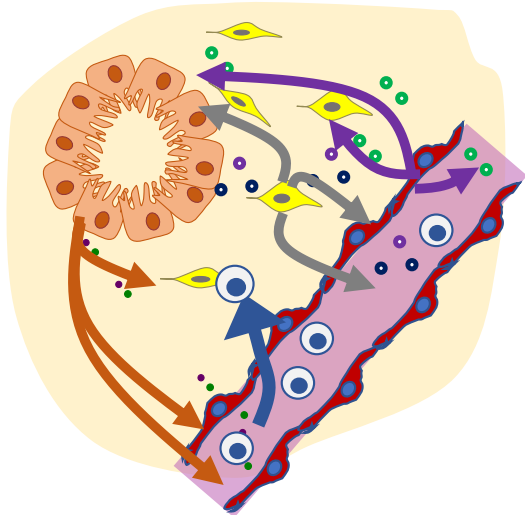
Eutopic Endometrium Model



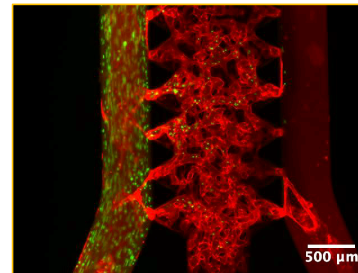
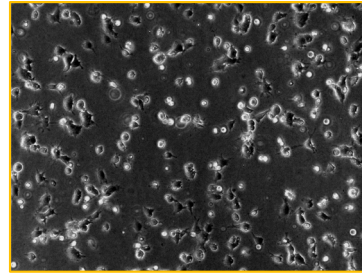
Hernandez-Gordilla et al, *Biomaterials* 2020; Gnecco, Brown et al, in prep

Modeling the Birth of Lesions - Drug Target!

Cyclic Hormone Stimulation -> Wound Healing Response -> Progression



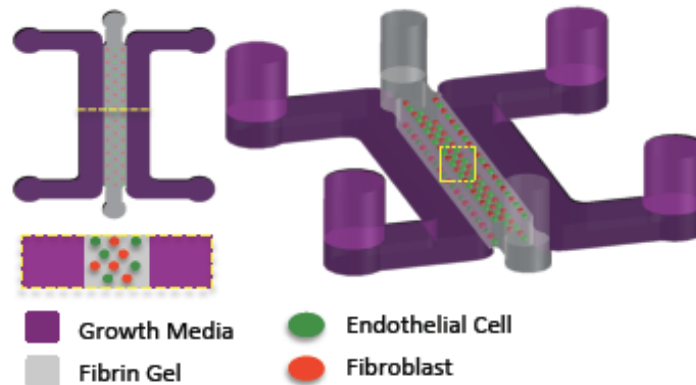
Recruitment /differentiation of circulating (immune/stem) cell



**Predicate
MicroVascularized
Devices**

Roger Kamm Lab

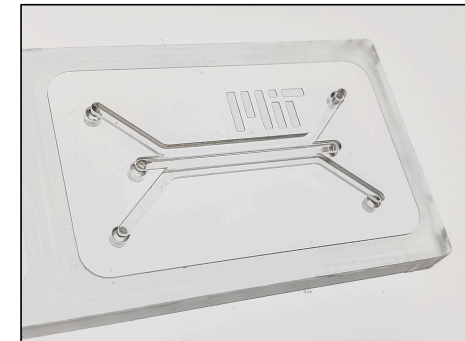
Vickerman et al., Lab Chip, 2008,
Chung et al., Lab Chip, 2009
Shin et al., Nat Prot, 2012
Chen et al., Nat Prot, 2017



New – U01 NIBIB Immune Chips
Mesoscale Thermoplastic Devices
Integrated with Pumps



**Prototypes - Micro-machined &
Bonded @ MIT**



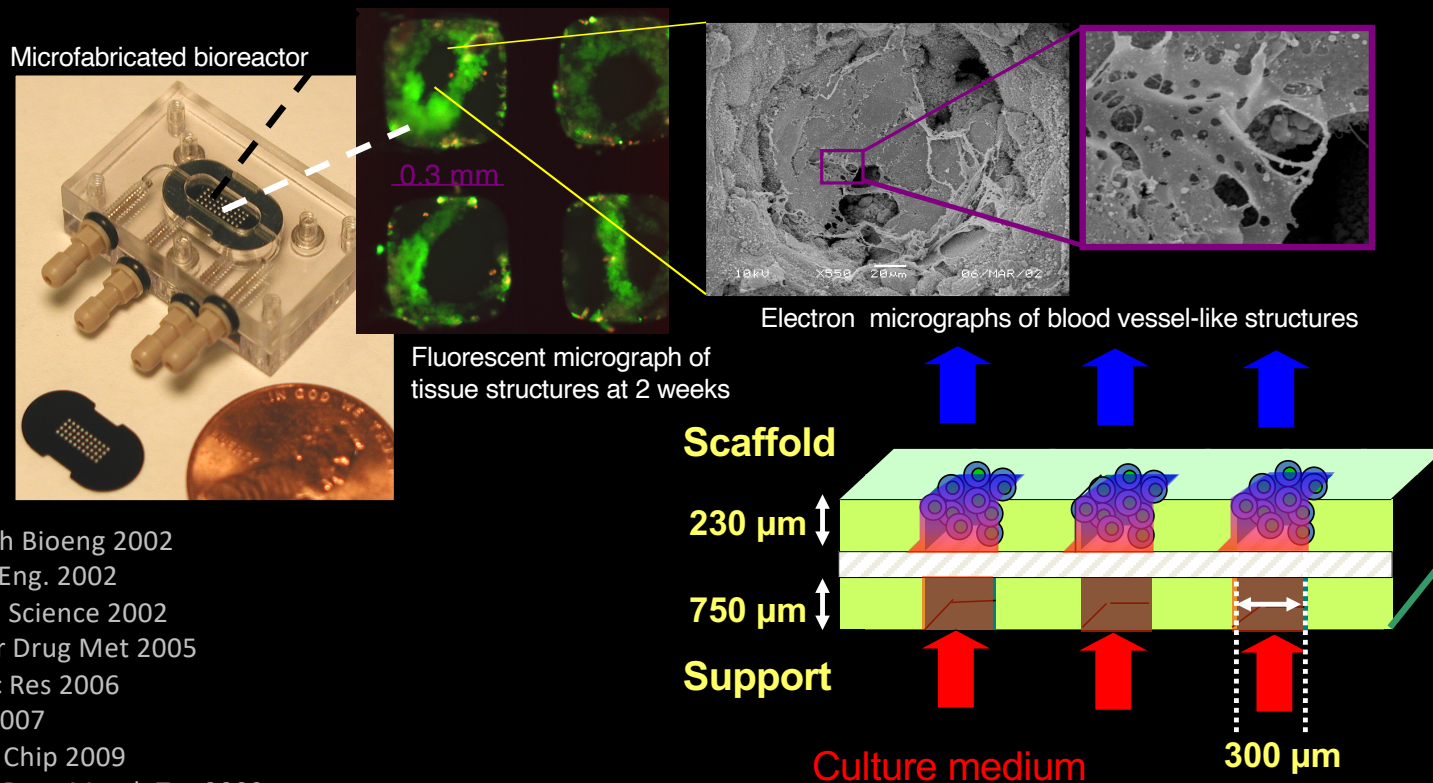
Production outsourced

Microreactors for 3D liver tissue engineering **Fit for purpose assays**

Ebrahimkani,..Griffith, "Bioreactors to Support Liver Function in Vitro," Adv Drug Delivery Rev, (2014).

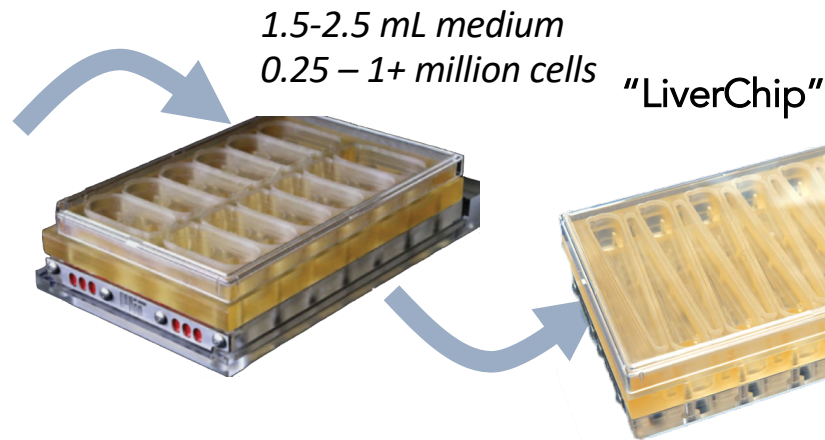
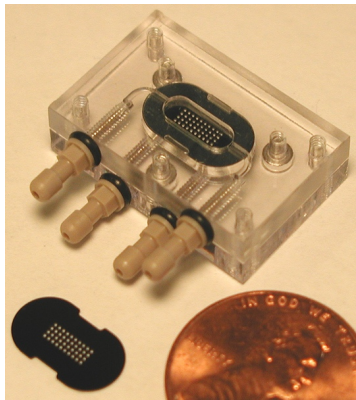
Griffith, Wells, Stolz ,Hepatology (2014); Wheeler... Lauffenburger, Griffith, Wells, British J Cancer, (2014)

Tissue formed from isolated liver cells seeded into channels

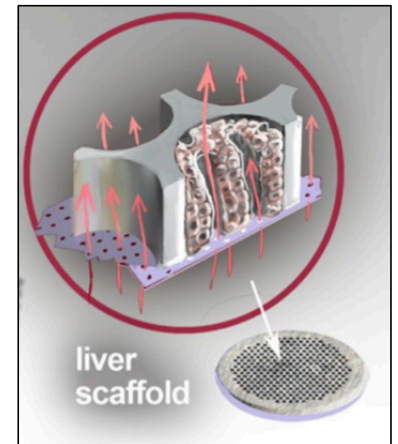
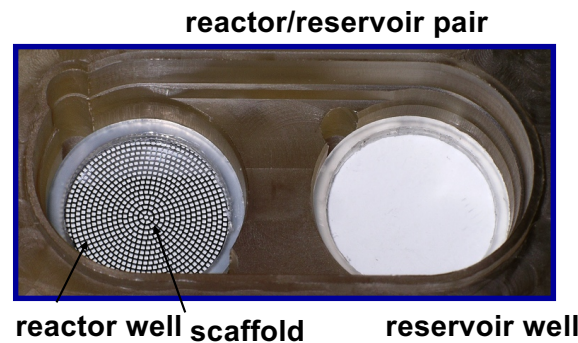
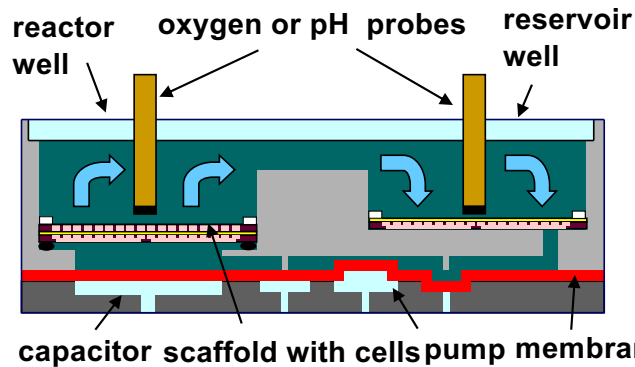


