

ORGANS-ON-CHIPS

ADVANCED *IN VITRO* MODELS FOR HUMAN PHYSIOLOGY AND DISEASE

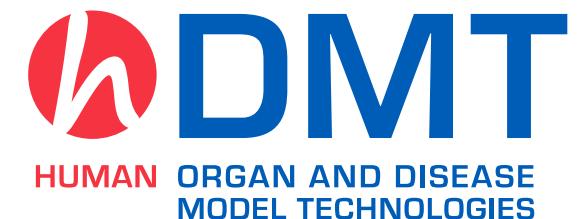
Dr. Andries D. van der Meer

Tenure Track Assistant Professor

Applied Stem Cell Technologies

University of Twente

UNIVERSITY OF TWENTE.



Organs-on-Chips

- Microfluidic devices
- Human-derived cell material
- Physiological realism
- Design by ‘microenvironment engineering’

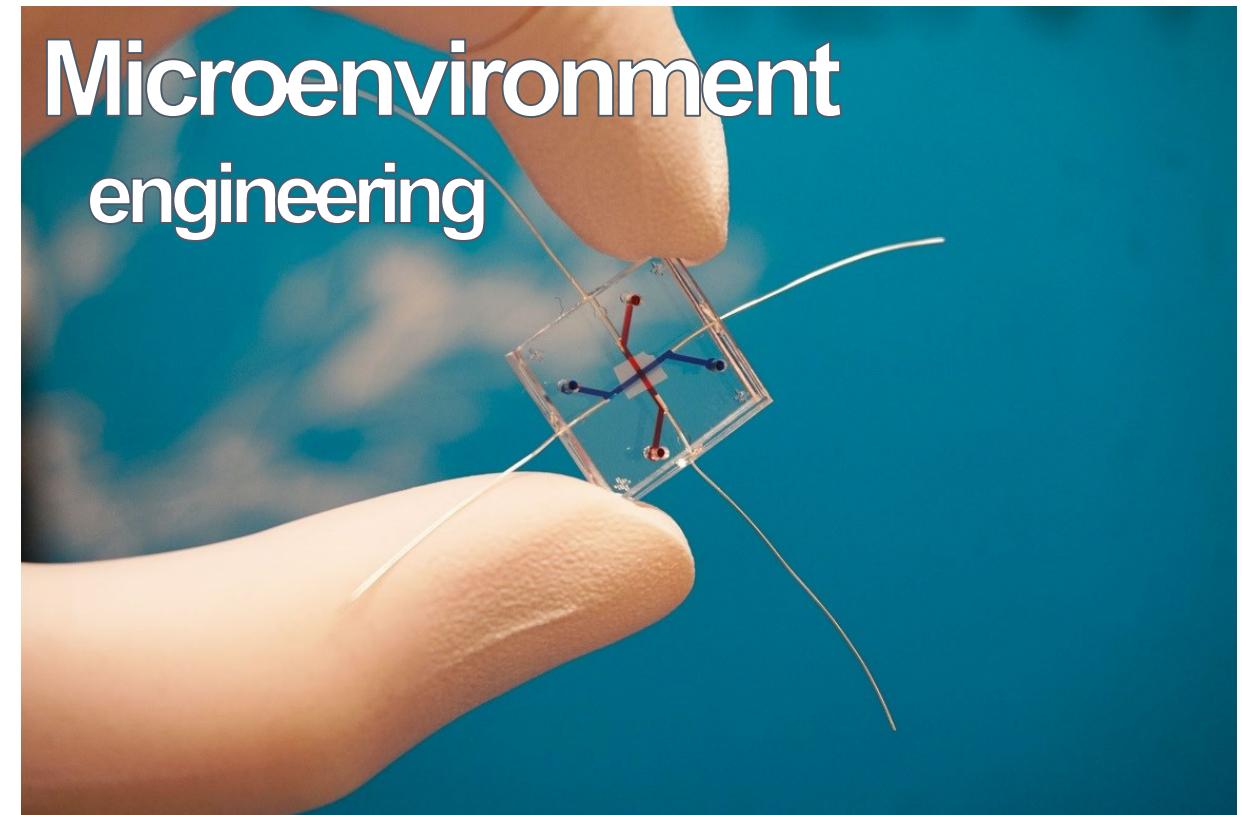
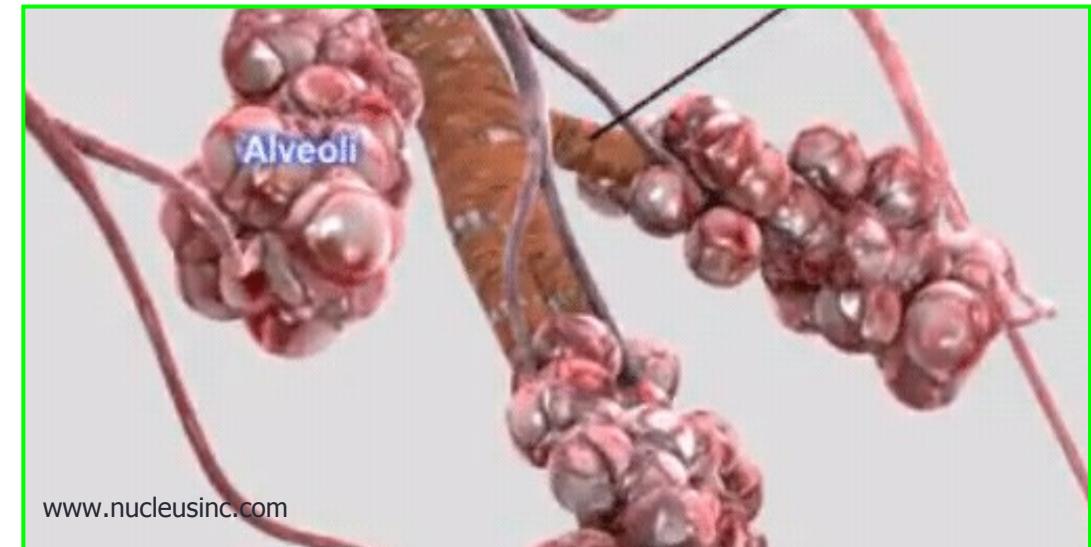
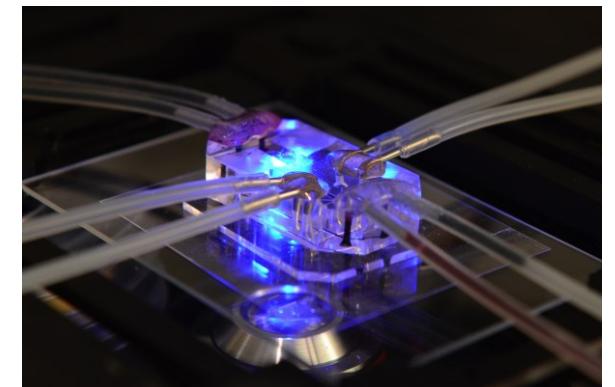


Image: BIOS/Lab on Chip, UT

- Van der Meer, Van den Berg. **Integrative Biology** 2012, 4:461
- Huh, Hamilton, Ingber, **TRENDS in Cell Biology** 2011, 21:745

Lung-on-Chip

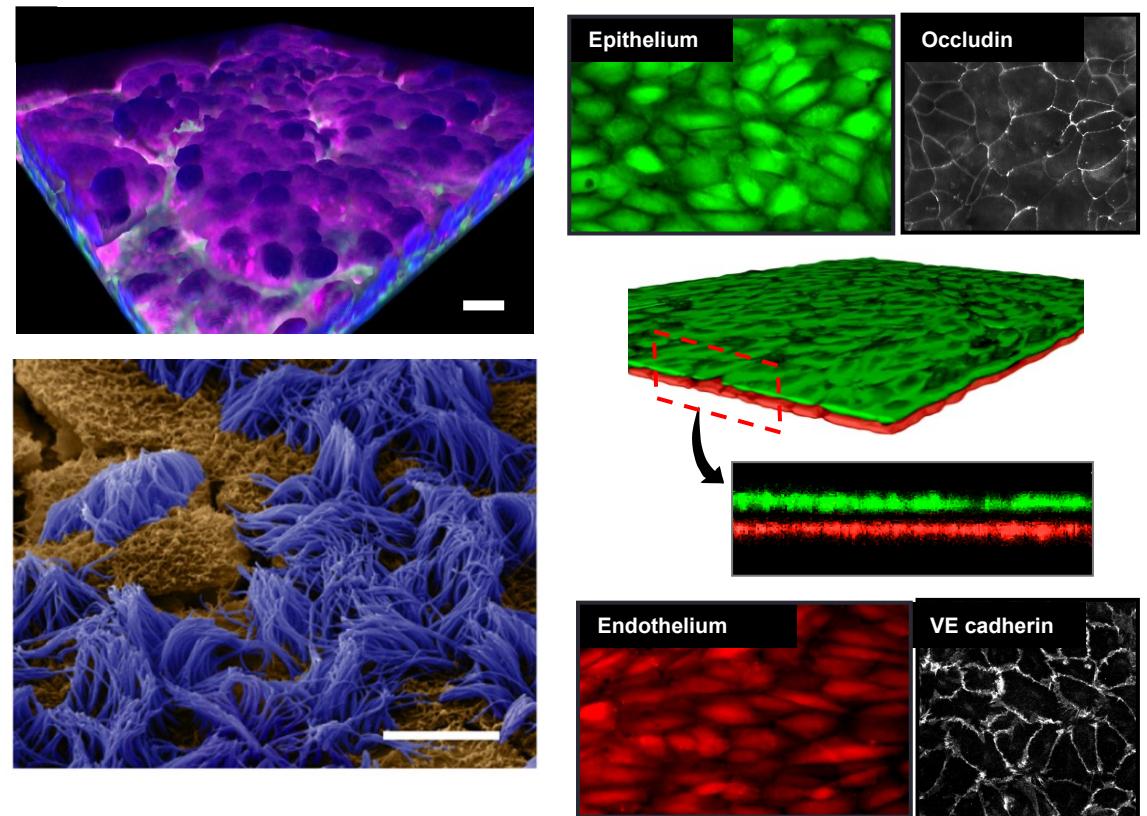
- Alveoli
 - Epithelial-endothelial interface
 - Air-liquid interface
 - Mechanical strain



