University of Rochester

Co-Founder:
SiMPore
Precision Membrane Technologies
Parverio
Small Revelations
SiObex

The Modular μSiM as a Tool for Studying How Systemic Stressors Cause Brain Injury

James L. McGrath, PhD

Biomedical Engineering and the Translational Center for Barrier Microphysiological Systems

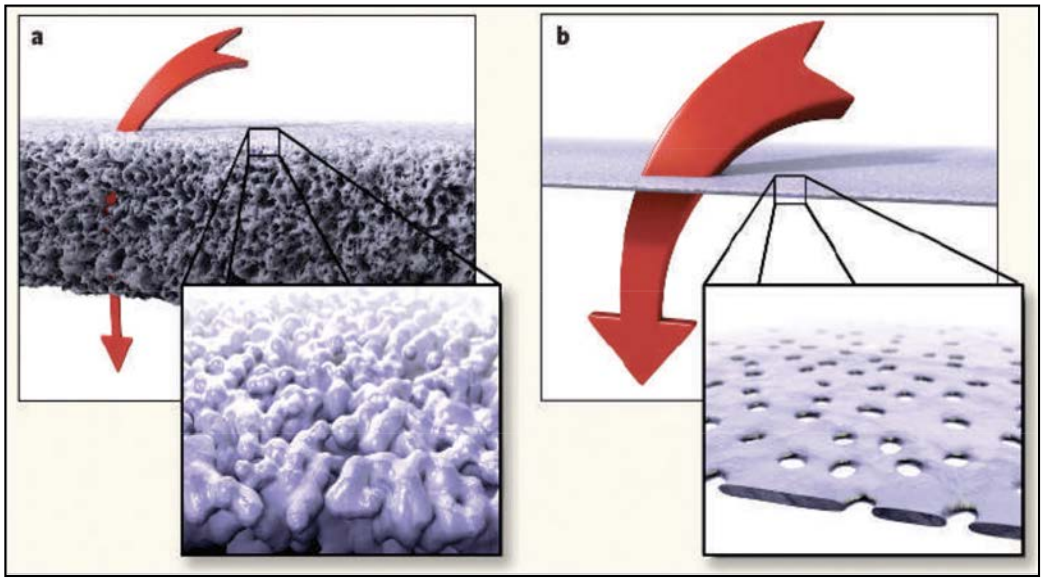
TraCe-bMPS

Nanomembrane Research Group

Summer Immersion on Innovative Approaches in Science

Johns Hopkins, Baltimore · June 16, 2026

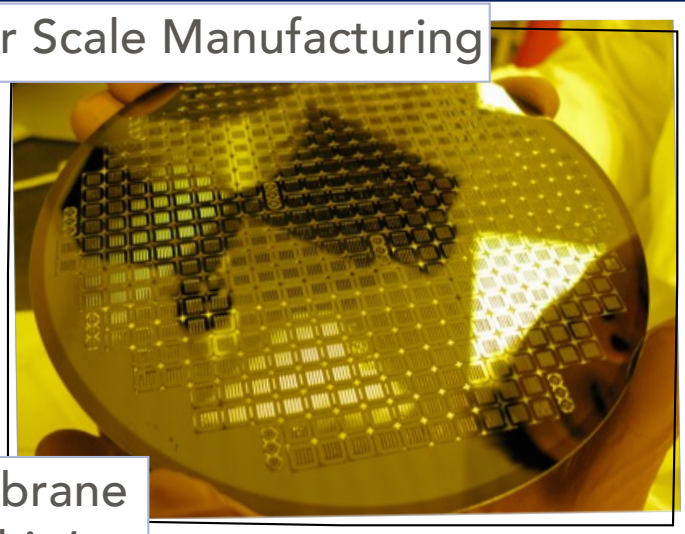
SILICON NANOMEMBRANES



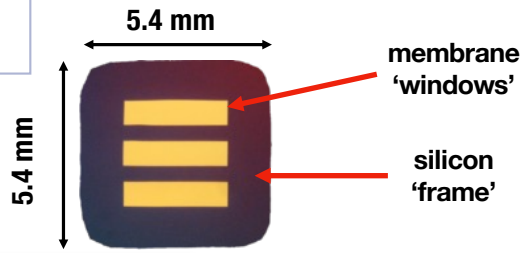
Striemer et al. (2007) **Nature 445:749-753**

*Art is from A. van den Berg and M. Wessling, Nature 445, p. 726

Wafer Scale Manufacturing



Membrane 'Chip'