Powers, et al Biotech Bioeng 2002
Powers et al Tissue Eng. 2002
Griffith & Naughton Science 2002
Sivaraman et al Curr Drug Met 2005
Yates et al Adv Canc Res 2006
Hwa et al FASEB J 2007
Domansky et al Lab Chip 2009
Dash et al Exp Opin Drug Metab Tox 2009

Gen 0 Platform: LiverChip multiwell pneumatically-driven microreactor *on-board pumping*

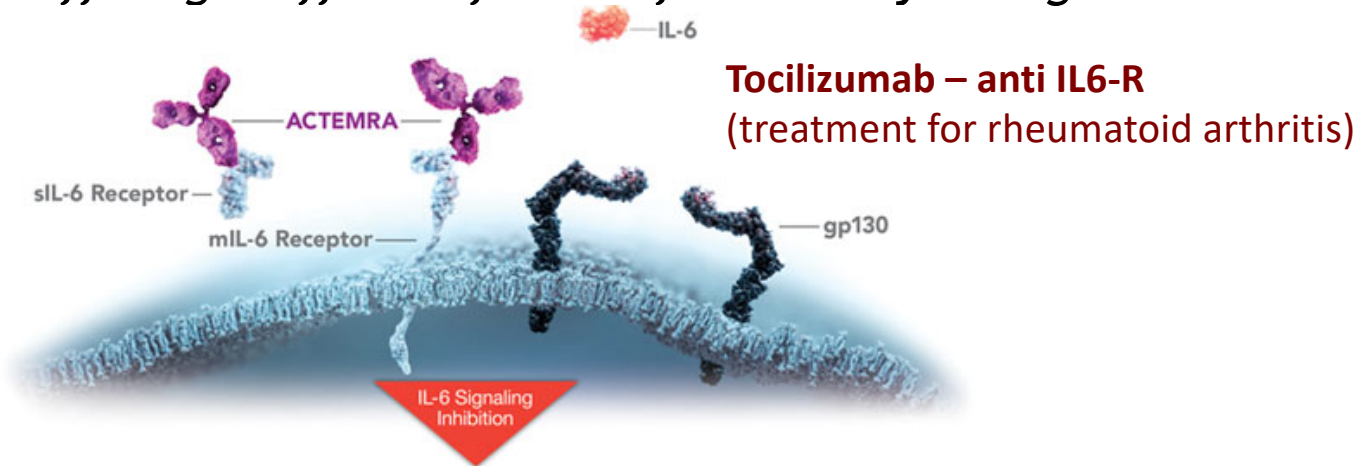


cnBio innovations
A member of **cn** innovations



Inman, W, Domansky, K, Serdy J, Owens, B, Trumper, D, Griffith, LG, "Design, modeling and fabrication of a constant-flow pneumatic pump," *J. Micromech. Microeng.* 17, 891-899 (2007).

Example “ADME-TOX” Problem that Requires Liver MPS: *Off Target Effects of Anti-Inflammatory Biologics*



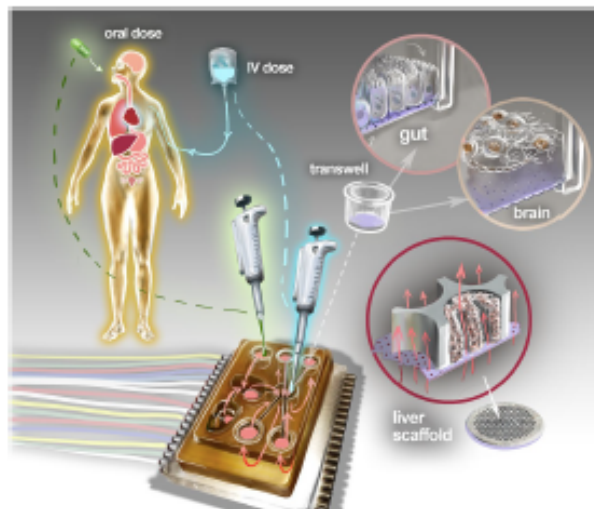
Causes 1.8-fold decrease in plasma AUC for Simvastatin (& other drugs), a CYP3A4 substrate → FDA warning

Recapitulated phenotype in long-term “immunocompetent” liver microreactor culture *with Amgen: Long et al, Drug Met Dispos 2016*

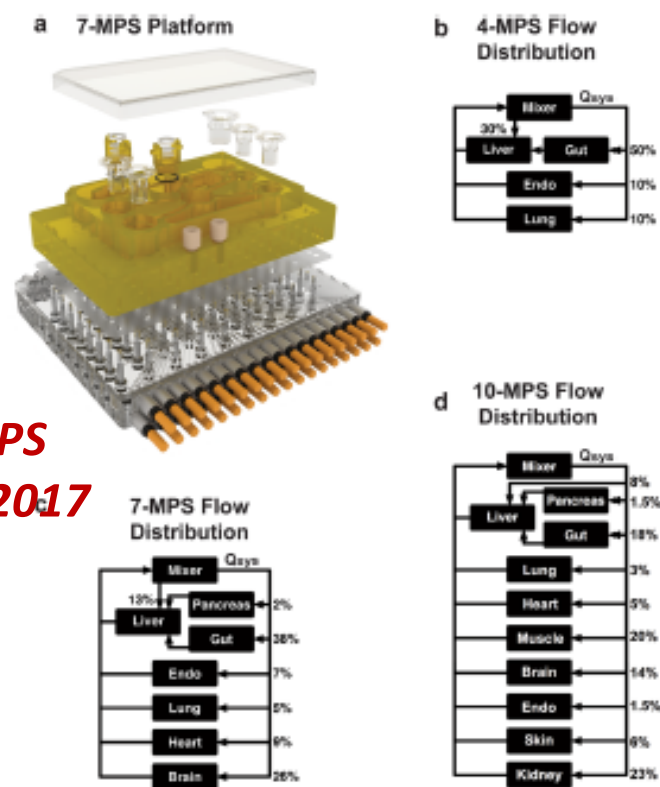
- required weeks-long culture, multiple doses, etc

Interconnected Microphysiological Systems for Quantitative Biology and Pharmacology Studies

Collin D. Edington¹, Wen Li Kelly Chen¹, Emily Geishecker¹, Timothy Kassir^{1,4}, Luis R. Soenksen^{1,2,4}, Brij M. Bhushan^{1,4}, Duncan Freake⁵, Jared Kirschner⁵, Christian Maass¹, Nikolaos Tsamandouras¹, Jorge Valdez¹, Christi D. Cook^{1,3}, Tom Parent⁵, Stephen Snyder⁵, Jiajie Yu¹, Emily Suter¹, Michael Shockley¹, Jason Velazquez¹, Jeremy J. Velazquez¹, Linda Stockdale¹, Julia P. Papps^{1,3}, Iris Lee¹, Nicholas Vanni¹, Mario Gamboa¹, Matthew E. LaBarge¹, Zhe Zhong¹, Xin Wang¹, Laurie A. Boyer⁶, Douglas A. Lauffenburger^{1,3,6,8}, Rebecca L. Carrier⁷, Catherine Communal¹, Steven R. Tannenbaum^{1,8}, Cynthia L. Stokes⁹, David J. Hughes¹⁰, Gaurav Rohatgi⁵, David L. Trumper^{2,4}, Murat Cirit^{1,8} & Linda G. Griffith^{1,2,3,8}



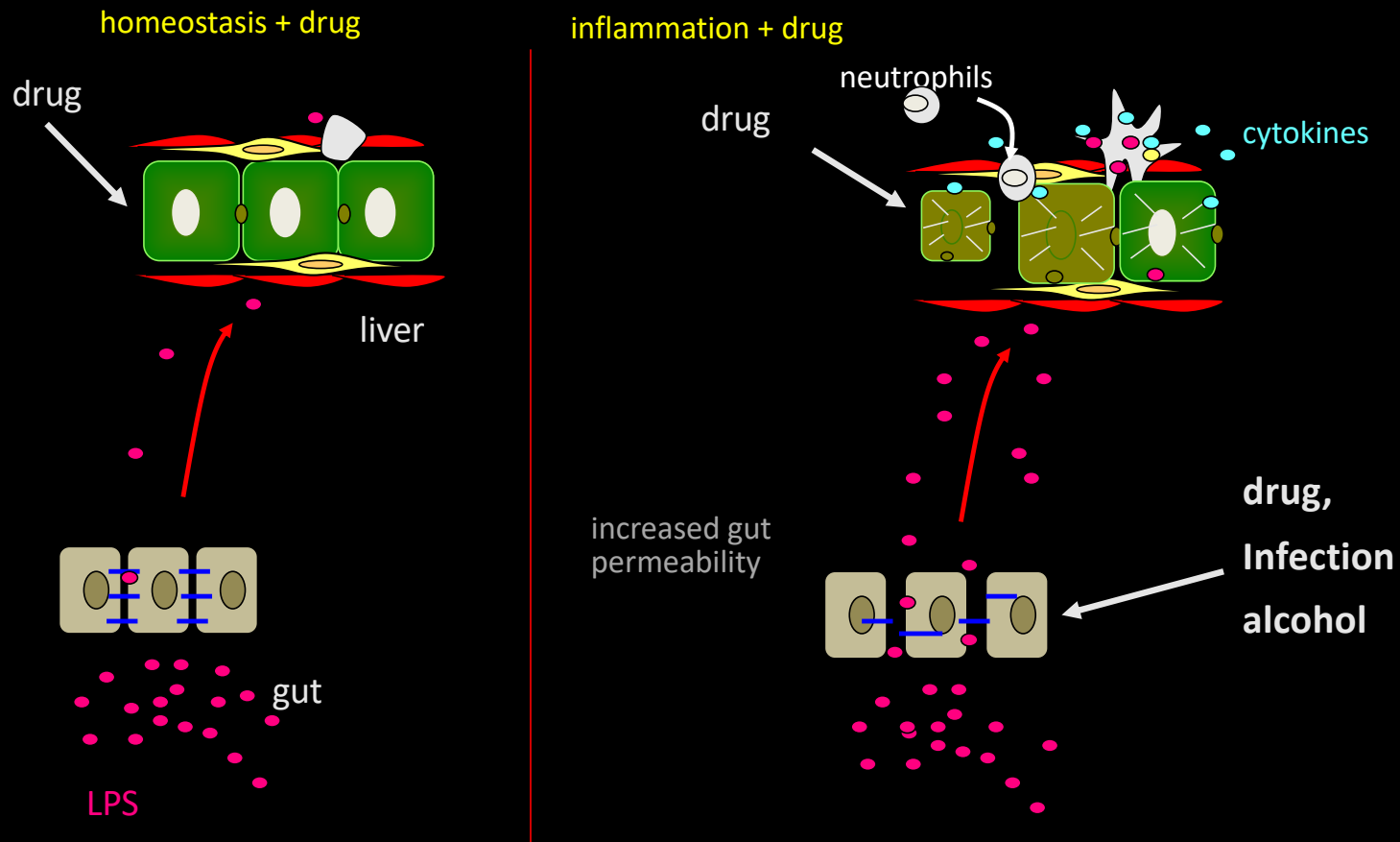
Focus on technology for chronic, systemic inflammatory diseases – target identification, not just ADME/Tox!