Organ-on-Chip Technology

- Alveolus
- Small airway
- Proximal tubule
- Glomerulus
- Small intestine

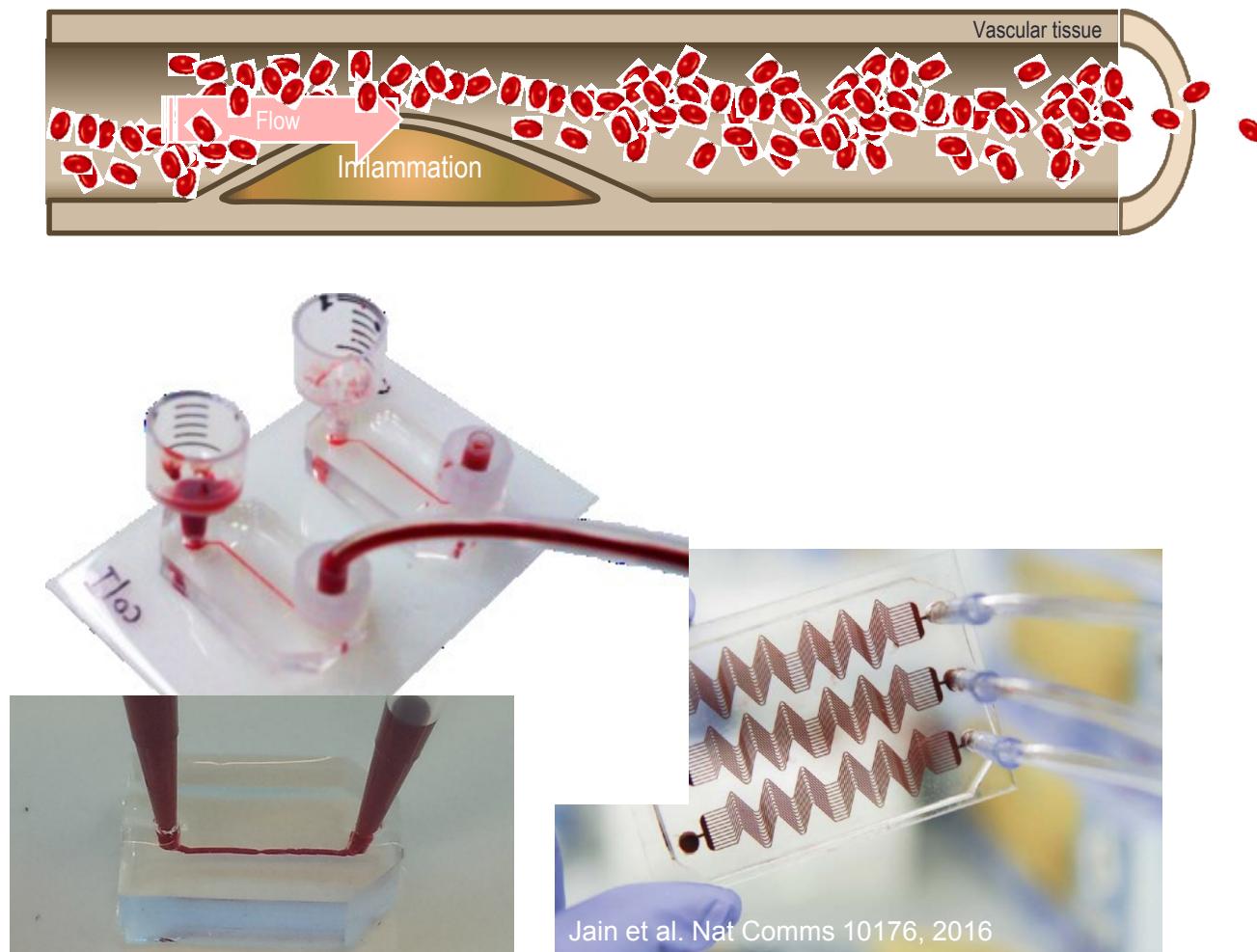
- Huh, et al.. **Science** 2010, 328:1662
- Huh, et al.. **Science Transl Med** 2012, 4:147
- Benam, et al. **Nature Methods** 2016, 13:151
- Kim, et al. **Lab on a Chip** 2012, 12:2165
- Kim, et al. **PNAS** 2016, 113:e7
- Musah, et al. **Nat Biomed Eng** 2017, 1:0069
- Jang, et al. **Integr Biol** 2013 5:1119



Blood Vessels-on-Chips

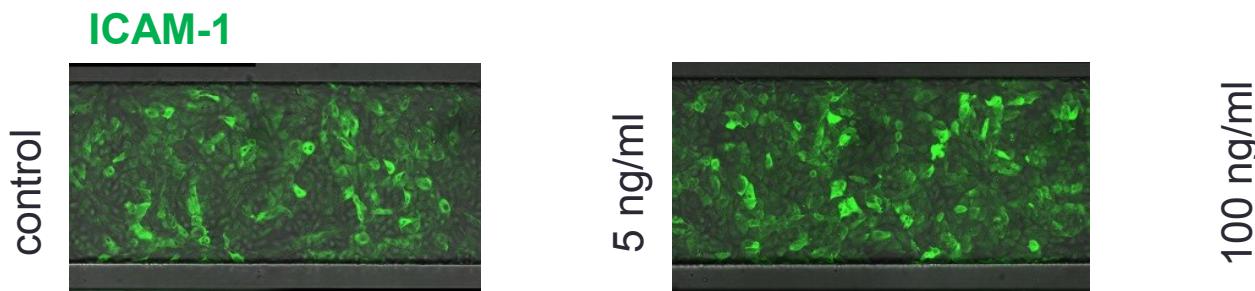
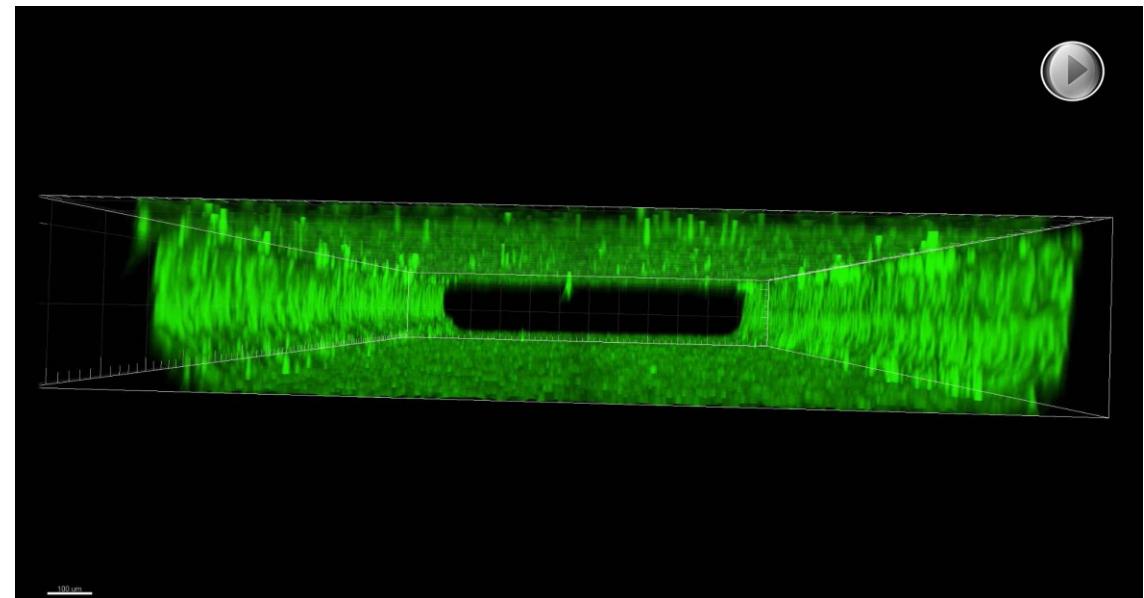
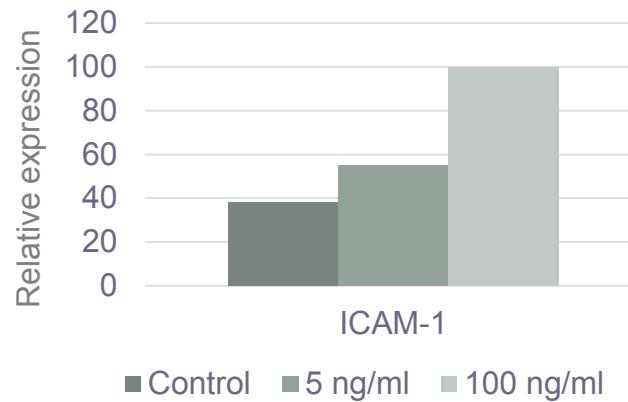
- Organ-on-chip engineering
 - 3D tissues, linking chips into a ‘body-on-a-chip’
- Vascular biology
 - Nutrient transport
 - Inflammation, fibrosis, thrombosis
- Vessel wall
- Flow patterns
- Blood
- **Perfusing an organ-on-chip with blood**

• Jain, Van der Meer, et al. **Biomedical Microdevices** 2016, 18:73
 • Westein, Van der Meer, et al. **PNAS** 2013, 110:1357