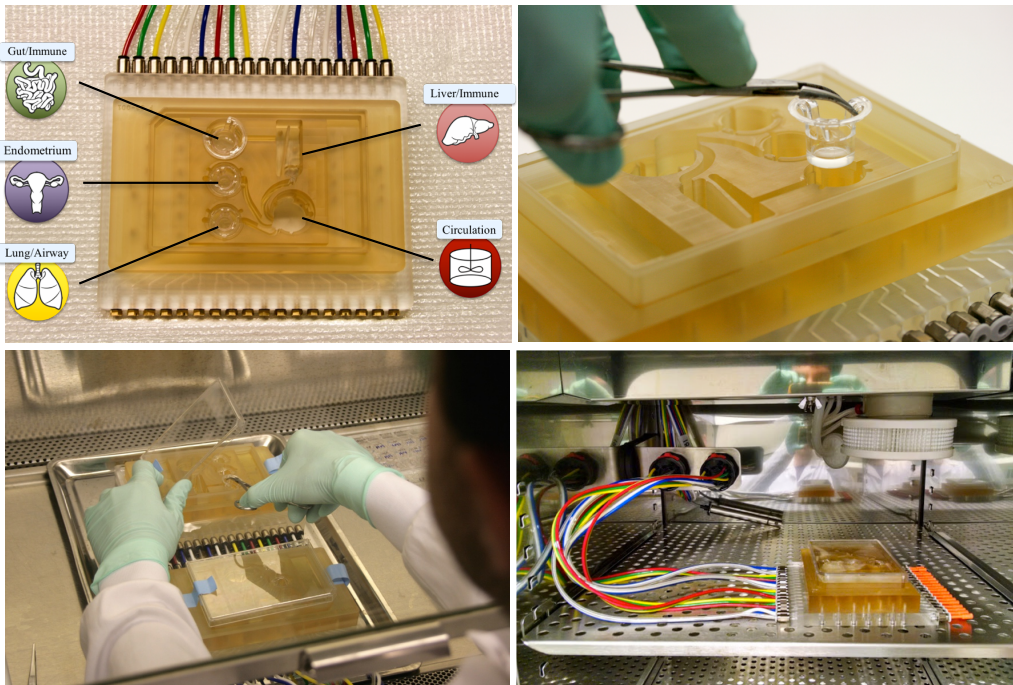
DARPA (NIH) MPS Program 2012-2017 (+ continuing)

gut-liver (leaky gut) – modulation of tolerance and immunity

Inspired by Cindy Afshari, Amgen

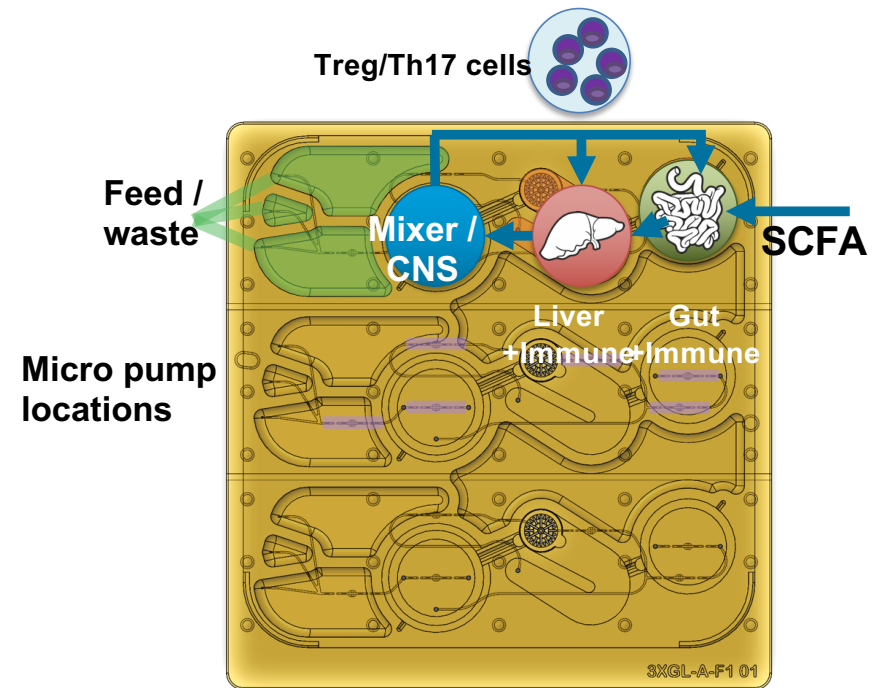


Multi-Organ Platform with immune cell-friendly pumps



Gut-Liver + Immune 4+ organs

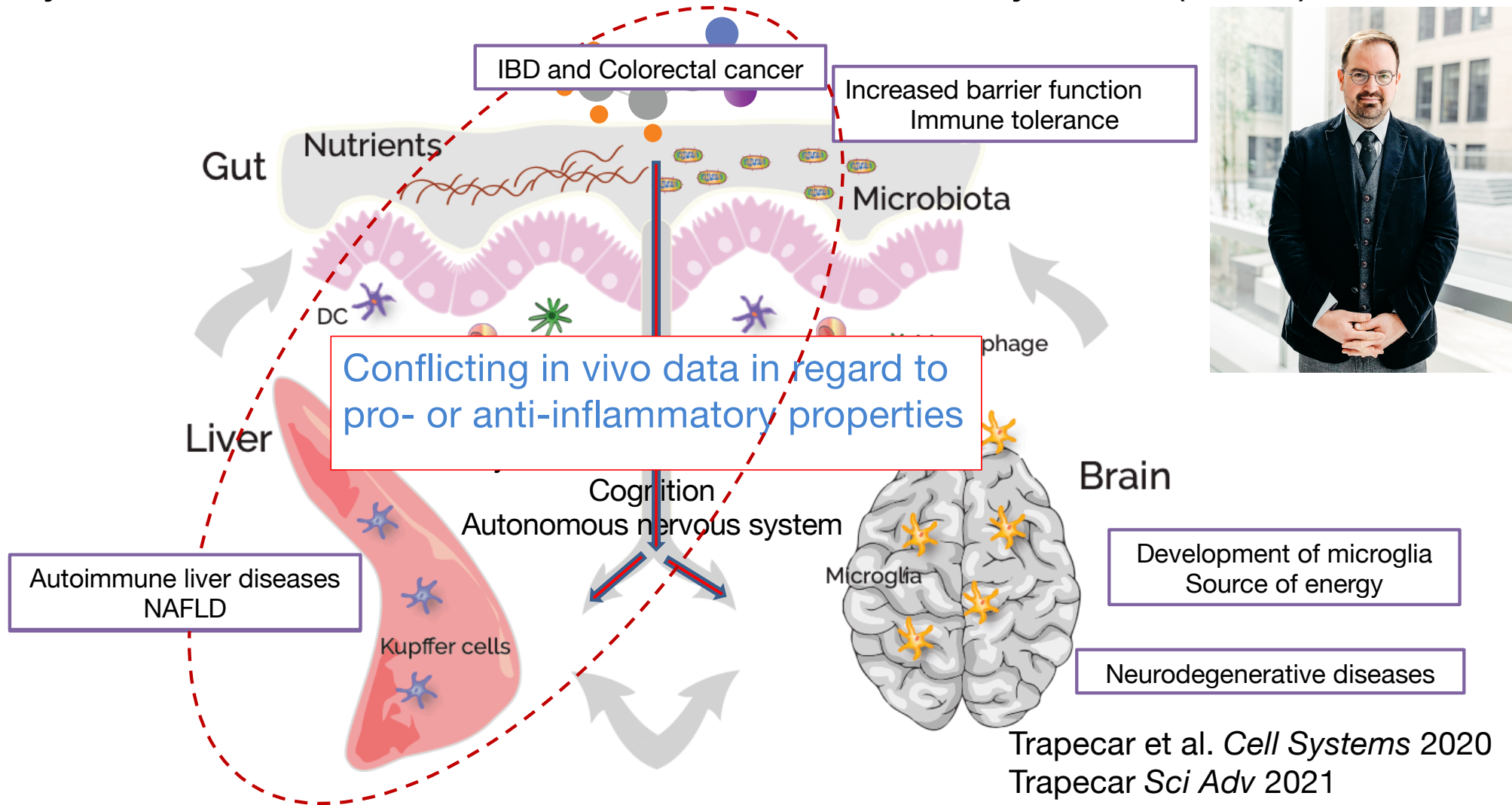
Chen et al., Biotech Bioeng. 2017 *Edington, Chen, et al Sci Rep 2018*
Tsamandouros et al. AAPJ, 2017 *Maas et al. Sci Rep, 2018,*



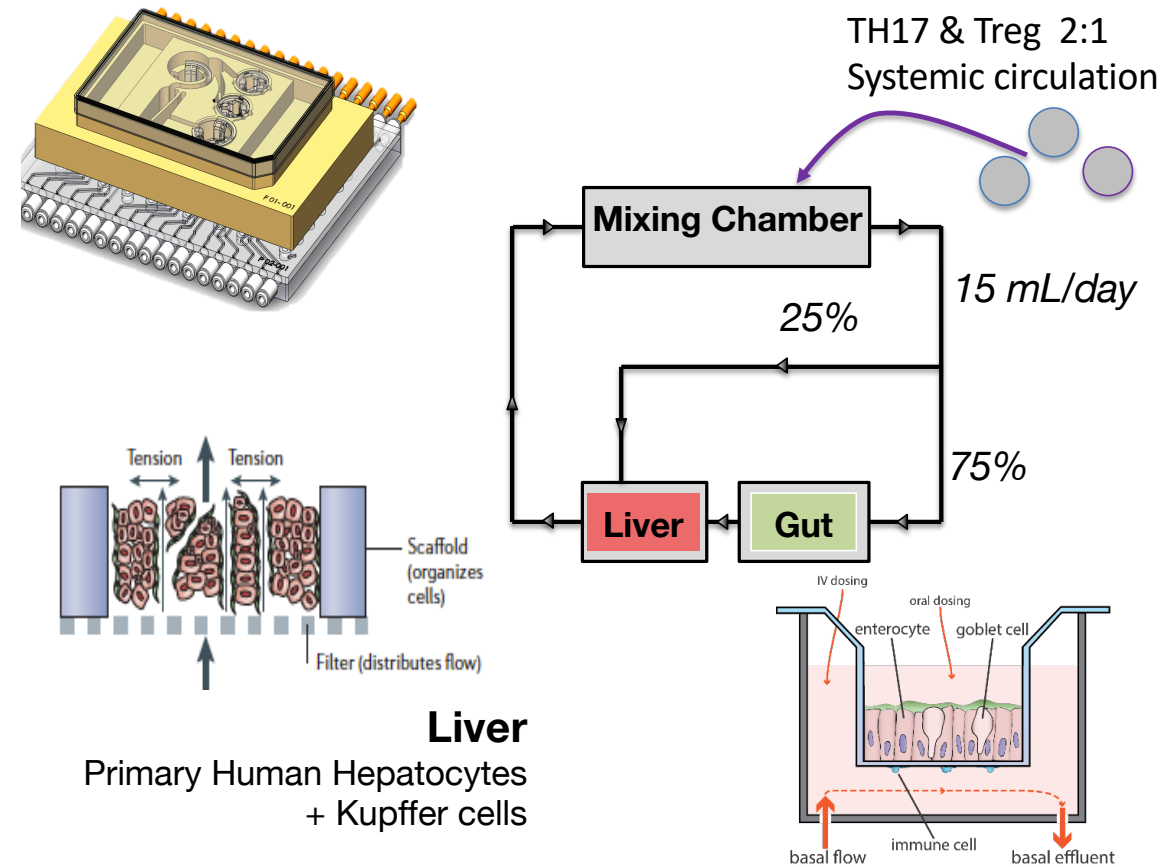
Gut-Liver-(CNS) / 3 per platform

Trapecar et al Cell Systems, 2020
Trapecar et al, Sci Adv 2021

Systemic Effects of Gut-derived Short-Chain Fatty Acids (SCFA)

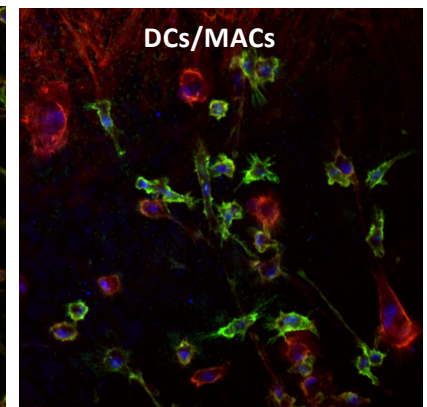
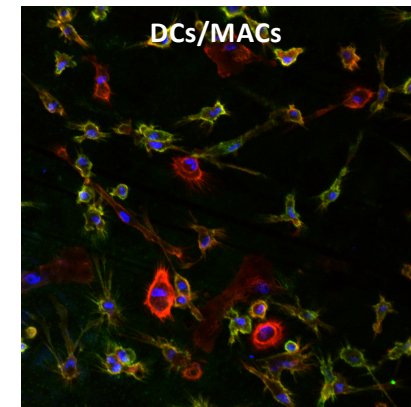
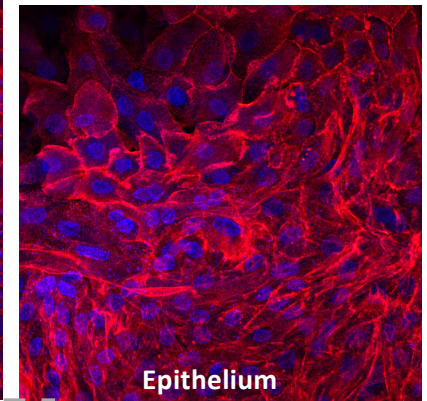
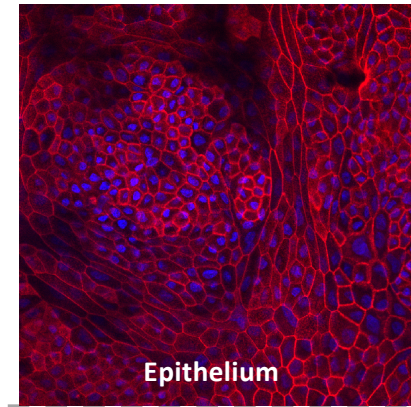


How Do Short Chain Fatty Acids alter Gut-Liver Interactions in the context of Ulcerative Colitis?



Healthy donor

UC donor



DAPI/CD14/Actin

DAPI/CD14/Actin

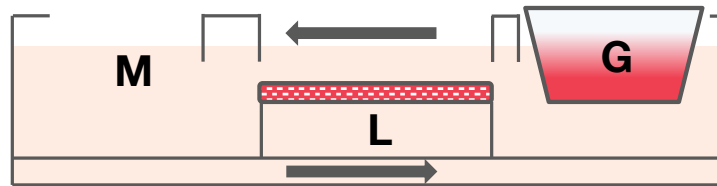
Trapecar et al. Cell Systems 2020

Trapecar et al Science Advances, in revision 2020

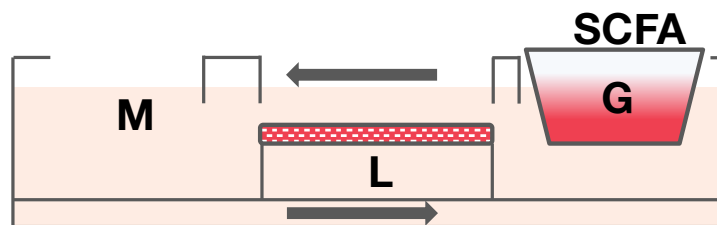
Chen et al Biotech Bioeng 2017; Tsamandouros et al AAPS J 2017

Gut_{monocyte, dendritic}-Liver_{Kupffer} (+ T Cell) Interactions From Simple to Complex

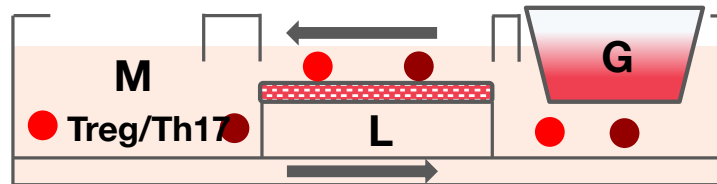
Gut - Liver



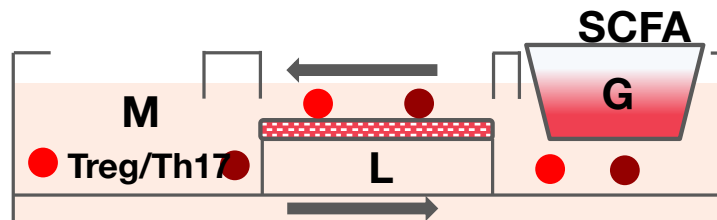
Gut - Liver
+ SCFA



Gut - Liver
+ Treg & Th17



Gut - Liver
+ SCFA
+ Treg & Th17



4 day interaction

(1 media change at day 2)



G – Gut MPS

L- Liver MPS

M-Mixer

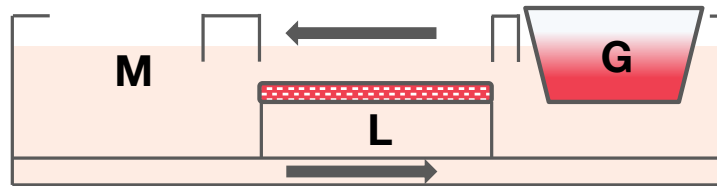
Treg/Th17- Treg/Th17 cells

SCFA-Short-chain Fatty Acids

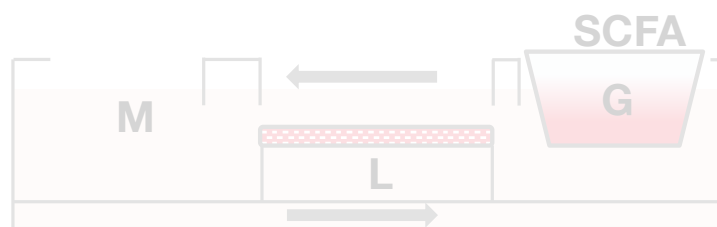
Trapecar et al. Cell Systems 2020
Trapecar et al Sci Adv 2021

Gut_{monocyte, dendritic}-Liver_{Kupffer} (+ T Cell) Interactions From Simple to Complex

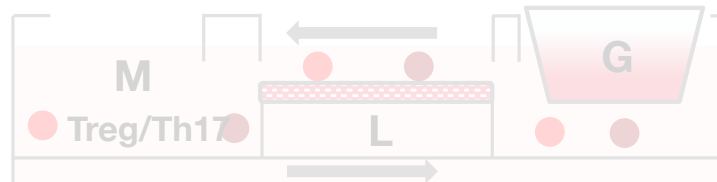
Gut - Liver



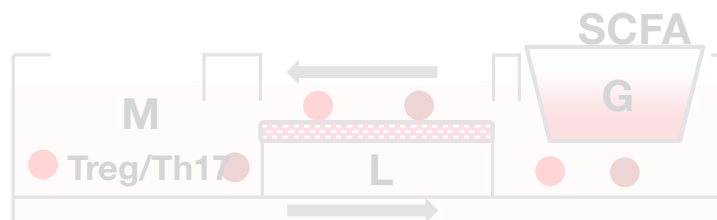
Gut - Liver
+ SCFA



Gut - Liver
+ Treg & Th17



Gut - Liver
+ SCFA
+ Treg & Th17



4 day interaction

(1 media change at day 2)