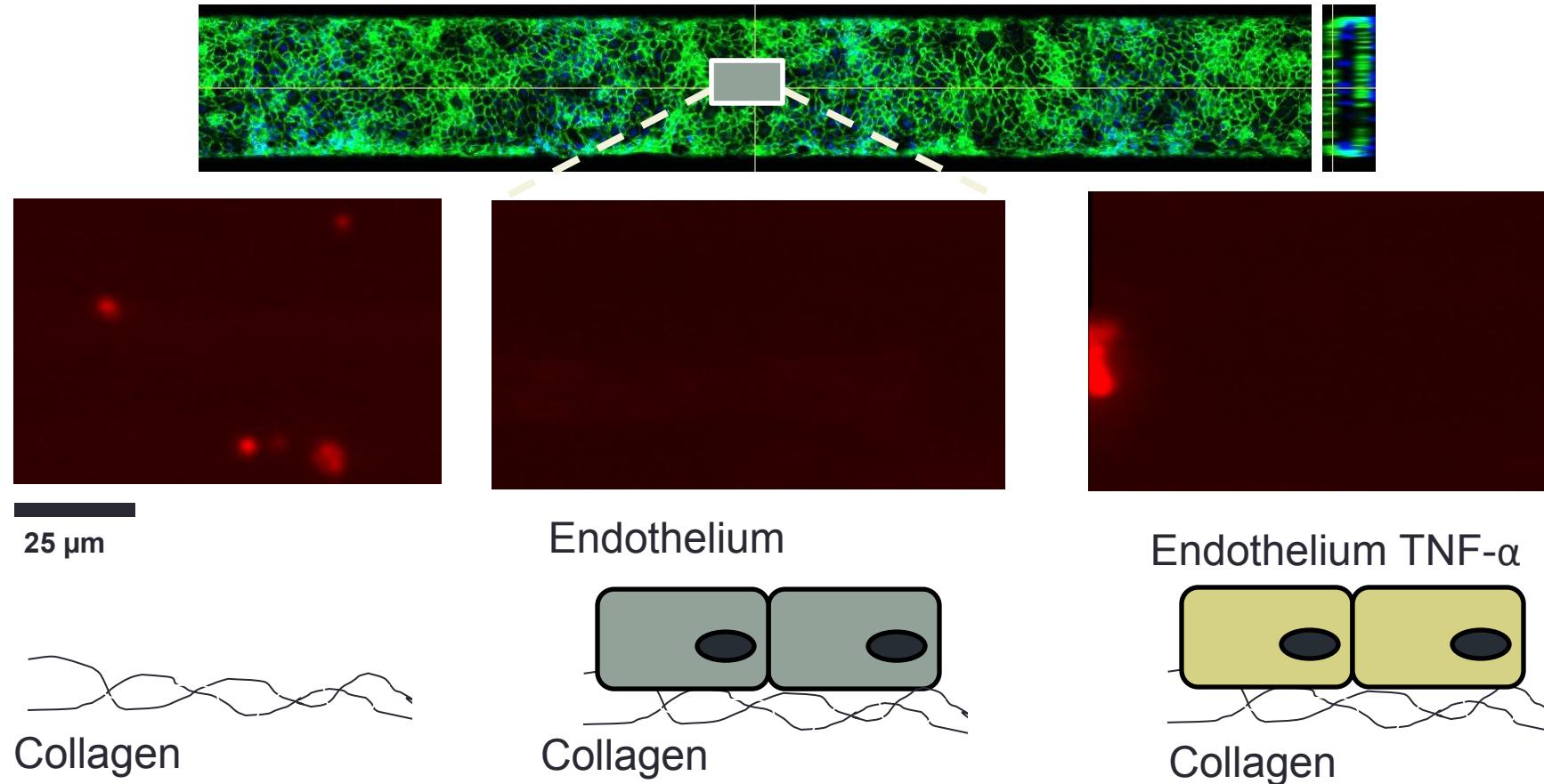


Vessel-on-a-Chip: Vessel Wall

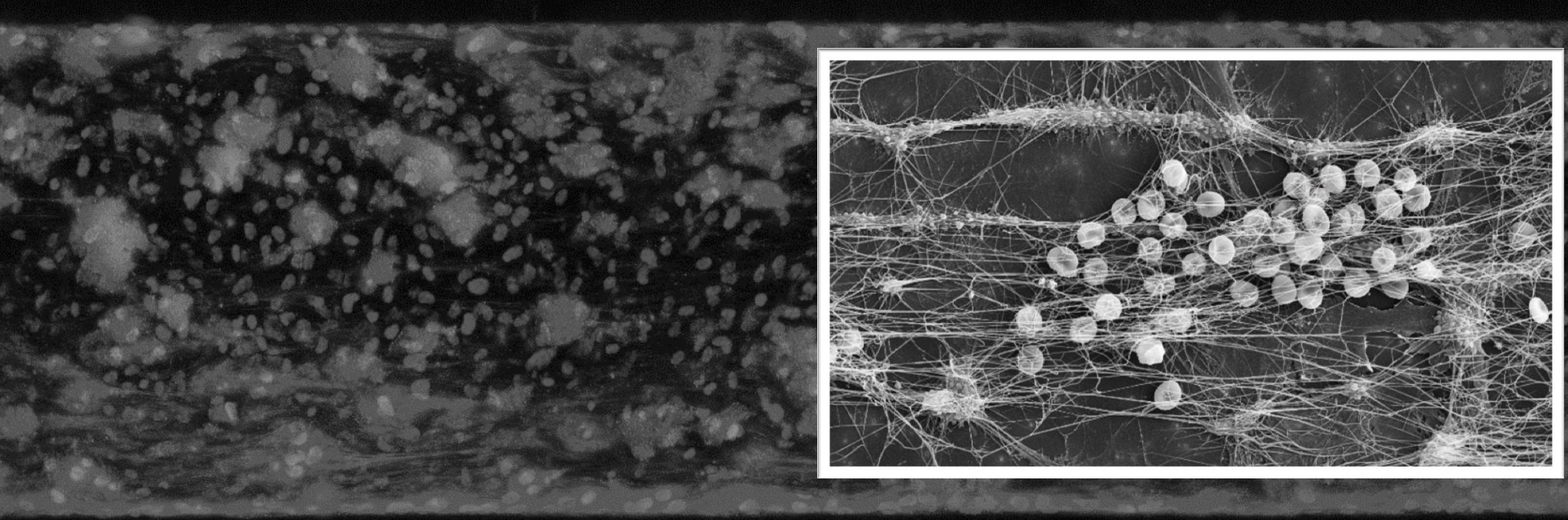
- Vascular endothelium
 - Endothelial inflammation by TNF- α



Vessel-on-a-Chip: Blood Perfusion



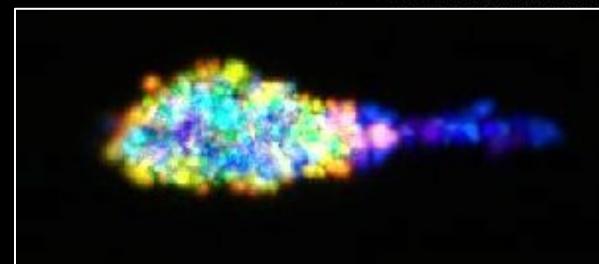
- Jain, Van der Meer, et al. **Biomedical Microdevices** 2016, 18:73



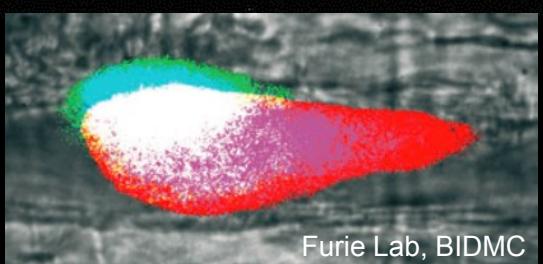
Blue, nuclei; Green, fibrin; Red, platelets

100 μm

- Jain, Van der Meer, et al. **Biomedical Microdevices** 2016, 18:73
- SEM Image: James Weaver, Wyss Institute



Thrombus-on-a-chip

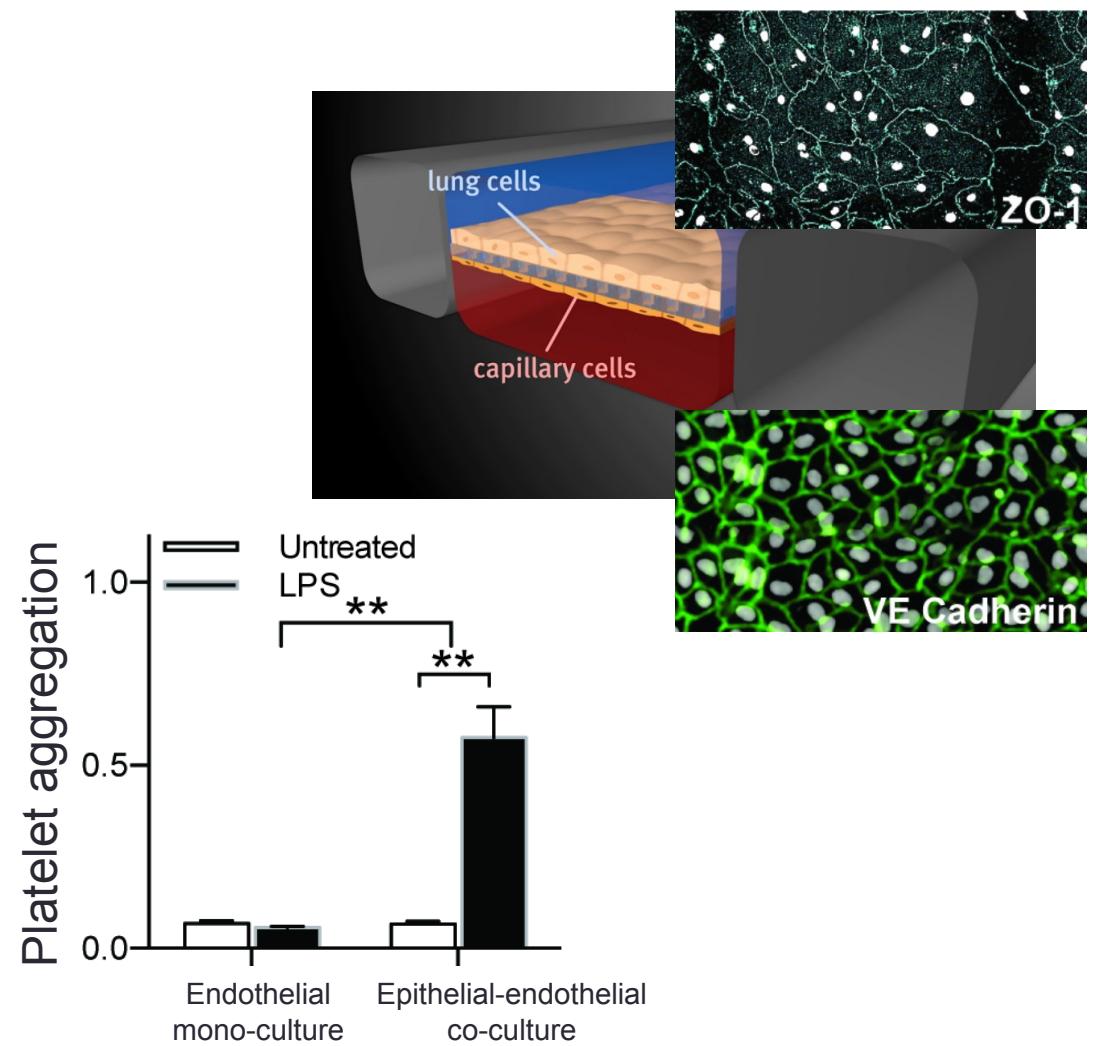


Thrombus-in-a-mouse

Furie Lab, BIDMC

Vessel-on-a-Chip in Organs-on-Chips

- Lung-on-Chip
 - Epithelium treated with lipopolysaccharide (LPS)
 - Endothelial activation
 - Platelet aggregation

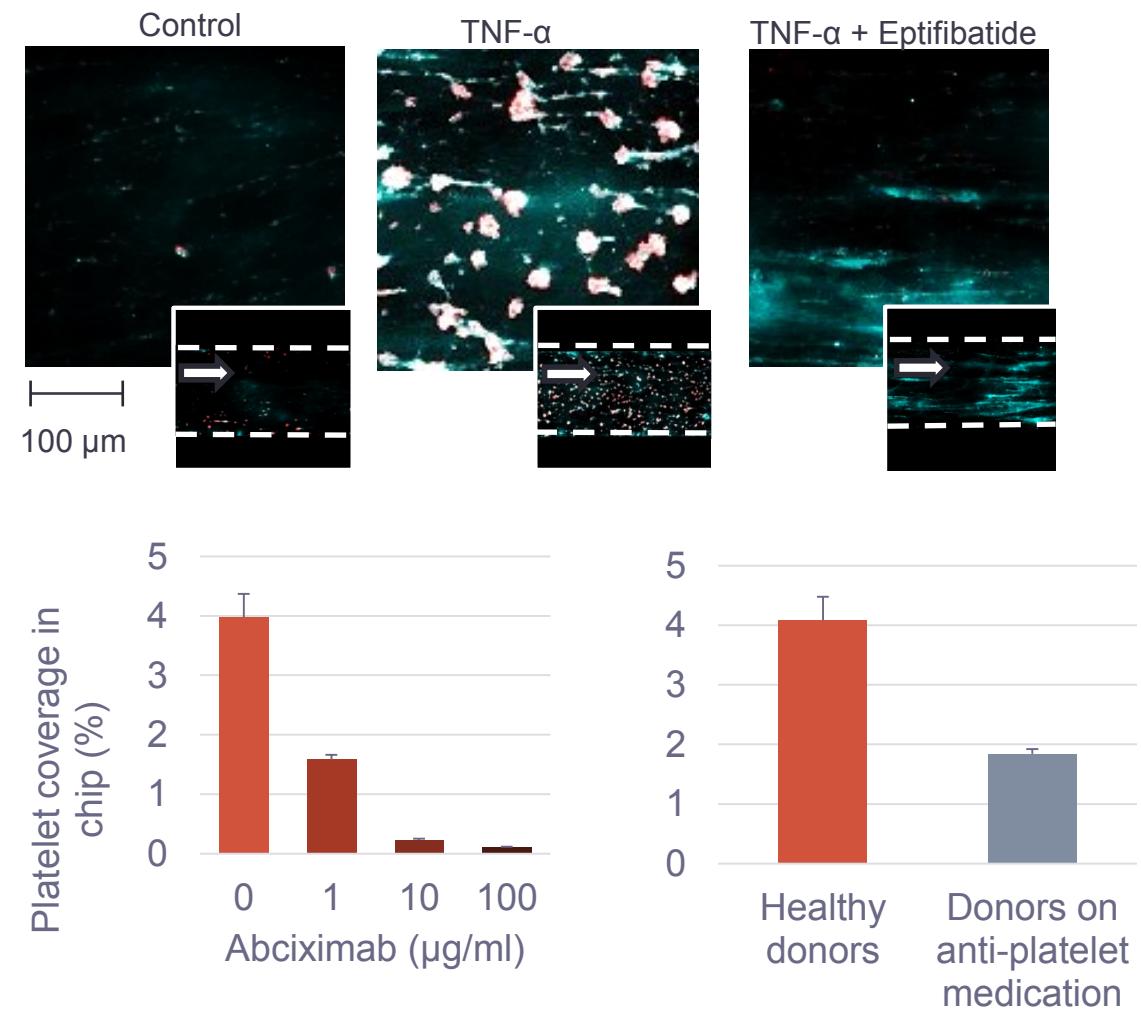


• Jain, Barille, Van der Meer, et al. **Clinical Pharmacology & Therapeutics** 2017, DOI:10.1002/cpt.742

Vessel-on-a-Chip: Drug Efficacy & Toxicity

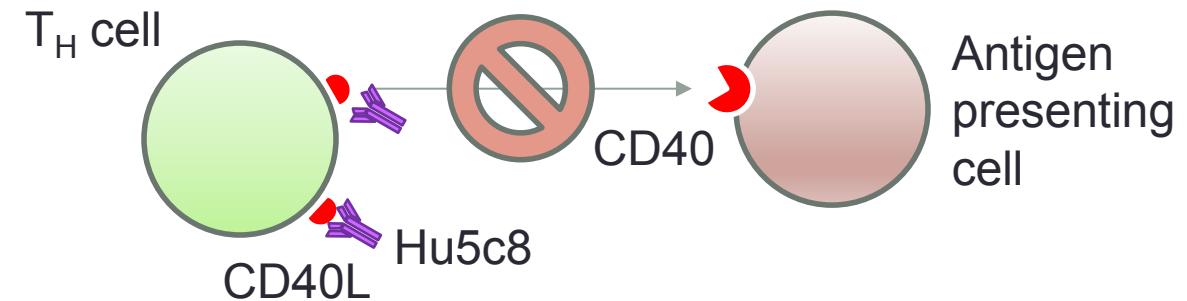
- Drug response
 - Eptifibatide (Integrilin®)
 - Abciximab (ReoPro®)
 - Patients with anti-platelet medication (aspirin and/or clopidogrel [Plavix®])

- Jain, Van der Meer, et al. **Biomedical Microdevices** 2016, 18:73
- Jain, Barille, Van der Meer, et al. **Clinical Pharmacology & Therapeutics** 2017, DOI:10.1002/cpt.742
- Barille, Van der Meer, et al. **Clinical Pharmacology & Therapeutics** 2018, DOI:10.1002/cpt.1054



Vessel-on-a-Chip: Drug Efficacy & Toxicity

- CD40-CD40L (CD154) in T_H -cell function
- Anti-CD40L mAb (e.g. Hu5c8)
- Trials with auto-immune patients (e.g. Lupus, Crohn's disease), and organ transplant recipients



thepharmaletter

* Up to date news for the Pharmaceutical and Biotechnology industries

HOME NEWS ▾ IN DEPTH ▾ CONFERENCES ▾ FOCUS ON ▾ EVENTS COMPANIES REPORTS IN BRIEF

Biogen halts remaining trials of Antova

after uncovering an additional thromboembolic event in a patient

With:

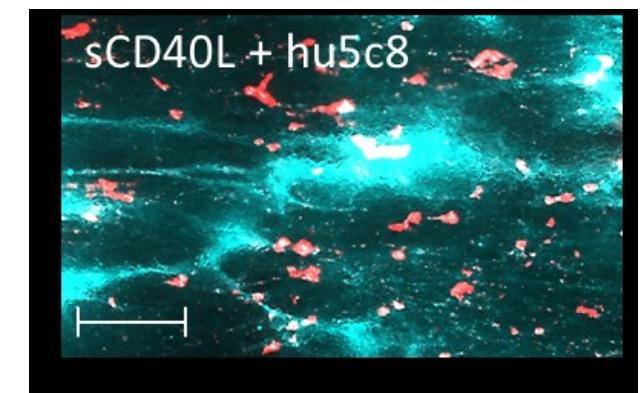
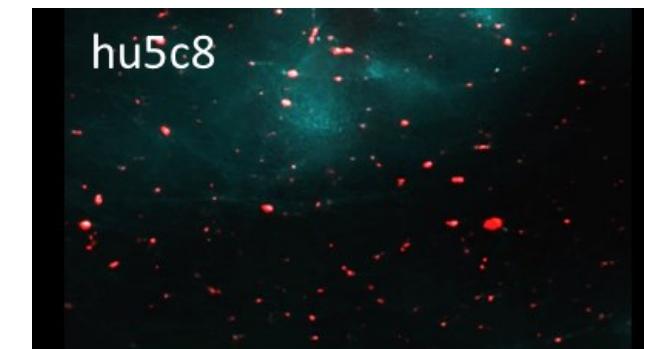
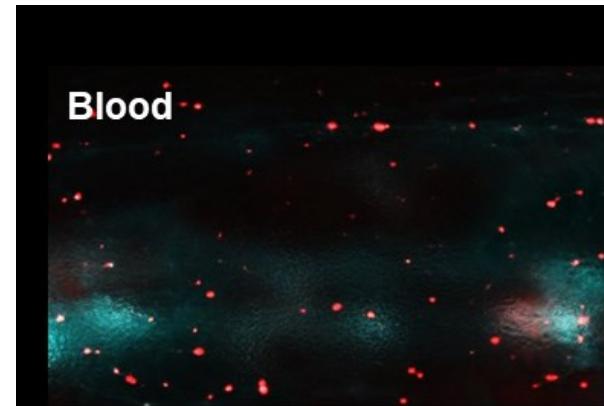


importance attached to the drug, which some analysts have suggested could have had blockbuster potential.



Vessel-on-a-Chip: Drug Efficacy & Toxicity

- Hu5c8-induced thrombosis
 - 240 µg/ml Hu5c8
- Platelet aggregation (**red**)
- Fibrin formation (**cyan**)
- 10 ng/ml soluble CD40L
 - Lupus patients plasma levels



With:

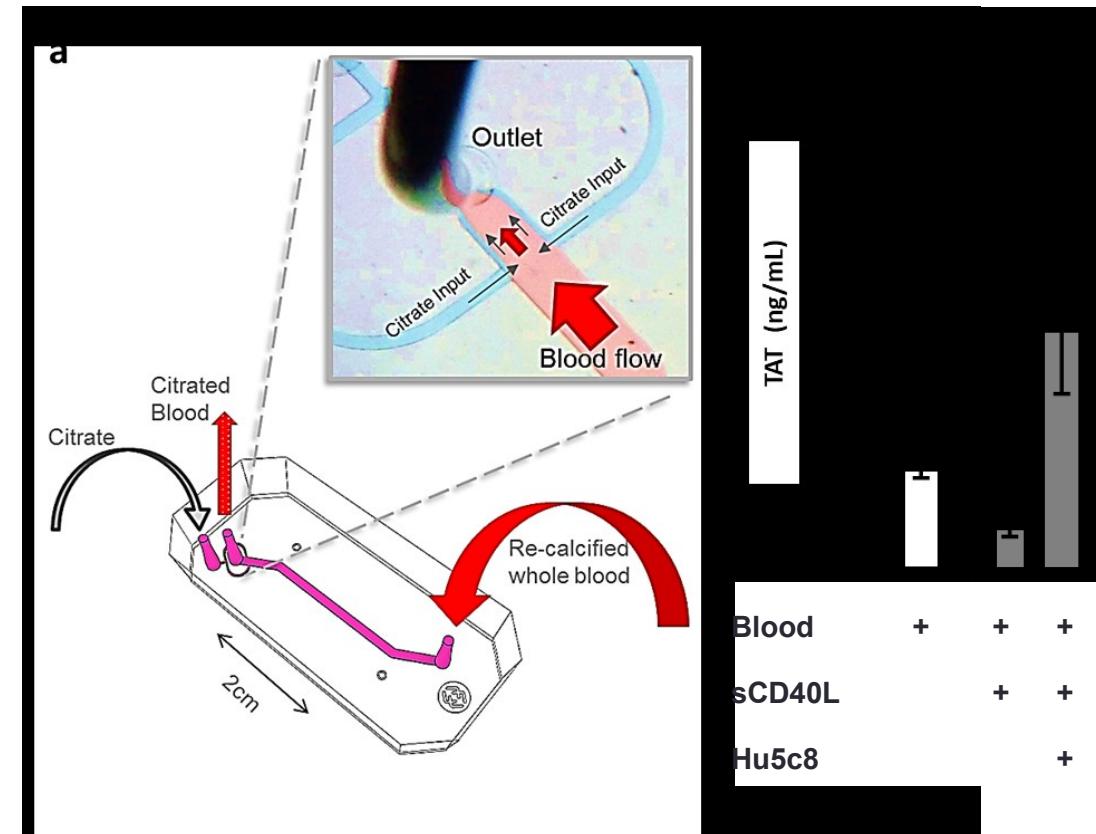


- Barille, Van der Meer, et al. **Clinical Pharmacology & Therapeutics** 2018, DOI:10.1002/cpt.1054



Vessel-on-a-Chip: Drug Efficacy & Toxicity

- Hu5c8-induced thrombosis
 - 10 ng/ml sCD40L
 - 240 µg/ml Hu5c8
- Thrombin-antithrombin (TAT) Complex release



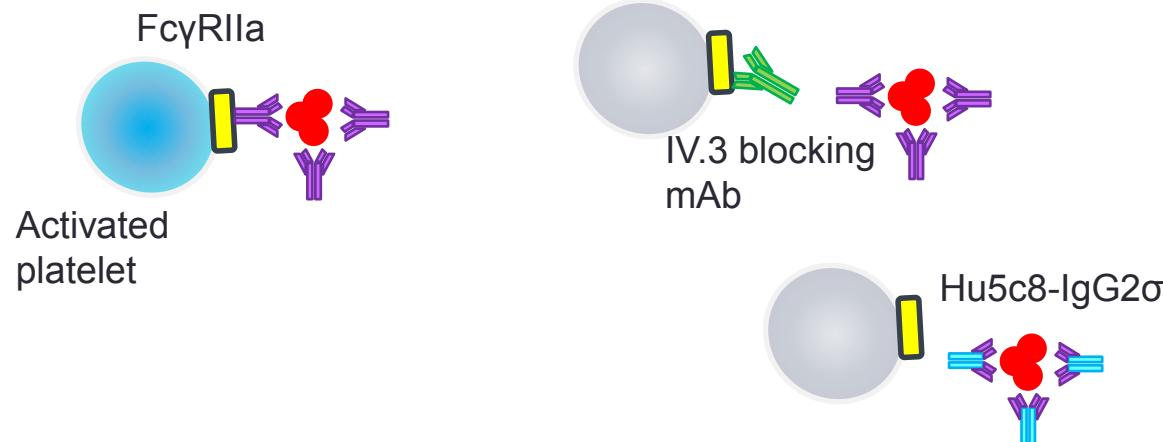
With:



- Barille, Van der Meer, et al. **Clinical Pharmacology & Therapeutics** 2018, DOI:10.1002/cpt.1054