G – Gut MPS

L- Liver MPS

M-Mixer

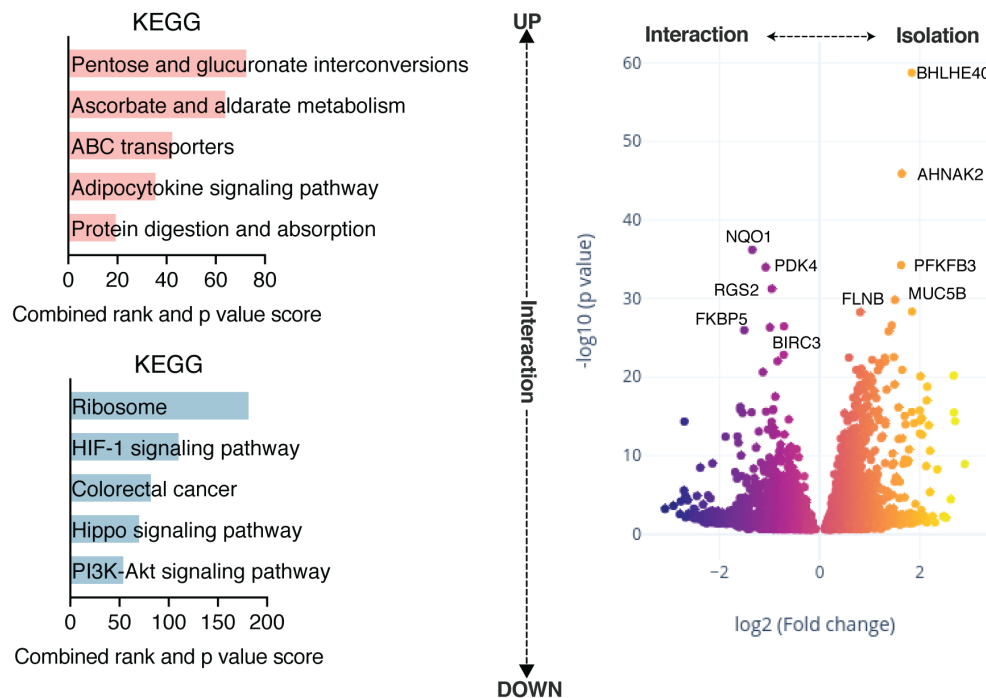
Treg/Th17- Treg/Th17 cells

SCFA-Short-chain Fatty Acids

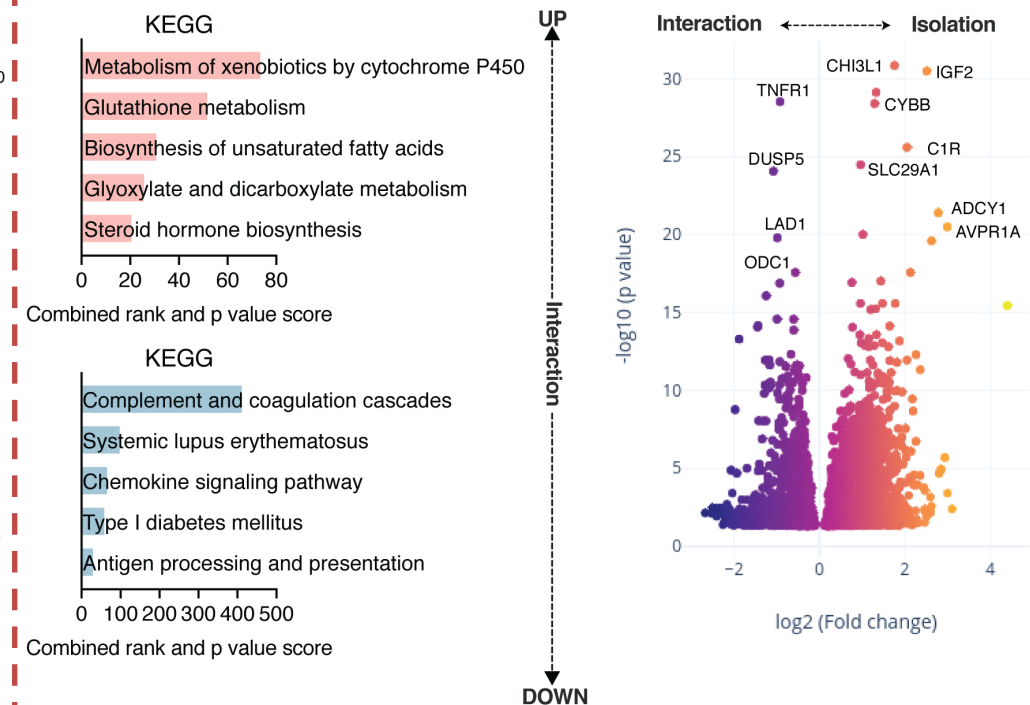
Trapecar et al. Cell Systems 2020
Trapecar et al Sci Adv 2021

Gut-Liver Interaction leads to increased metabolism and reduced immune activation transcripts

Gut in interaction



Liver in interaction

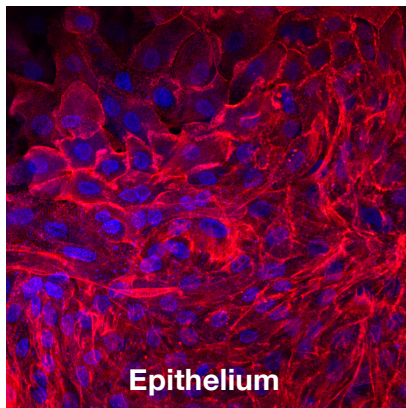


Epithelial activation status directs CD4 Treg/Th17 polarization

Trapecar et al. Cell Systems 2020

Trapecar et al in revision 2020

UC donor

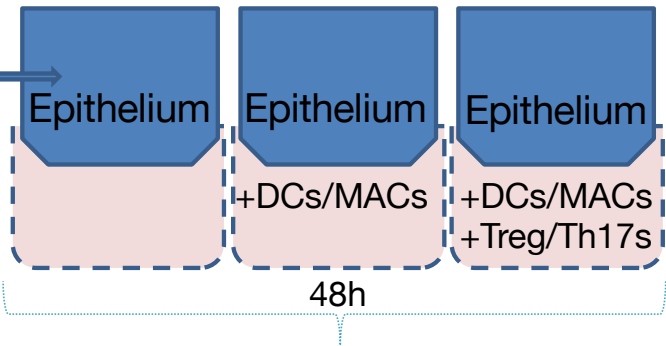


Epithelium

UC organoids

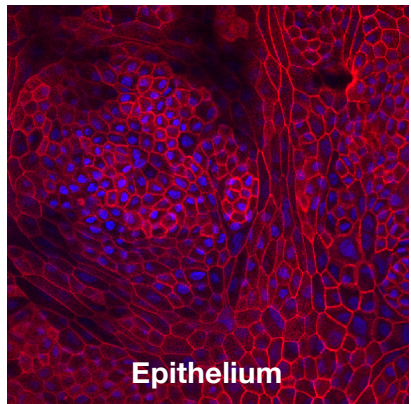


Transwell inserts



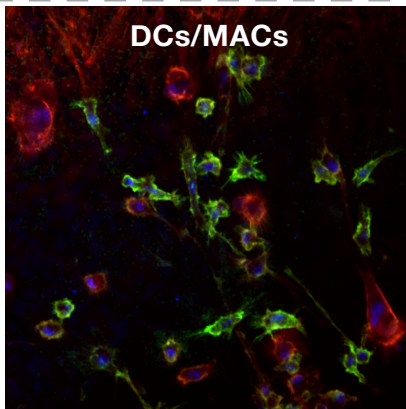
Multiplexing 41 cytokines /chemokines
in basal medium

Healthy donor



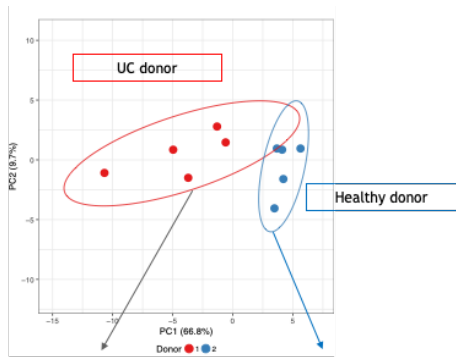
Epithelium

DCs/MACs



DAPI/CD14/Actin

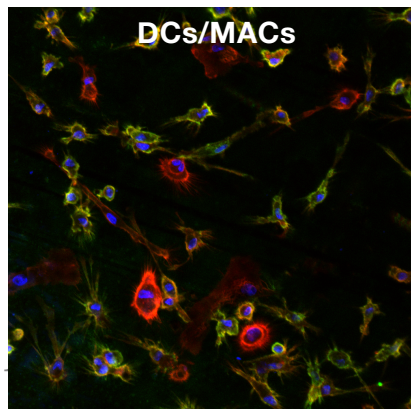
DONOR	DONOR	DONOR	DONOR
Th1beta	Th1beta	Th1beta	UC donor
Th1alpha	Th1alpha	Th1alpha	Healthy donor
MCP-1	MCP-1	RANTES	
MIP-1beta	MIP-1beta	MIP-1beta	Higher
MIP-1alpha	MIP-1alpha	MIP-1alpha	Lower
MCP-1	MCP-1	MCP-1	
IL8	IL8	IL8	
IL7	IL7	IL7	
IL6	IL6	IL6	
IL5	IL5	IL5	
IL4	IL4	IL4	
IL3	IL3	IL3	
IL2	IL2	IL2	
IL1beta	IL1beta	IL1beta	
IL1alpha	IL1alpha	IL1alpha	
IL1RA	IL1RA	IL1RA	
IL17A	IL17A	IL17A	
IL17B	IL17B	IL17B	
IL17C	IL17C	IL17C	
IL17D	IL17D	IL17D	
IL17E	IL17E	IL17E	
IL17F	IL17F	IL17F	
IL17G	IL17G	IL17G	
IL17H	IL17H	IL17H	
IL17I	IL17I	IL17I	
IL17J	IL17J	IL17J	
IL17K	IL17K	IL17K	
IL17L	IL17L	IL17L	
IL17M	IL17M	IL17M	
IL17N	IL17N	IL17N	
IL17O	IL17O	IL17O	
IL17P	IL17P	IL17P	
IL17Q	IL17Q	IL17Q	
IL17R	IL17R	IL17R	
IL17S	IL17S	IL17S	
IL17T	IL17T	IL17T	
IL17U	IL17U	IL17U	
IL17V	IL17V	IL17V	
IL17W	IL17W	IL17W	
IL17X	IL17X	IL17X	
IL17Y	IL17Y	IL17Y	
IL17Z	IL17Z	IL17Z	
IL17A1	IL17A1	IL17A1	
IL17A2	IL17A2	IL17A2	
IL17A3	IL17A3	IL17A3	
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IL17A6	IL17A6	IL17A6	
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IL17A100	IL17A100	IL17A100	