Vessel-on-a-Chip: Drug Efficacy & Toxicity

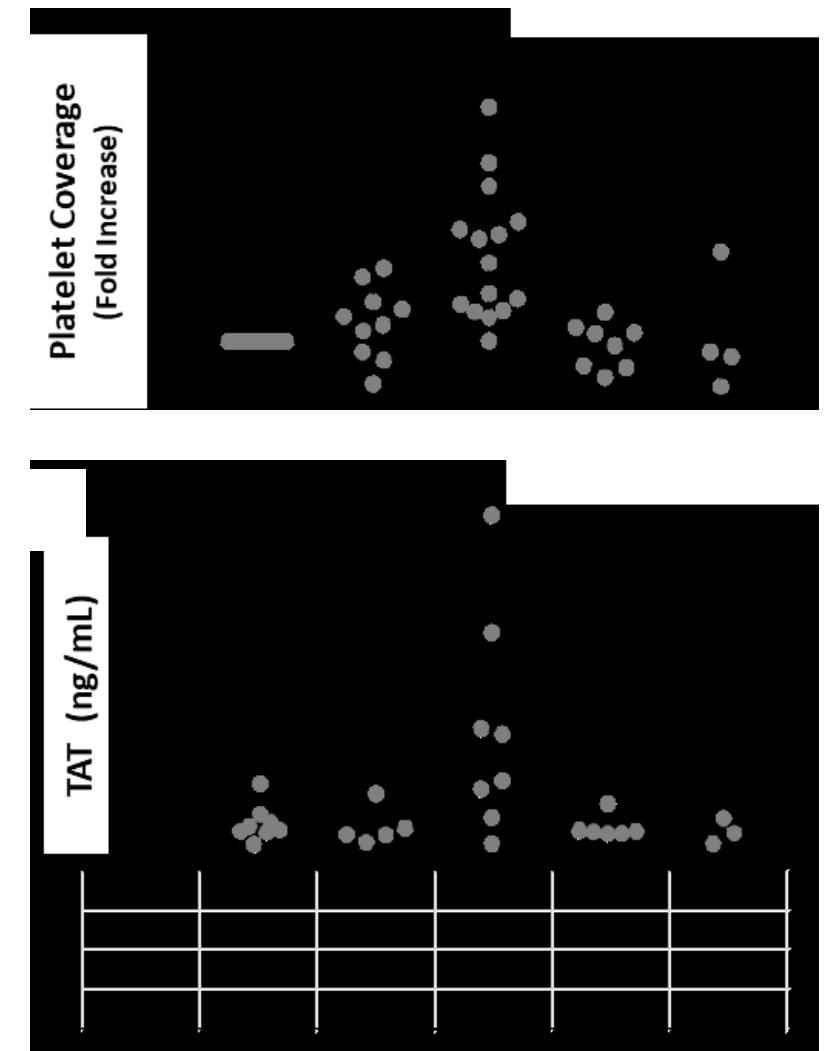
- Hu5c8-induced thrombosis
- Inhibited by interfering with Fc γ Receptor signaling



With:

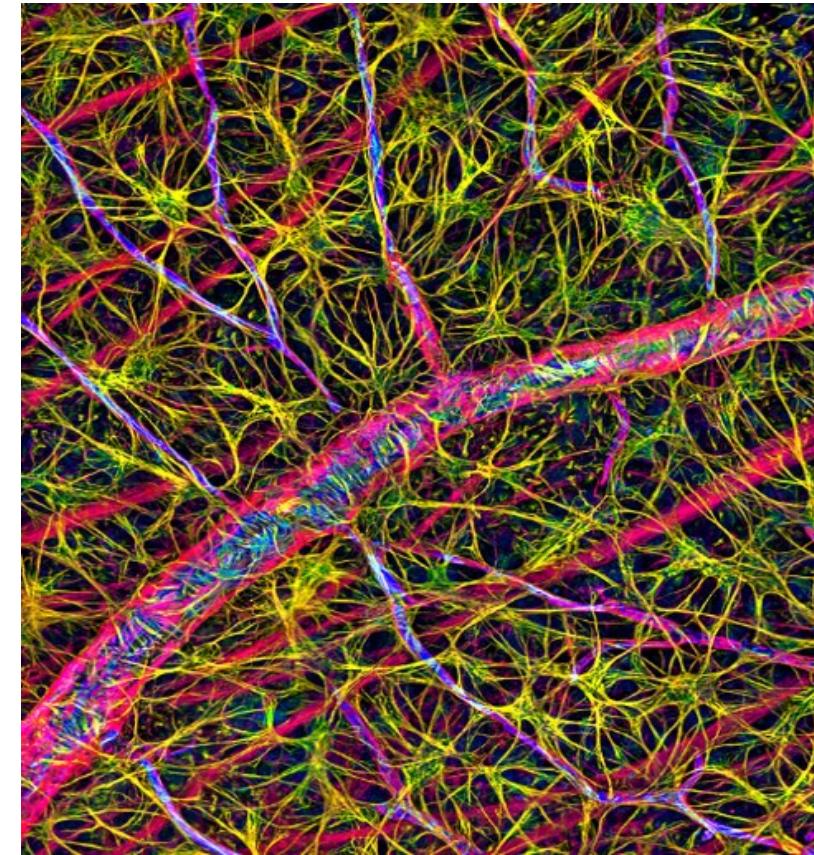


- Barille, Van der Meer, et al. **Clinical Pharmacology & Therapeutics** 2018, DOI:10.1002/cpt.1054



3D Vessels

- Blood vessels
 - Circular
 - Vessel-tissue interaction

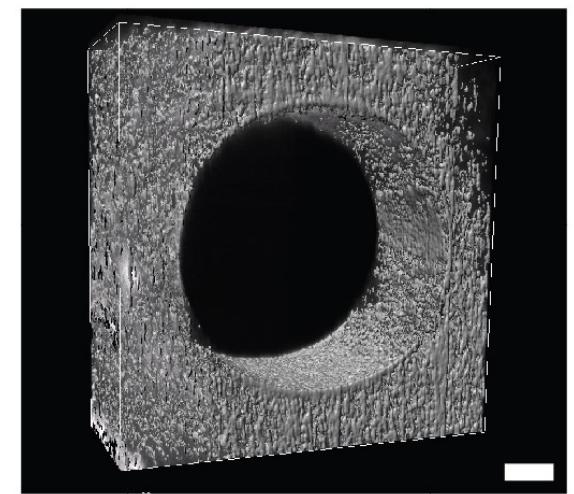
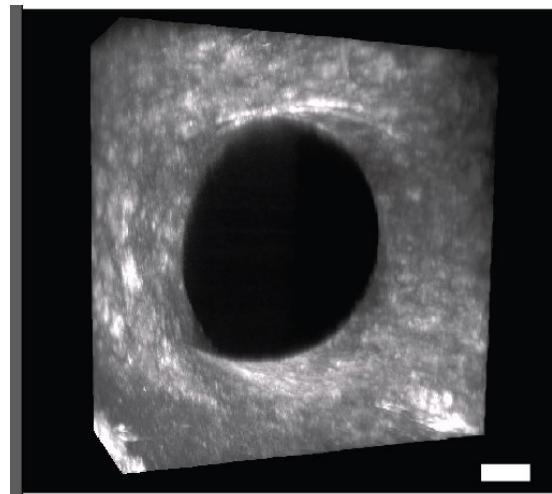
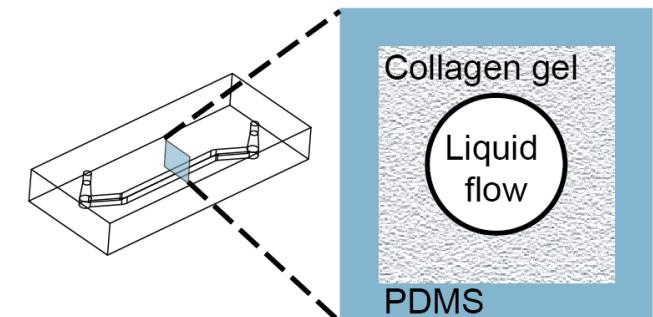


Thomas Deerinck, UCSD

- Herland, Van der Meer, et al. **PLOS ONE** 2016,
11:e0150360

3D Vessels-on-a-Chip

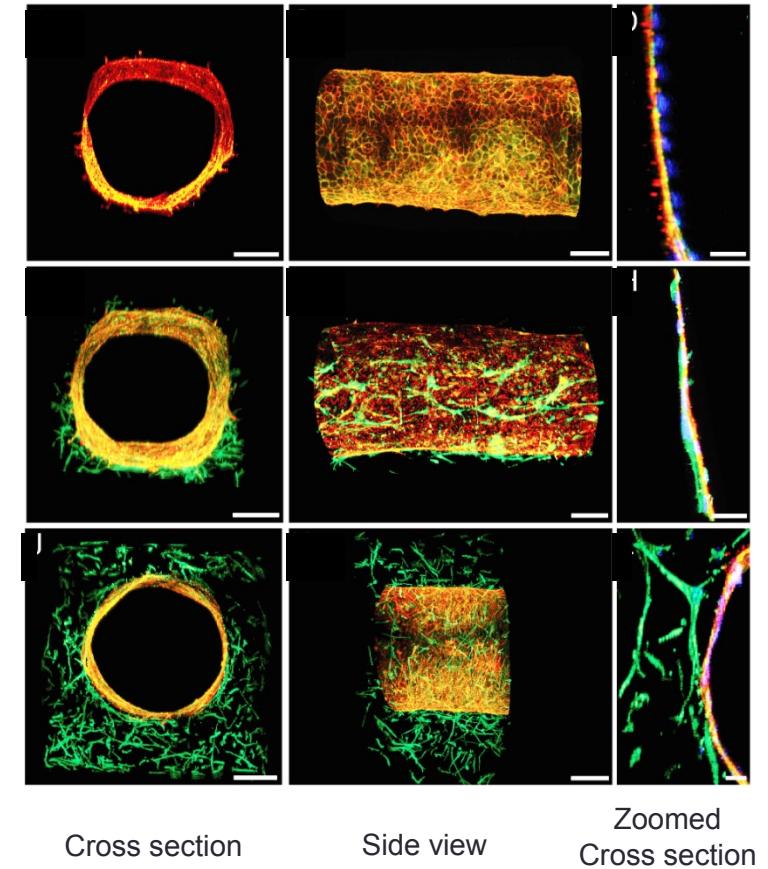
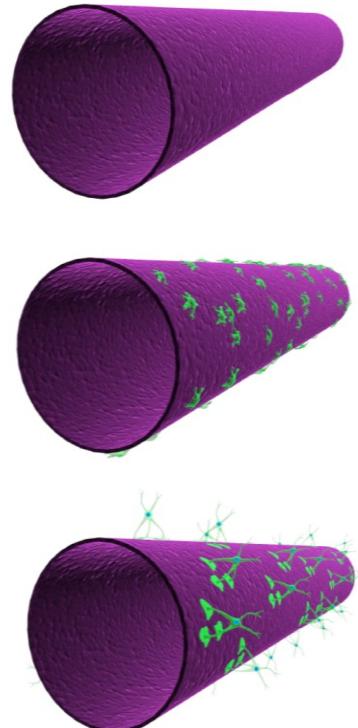
- 3D lumens in extracellular matrix
 - Circular
 - Co-cultures



• Herland, Van der Meer, et al. **PLOS ONE** 2016,
11:e0150360

3D BBB-on-Chip

- Blood-Brain Barrier-on-Chip
 - 3D lumens in extracellular matrix
 - Brain microvascular endothelial cells
 - Pericytes
 - Astrocytes