Conversion into Th1/Th17
Inflammatory cells

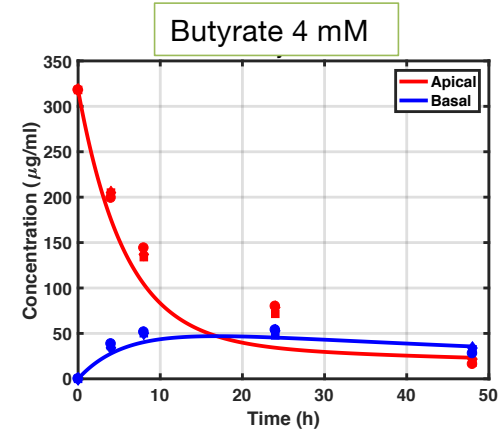
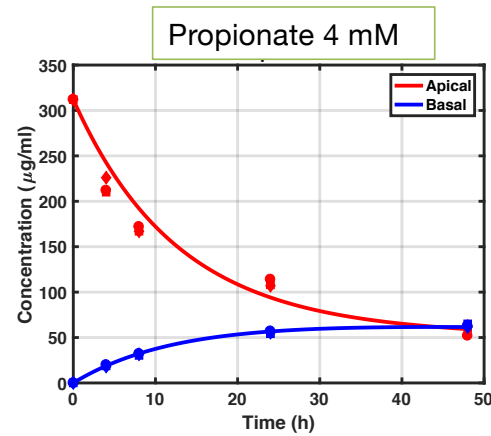
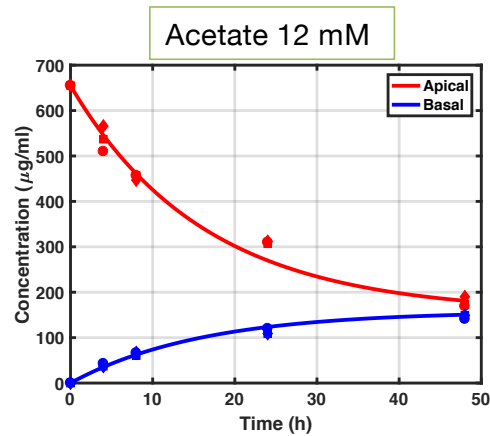
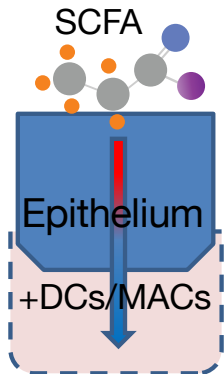
Treg dominated cell
phenotype maintained

DCs/MACs



DAPI/CD14/Actin

SCFA Metabolism (20 mM of Acetate:Propionate:Butyrate)



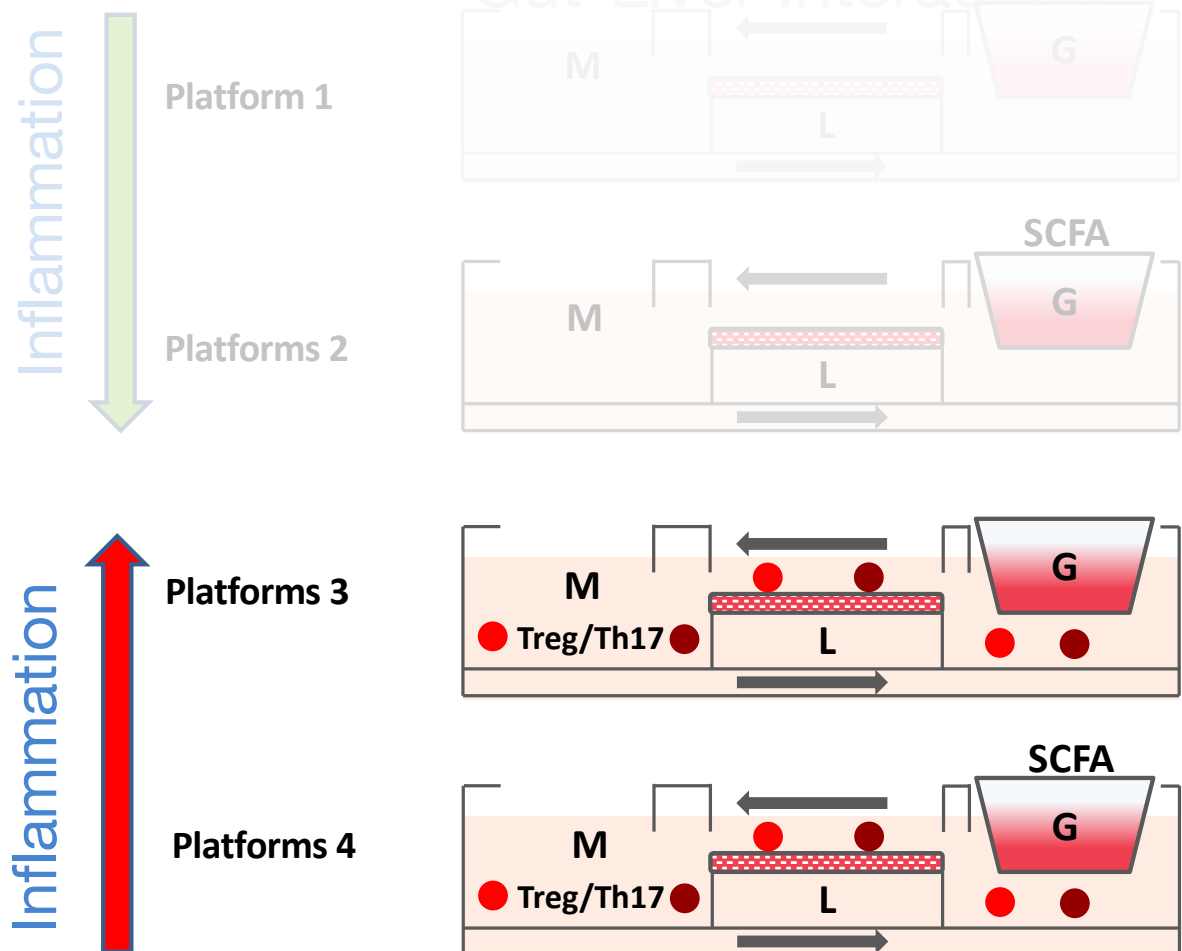
Literature shows that ~50% of butyrate is consumed by enterocytes which validates our model

Amount added (ug)	Acetate	Propionate	Butyrate
Start (t = 0 h)	328	156	159
End (t = 48 h)	315	129	73
Ratio (% loss)	4	18	54

Trapecar et al. Cell Systems 2020
Trapecar et al submitted 2020

Ac/Pr/Bu ratio after gut absorption is ~67/22/10.6. This is in accordance with a previous published in vivo ratio of 70/20/10 (Portal vein samples)

Gut-Liver Interaction



4 day interaction

(1 media change at day 2)



G – Gut MPS

L- Liver MPS

M-Mixer

Treg/Th17- Treg/Th17 cells

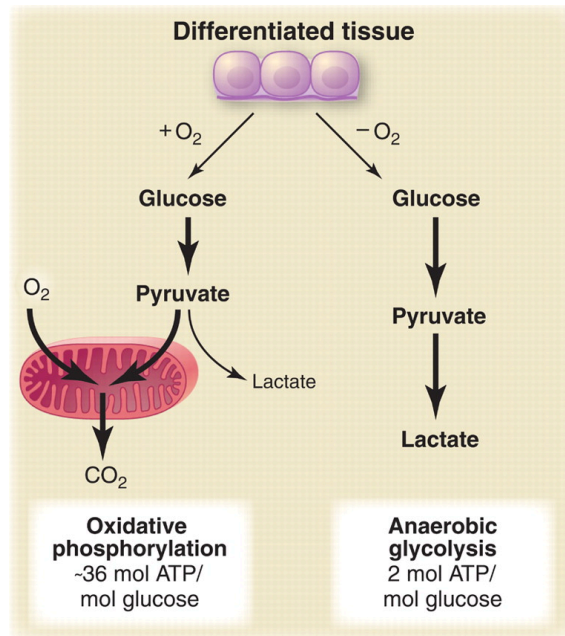
SCFA-Short-chain Fatty Acids

MIT BE
BIOLOGICAL ENGINEERING

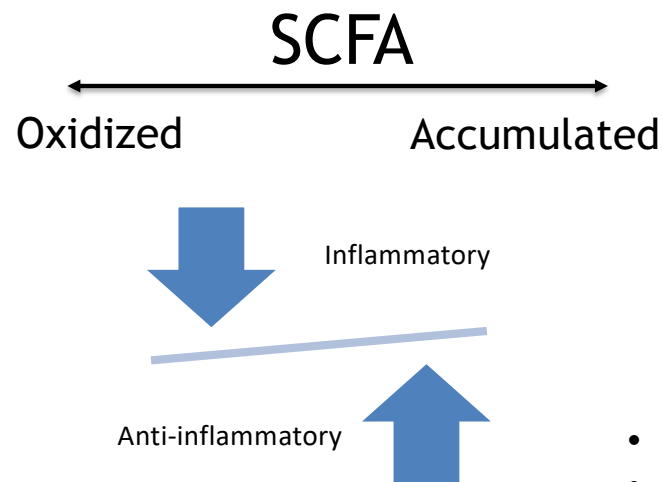
Trapezar et al submitted 2020



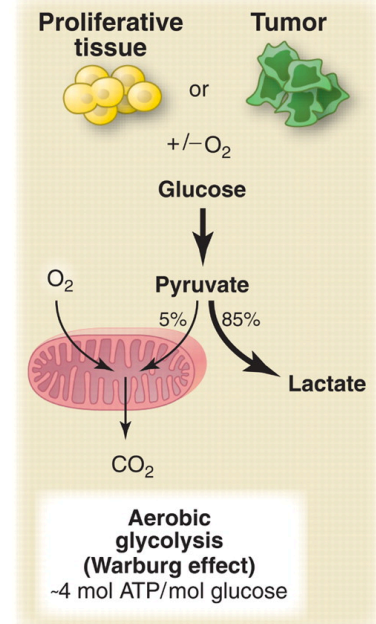
SCFA as a Double-edged Sword



- Anti-inflammatory program
- Macrophage polarization into M2
- Increased Treg differentiation
- Promoted proliferation