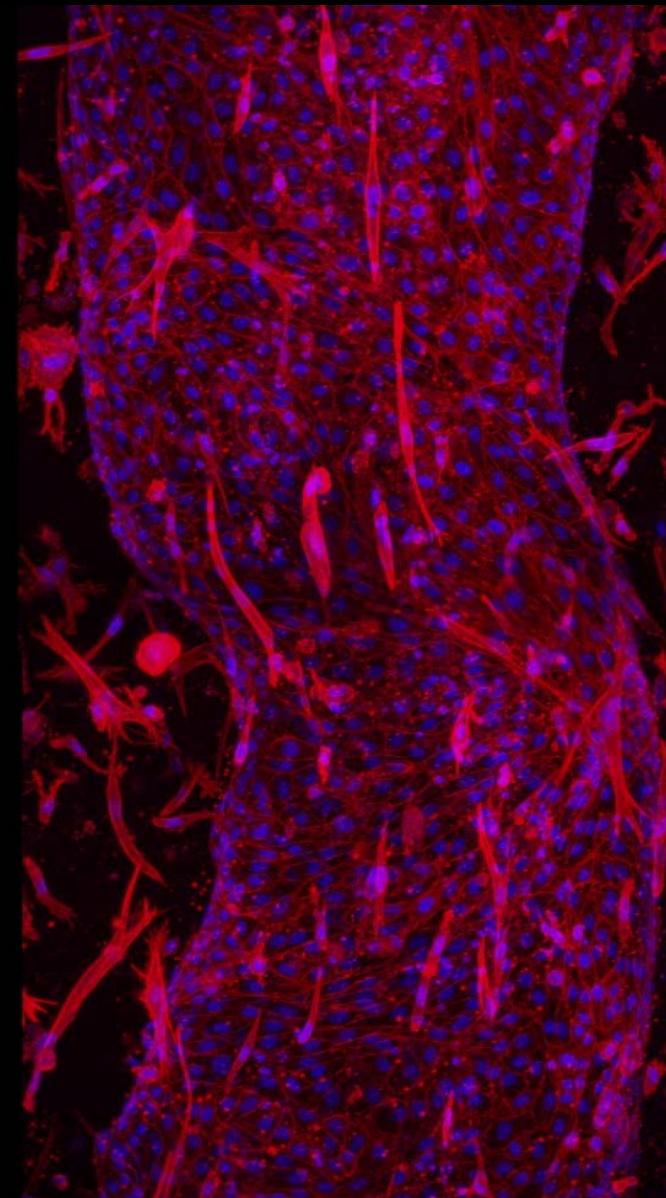
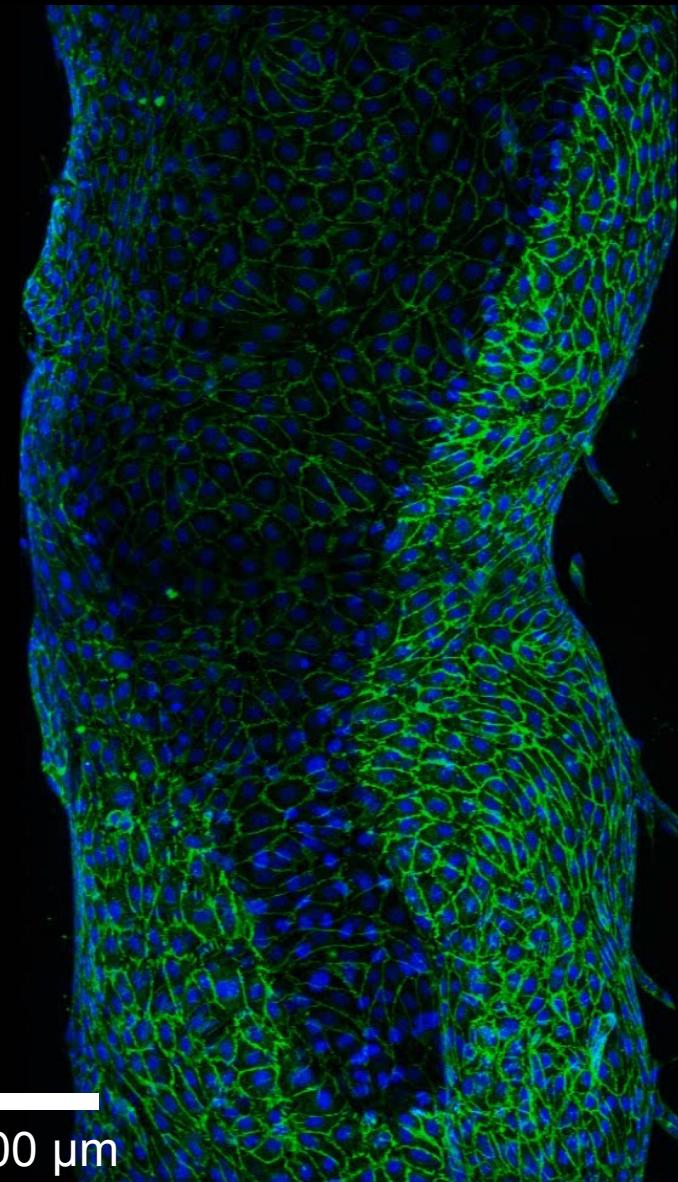


Cross section

Side view

Zoomed
Cross section

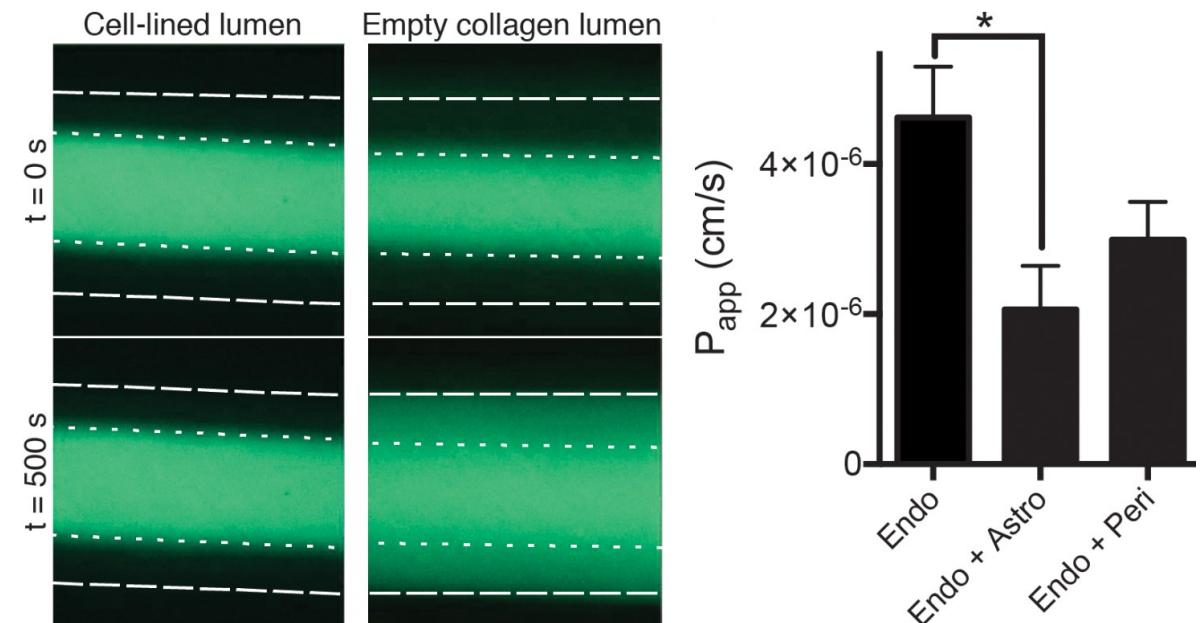
• Herland, Van der Meer, et al. **PLOS ONE** 2016,
11:e0150360



Human cerebral endothelial cells, human astrocytes. Green: VE-Cadherin, Blue: Nuclei, Red: F-actin

3D BBB-on-Chip

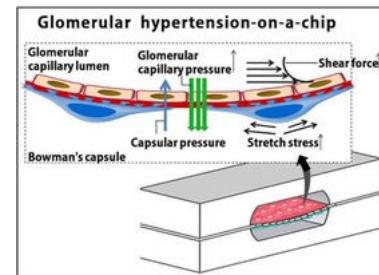
- Blood-Brain Barrier-on-Chip
 - Permeability, Fluorescent 3 kDa dextran



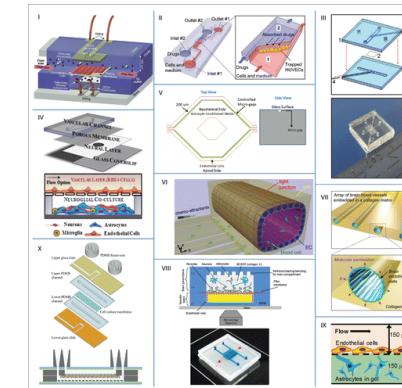
• Herland, Van der Meer, et al. **PLOS ONE** 2016,
11:e0150360

Work in Progress!

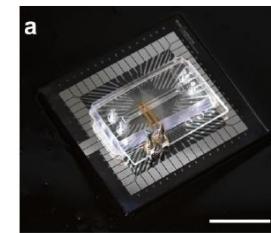
- Lung-on-chip
 - Alveolus
 - Small airway
- Gut-on-chip
 - Small intestine
 - Colon
- Blood-brain-barrier-on-chip
- Kidney-on-chip
 - Proximal tubule
 - Glomerulus
- Heart-on-chip
- Liver-on-chip
- Skin-on-chip
- Eye-on-chip
 - Cornea
 - Retina
- Bone marrow-on-chip
- Pancreas-on-chip
- Cancer-on-chip



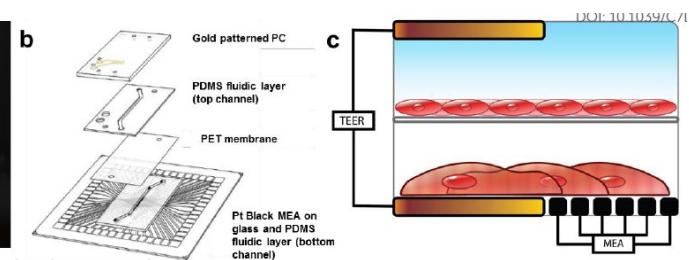
Zhou, Lin, et al.
Also: Musah, Ingber, et al.



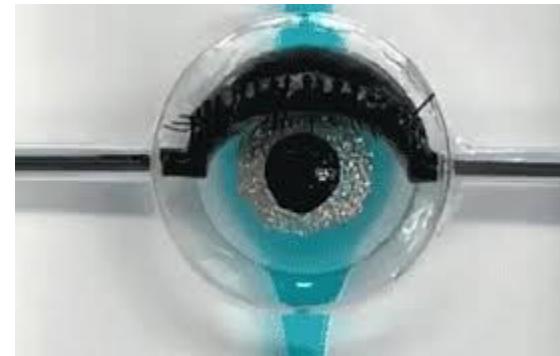
Van der Helm, Van der Meer, Segerink, et al.



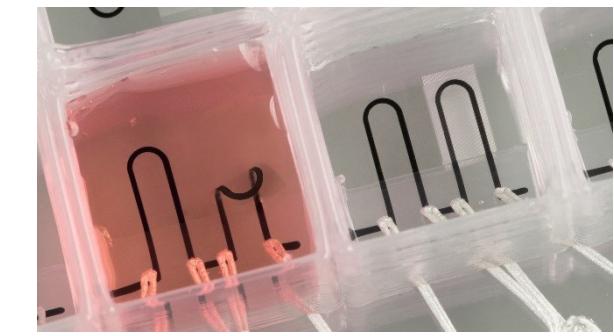
Maoz, Henry, Parker, Ingber, et al.