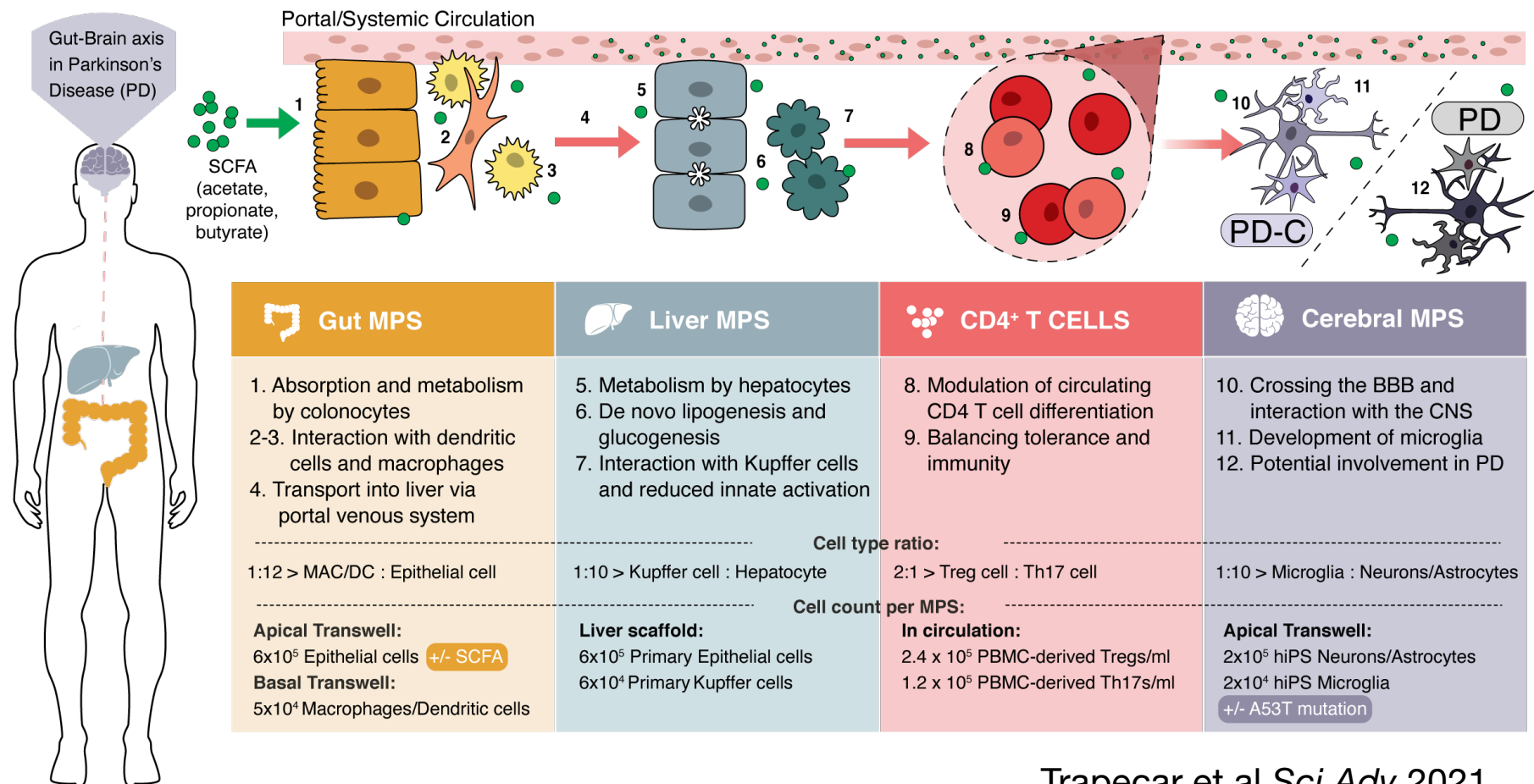
Trapecar et al. Cell Systems 2020
Trapecar et al submitted 2020



- Pro-inflammatory program
- HDAC inhibition
- Apoptosis
- CaCo-2 cells not suitable to study SCFA

Based on Heiden et al., Science 2009

DESIGN RATIONALE OF MICROPHYSIOLOGICAL SYSTEMS (MPSs) AND THEIR INTERACTION



The Frontier: Animal-Human Translation **without “Animal Chips”**

INSIGHTS | PERSPECTIVES

sciencemag.org SCIENCE

742 14 FEBRUARY 2020 • VOL 367 ISSUE 6479

MEDICINE

Translating preclinical models to humans

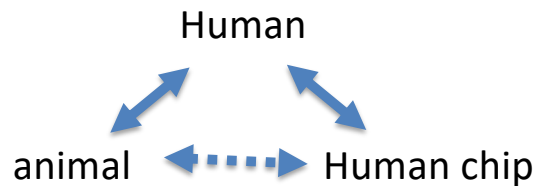
Computational models for cross-species translation could improve drug development

By Douglas K. Brubaker
and Douglas A. Lauffenburger

tive models that incorporate cross-species
differences in data types and phenotypes
into translation

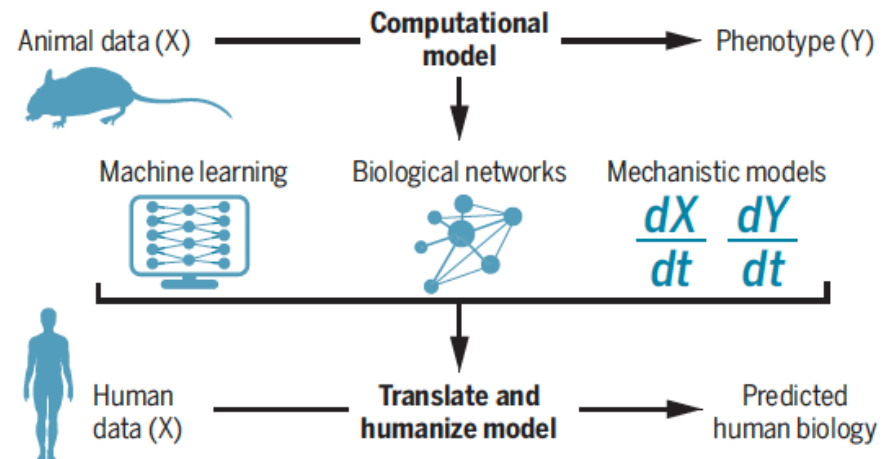
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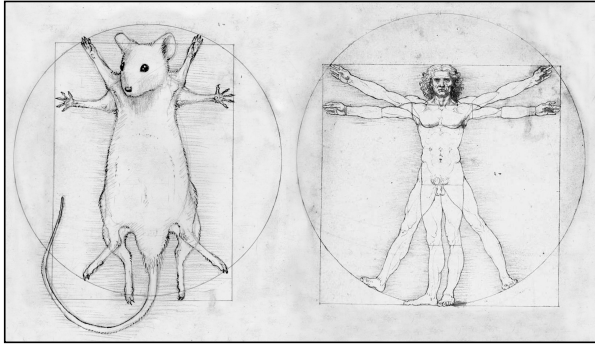
If we have the right data sets – do
we even need animal chips?



Systems model–based cross-species translation

Translating computational systems models of molecular (X) to phenotypic (Y) associations from animal models to humans provides a powerful framework for translating therapeutic concepts from preclinical to clinical stages.

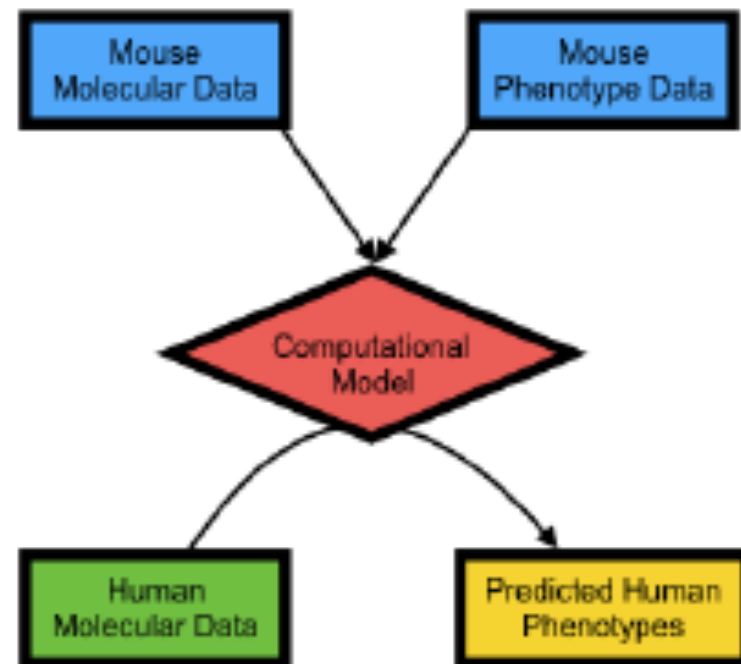




Instead of direct translation of observations,
use mathematical framework
to translate
computational models

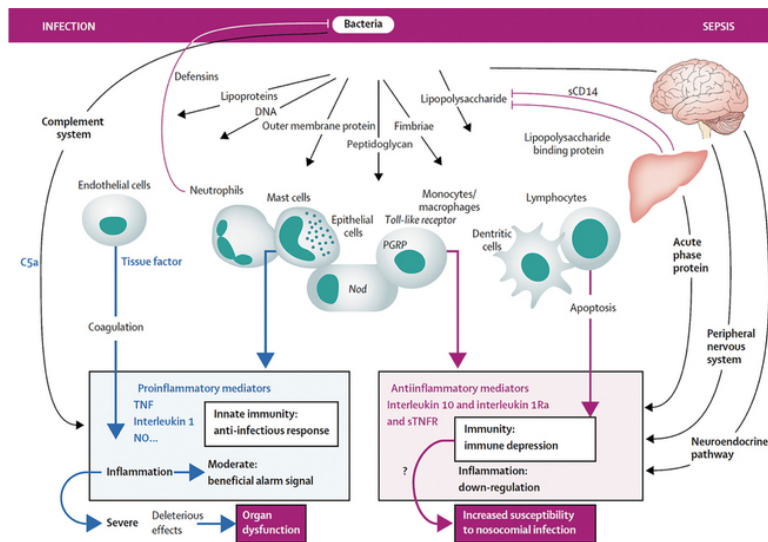
Likely easier to construct computational
models based on animal studies, so
then ‘humanize’ those models to
emphasize relevance to human context

***Conceptual framework to
address challenge of
“translation” across species –
e.g., animal studies to human subjects***



Translation of Transcriptomic Data from Mouse to Human

-- 36 case studies of inflammatory pathologies

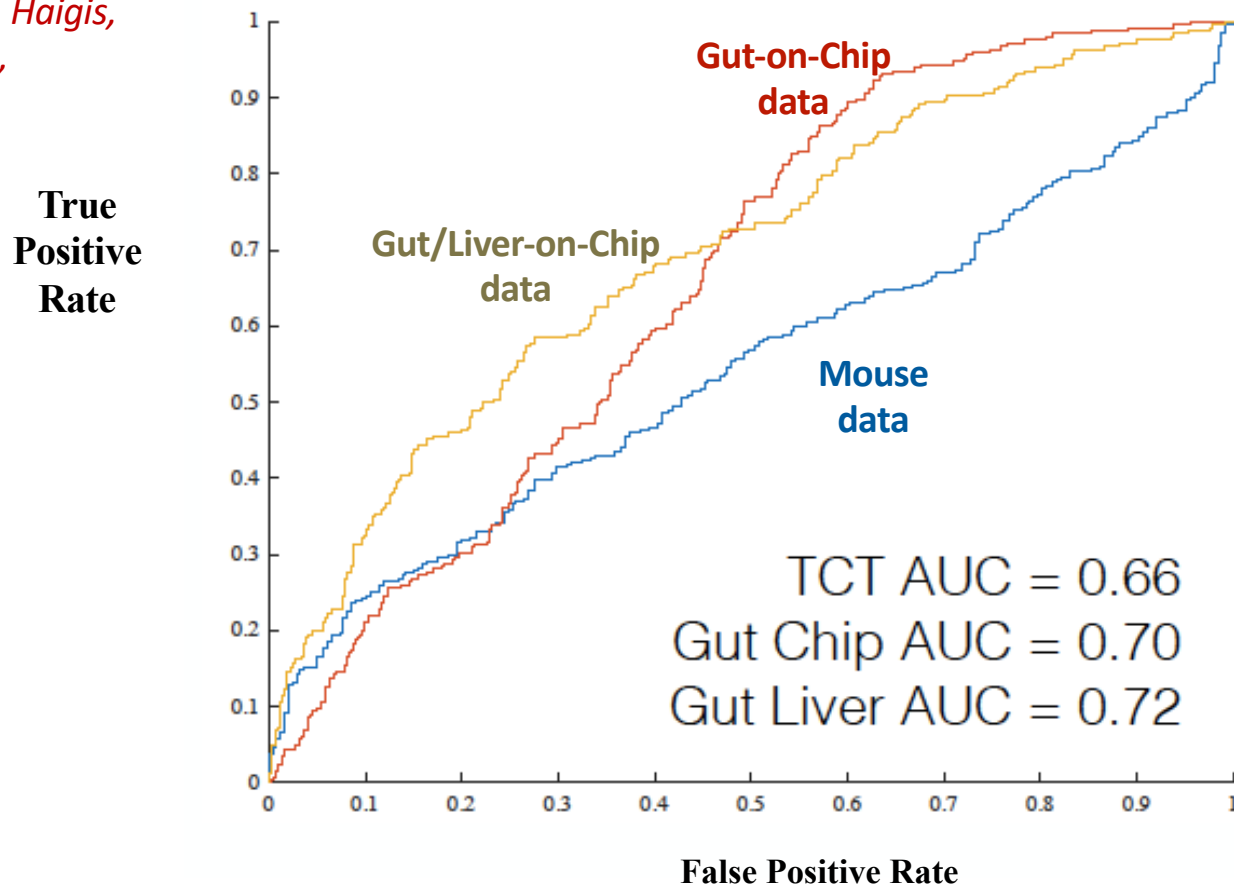


[Brubaker *et al*, PLoS Comp Biol (2019)]

Species	Disease	GEO Accession	Microarray Platform(s)	Conditions and Sample Sizes	Tissue
Human	Burn	GSE37069	GPL570	Control (n = 37) Burn (n = 553)	White Blood Cells
Human	Trauma	GSE36809	GPL570	Control (n = 37) Trauma (n = 216)	Whole Blood
Human	Endotoxemia	GSE3284	GPL96 GPL 97	Control (n = 16) Endotoxin (n = 76)	Whole Blood
Human	Sepsis	GSE13904	GPL570	Control (n = 18) Sepsis (n = 158)	Whole Blood
Human	Sepsis	GSE9960	GPL570	Control (n = 16) Sepsis (n = 54)	Peripheral Blood Mononuclear Cells
Human	Sepsis	GSE28750	GPL570	Control (n = 20) Sepsis (n = 21)	Whole Blood
Human	Sepsis	GSE13015	GPL6106 GPL6047	Control (n = 29) Sepsis (n = 77)	Whole Blood
Mouse (C57BL/6J)	Burn	GSE7404	GPL1261	Control (n = 16) Burn (n = 16)	Leukocytes
Mouse (C57BL/6J)	Trauma	GSE7404	GPL1261	Control (n = 16) Trauma (n = 16)	Leukocytes
Mouse (C57BL/6J)	Endotoxemia: LPS	GSE7404	GPL1261	Control (n = 8) Endotoxemia (n = 8)	Leukocytes
Mouse (C57BL/6J)	Endotoxemia: LPS	GSE5663	GPL81	Control (n = 4) Endotoxemia (n = 5)	Blood
Mouse (C57BL/6J)	Sepsis: CLP	GSE5663	GPL81	Control (n = 4) Mild Sepsis (n = 5) Sepsis (n = 5)	Blood
Mouse (C57BL/6J)	Sepsis: SPS2	GSE26472	GPL6778	Control (n = 3) Sepsis (n = 8)	Blood
Mouse (A/J and C57BL/6J)	Sepsis: SA	GSE19668	GPL1261	Control A/J (n = 5) Control C57BL/6J (n = 5) Sepsis A/J (n = 20) Sepsis C57BL/6J (n = 20)	Blood

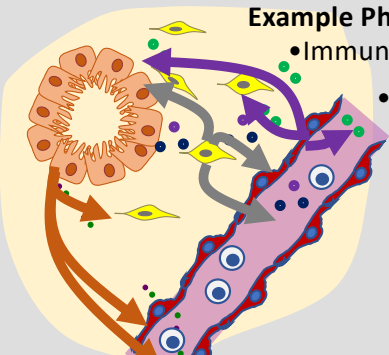
***Human ‘Gut / Liver on Chip’ Transcriptomic Data is more predictive of
In Vivo Human Pathophysiology than Mouse Model Data***

*Lauffenburger, Haigis,
Brubaker, et al,
unpublished*



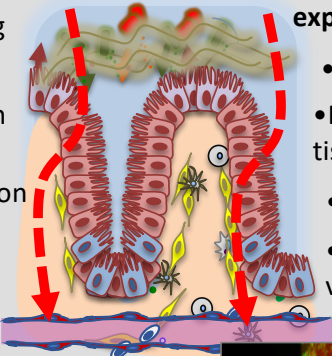
New MIT Industry Consortium – “MCELS”
(Roger Kamm, Director)

Core Activities: **Integration of Tissue Engineering, Microfluidics, Systems Biology/Immunology, and Synthetic Biology**



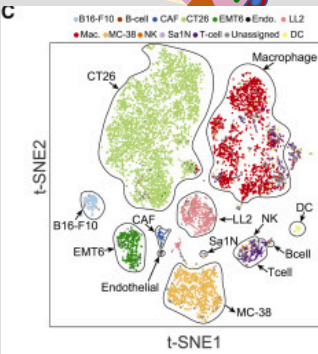
Example Phenomena

- Immune cell trafficking
- Inflammation
- BBB function
- Mucosal barrier function
- Microvascular permeability



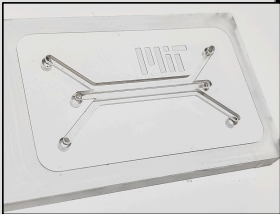
Established and experimental cell sources

- i-PSC-derived
- Patient-derived tissue banks
- microbiome
- iPSC programmed via synthetic biology



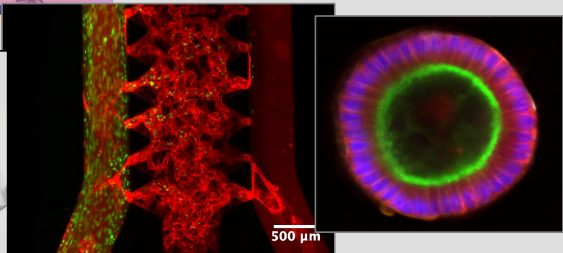
Deterministic and data-driven analytics

- Systems Biology / Immunology
- Species translation
- Heterogeneous data set integration



Translatable Technologies

- microfluidics
- mesofluidics
- 3D synthetic matrices



Applications

Liver

Gut /
microbiome

Tumor

CNS /
neuro

Skin /
subcu

PhysioMimetics Team (partial)

@ MIT

Griffith Lab *Tissue Engineering, Biomaterials, Transport Phenomena*

Collin Edington, Murat Cirit, Sam Raredon, Alex Wang, Pierre Sphabmixay, Jorge Valdez, Linda Stockdale, Catherine Communal, Emily Geishecker ++++++

Murat Cirit *Director, Translational Systems Pharmacology Group*

Christian Maas, Nikos Tsamandouros

Doug Lauffenburger Lab *Systems Biology*

Kelly Chen, Manu Kumar, Abby Hill, Brian Joughin +++

Dave Trumper Lab *Mechatronics*

Brij Bushnan, Luis Soensken, Dan Rathbone ++

Nick Fang Lab *Microfabrication*

Huifeng Du (Pierre S. Phabmixay) +

Steve Tannenbaum Lab *Analytical Chem/Tox*

Ravi Kodihalli, Ujjal Sarkar, Xin Wang+

Laurie Boyer Lab *Cardiac iPS*

Ravi Kodihalli, Ujjal Sarkar, Xin Wang

Rudolf Jaenisch Lab *Stem Cell Biology*

Julien Muffat +

@U Pitt Medical Center

Alan Wells Lab

Donna Stolz Lab

Venkat Venkataraman Lab

@U Wisconsin *brain MPS*

Bill Murphy Lab



Dave Trumper
mechatronics

@Northeastern University

Rebecca Carrier Lab

Gut engineering



Rebecca Carrier

@CN BioInnovations (UK) *Liverchip*

David Hughes, Emma Sceats, Emma Large

@ Continuum, LLC *Engineering Design*

Gaurav Rohatgi, Duncan Freake

Doug Kronke, Jared Kirschner +

Funding

DARPA MPS Program

NIH (NCATS/NCI)

Boehringer Ingelheim

Amgen

NSF STC "EBICS"

NIH T- RO1 (NIBIB)

NIH ICBP (NCI)

Army ICB Program

Begg Foundation