DOI: 10.1039/C7LC00001H



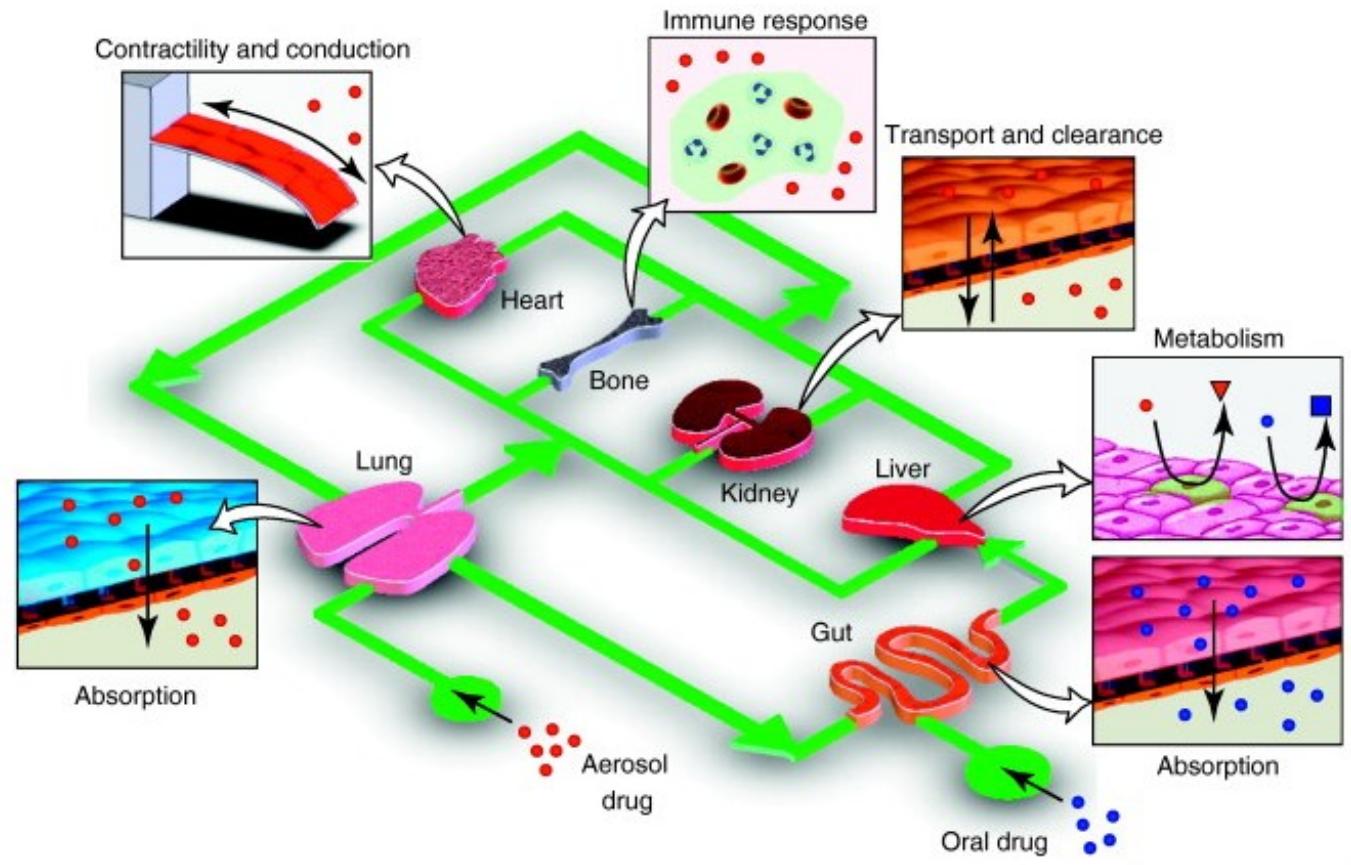
Huh, et al. UPenn.



Lewis, Parker, Ingber, et al.

Work in Progress!

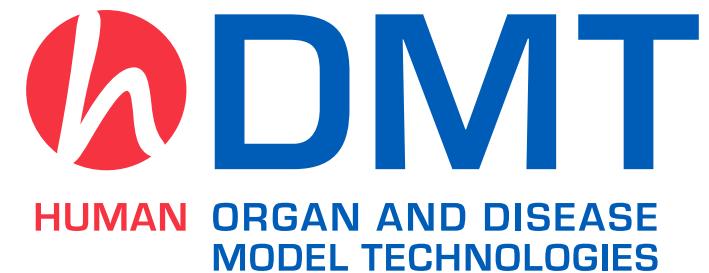
- Body-on-a-chip?



TRENDS in Cell Biology

- Huh, Hamilton, Ingber, **TRENDS in Cell Biology** 2011, 21:745

hDMT Organ-on-Chip Consortium



www.hdmt.technology

Exchanging expertise, sharing facilities, promoting collaboration

Networking, lobbying, facilitating communication, project management



Hubrecht
Institute
Developmental Biology
and Stem Cell Research



Universiteit
Leiden
The Netherlands



UNIVERSITY OF TWENTE.

VU medisch centrum

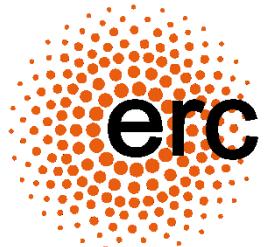


Delft University of Technology





UNIVERSITY OF TWENTE.



Robert Passier
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Heleen Middelkamp

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Anna Herland
Abhishek Jain

Geraldine Hamilton
Riccardo Barrile
Hyoungshin Park

Monicah Otieno
Calvert Louden

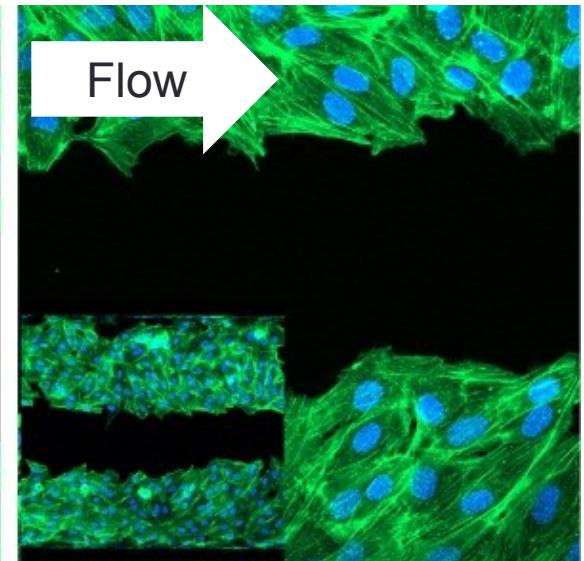
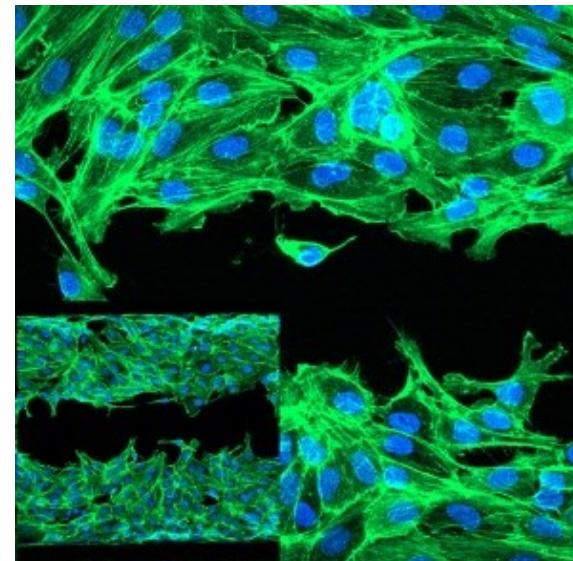
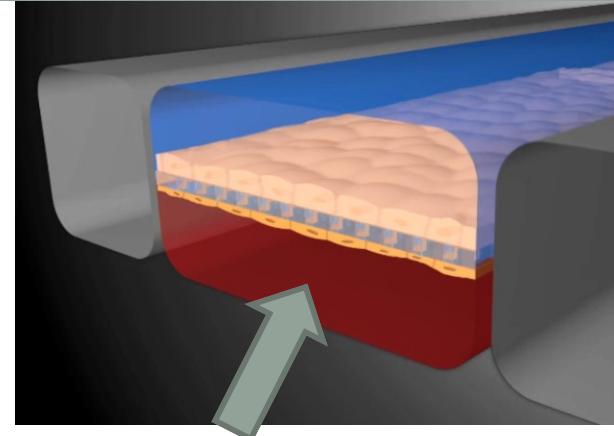
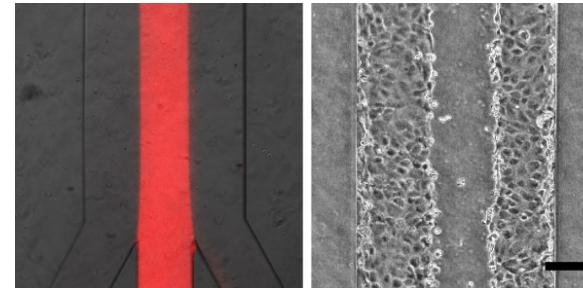
Jos Malda
Pedro Costa

Thank you!

ADDITIONAL SLIDES

Wound Healing on-Chip

- Wound healing
 - Endothelial monolayers
 - Controlled damage
 - Wound healing by endothelial migration

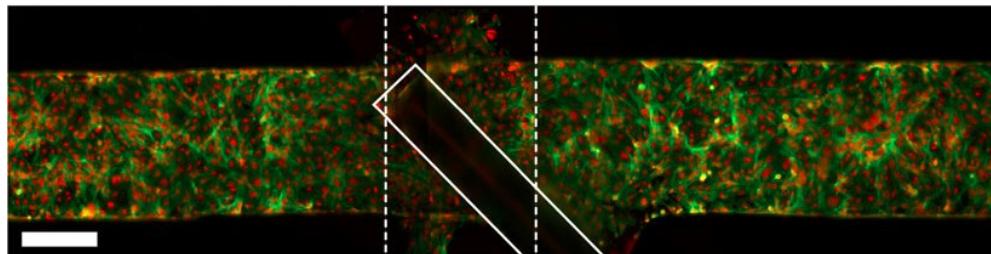


Wound healing under flow. Green, F-actin. Blue, nuclei

• Van der Meer, et al. *AJP Heart Circ Physiol* 2010, 298:H719

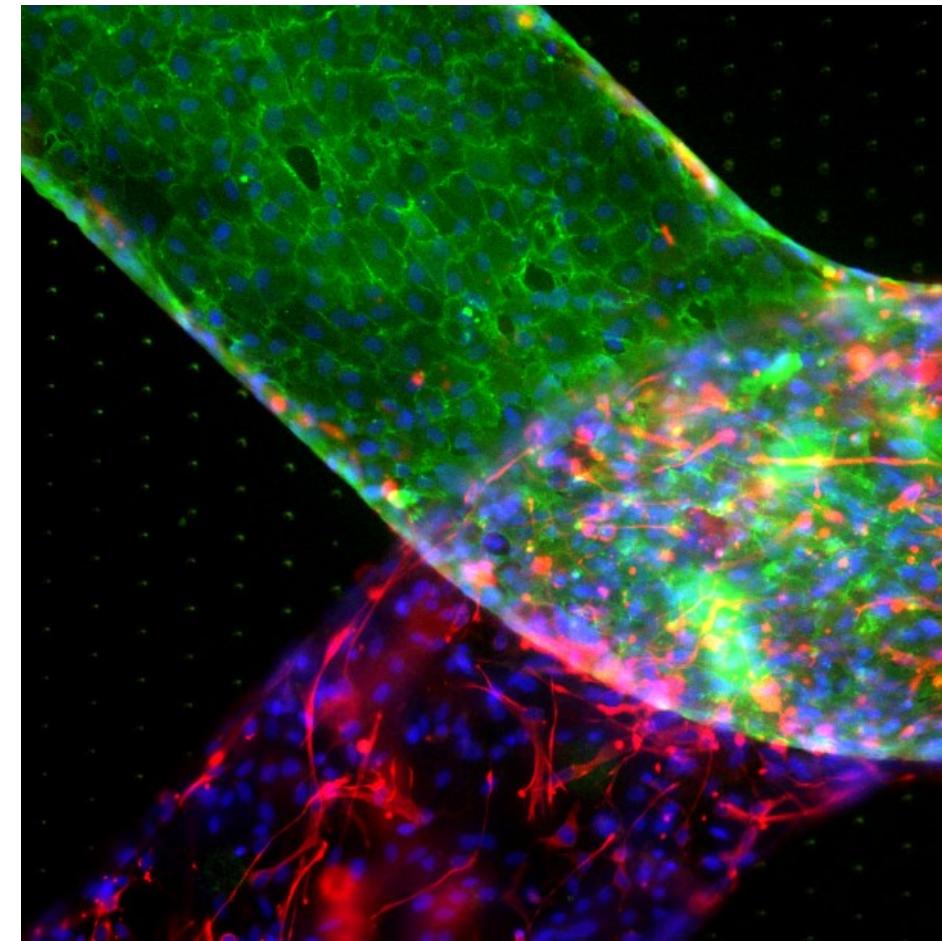
BBB-on-Chip

- Neurovasculature
 - Co-cultures of endothelium, astrocytes
 - Pericytes, neurons



Green: F-Actin, Red: Nuclei

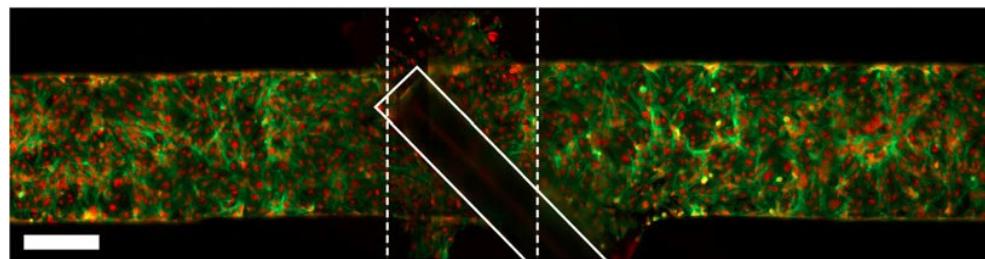
- Griep, Van der Meer, Van den Berg, et al. **Biomedical Microdevices** 2013, 15:145
- Van der Helm, Van der Meer, Eijkel, Van den Berg, Segerink. **Tissue Barriers** 2016, 4:e1142493



Green: PECAM-1/CD31, Red: GFAP, Blue: Nuclei

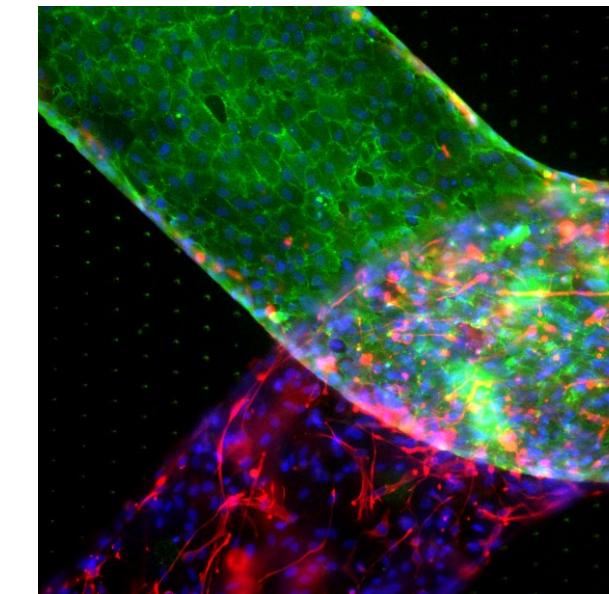
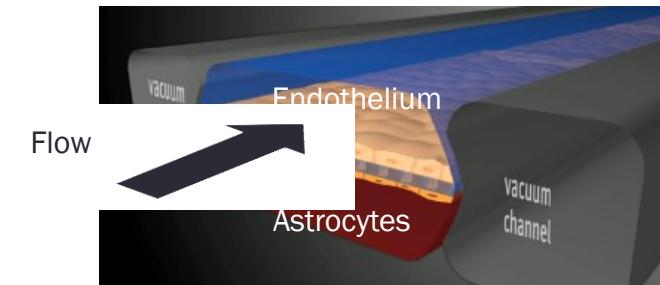
BBB-on-Chips

- Neurovasculature
 - Co-cultures of endothelium, astrocytes
 - Pericytes, neurons
 - Trans-endothelial Electrical Resistance (TEER), permeability



Green: F-Actin, Red: Nuclei

- Griep, Van der Meer, Van den Berg, et al. **Biomedical Microdevices** 2013, 15:145
- Van der Helm, Van der Meer, Eijkel, Van den Berg, Segerink. **Tissue Barriers** 2016, 4:e1142493

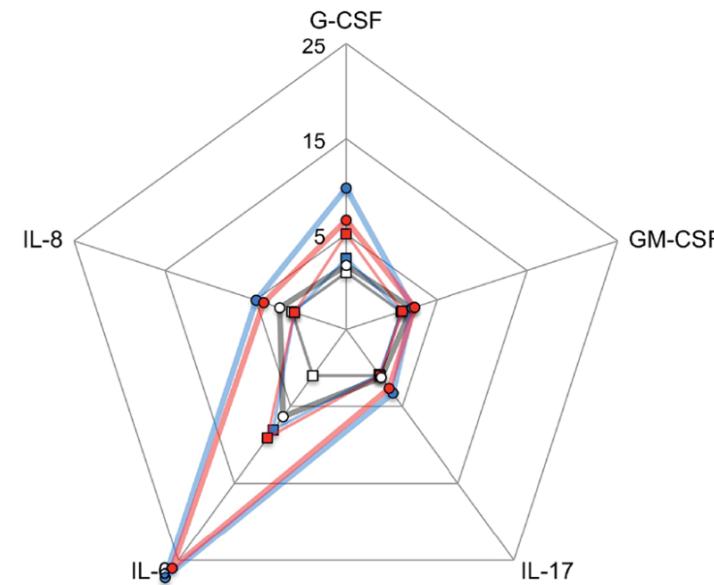


Green: PECAM-1/CD31, Red: GFAP, Blue: Nuclei

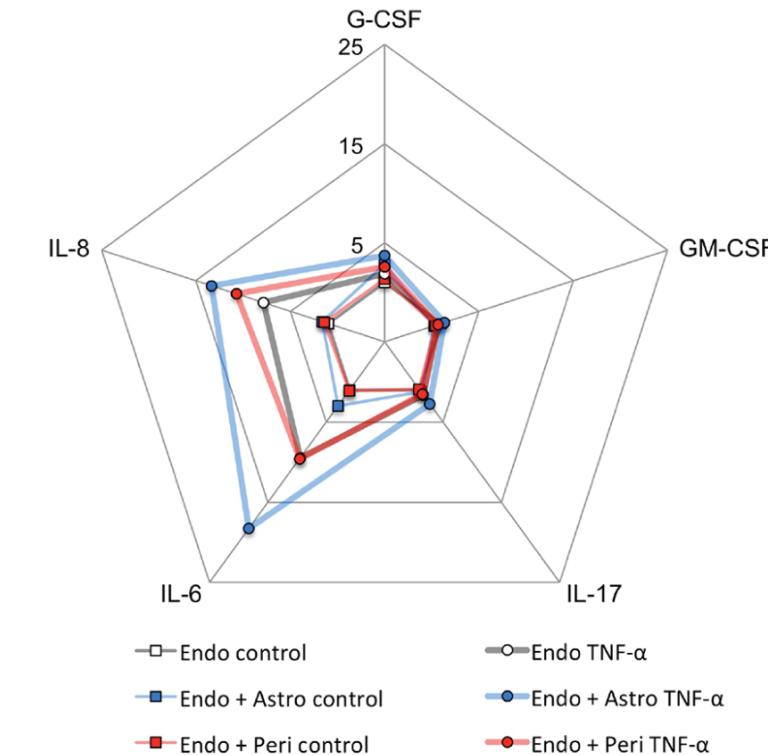
BBB-on-Chip

Cytokine release after 6 hours of 50 ng/ml TNF- α

3D BBB Chip



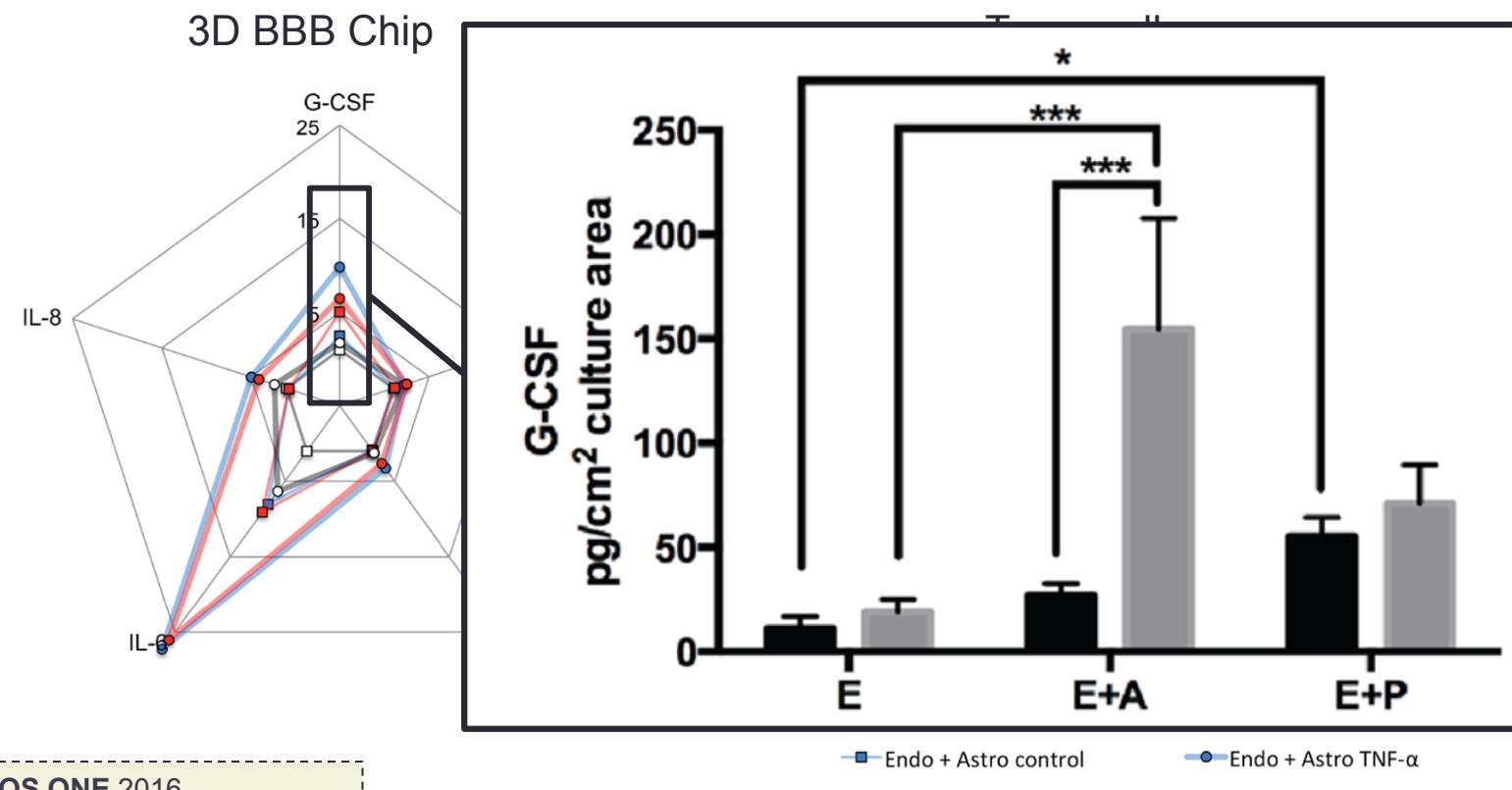
Transwell



- Herland, Van der Meer, et al. **PLOS ONE** 2016, 11:e0150360

BBB-on-Chip

Cytokine release after 6 hours of 50 ng/ml TNF- α



• Herland, Van der Meer, et al. **PLOS ONE** 2016,
11:e0150360