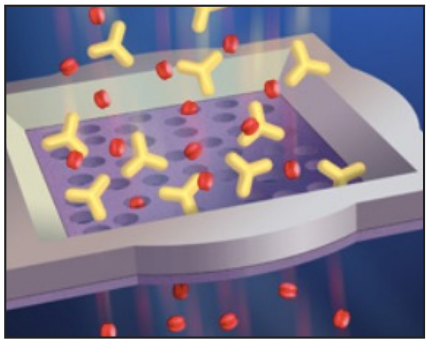


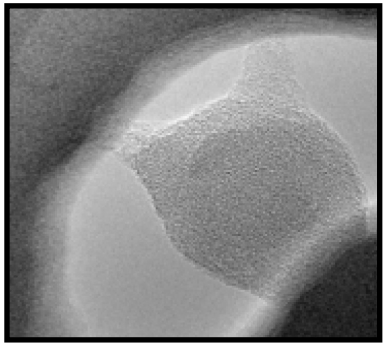
- Highly scalable silicon-based manufacturing
- Free standing membranes w/ thicknesses between 50 nm and 400 nm
- Pores between 15 nm and 20 μm
- Exceptionally permeable to diffusing species and pressure driven flow
- Optically transparent, electron transparent, quiet in Raman fluorescence.
- Inert, biocompatible, tolerant of high temperatures, acids, bases.

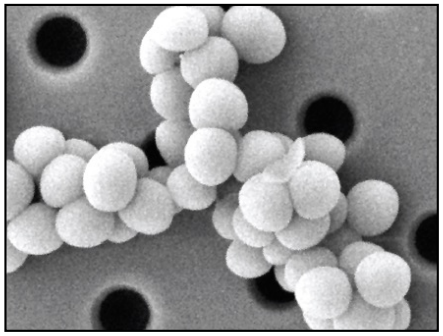
NANOMEMBRANE PORE SIZES

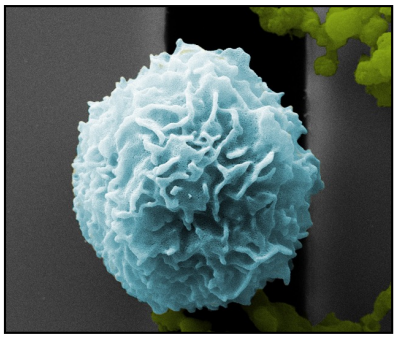
proteins | viruses & exosomes | bacteria | eukaryotic cells

water, salts, small molecules

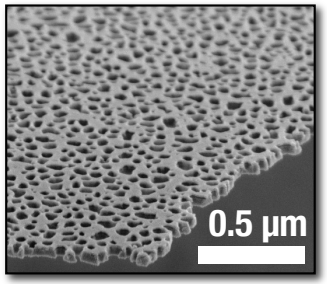


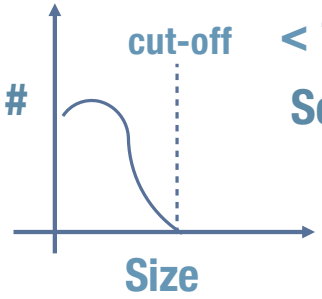






1 nm | 10 nm | 100 nm | 1 µm | 10 µm





< 100 nm thick

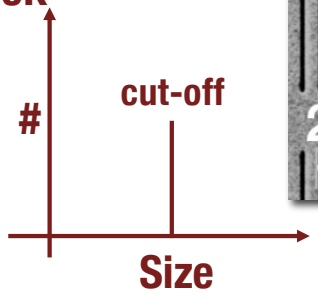
Self-Assembly w/ Pore Transfer

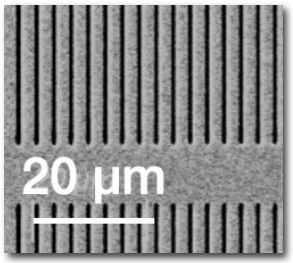
Silicon Nitride

> 200-400 nm thick

Photolithography

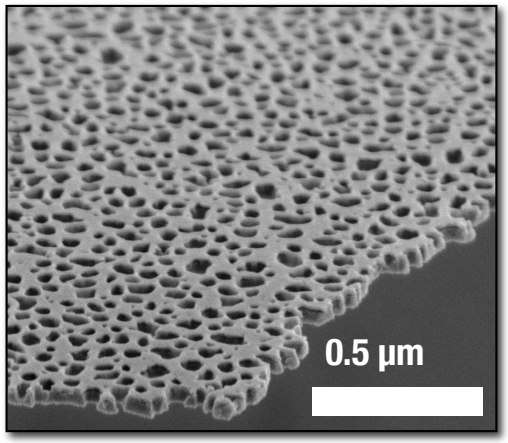
SiN, SiO_2

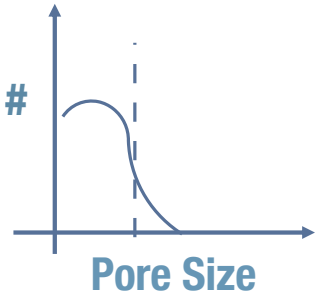




NANOMEMBRANES FOR BARRIER STUDIES

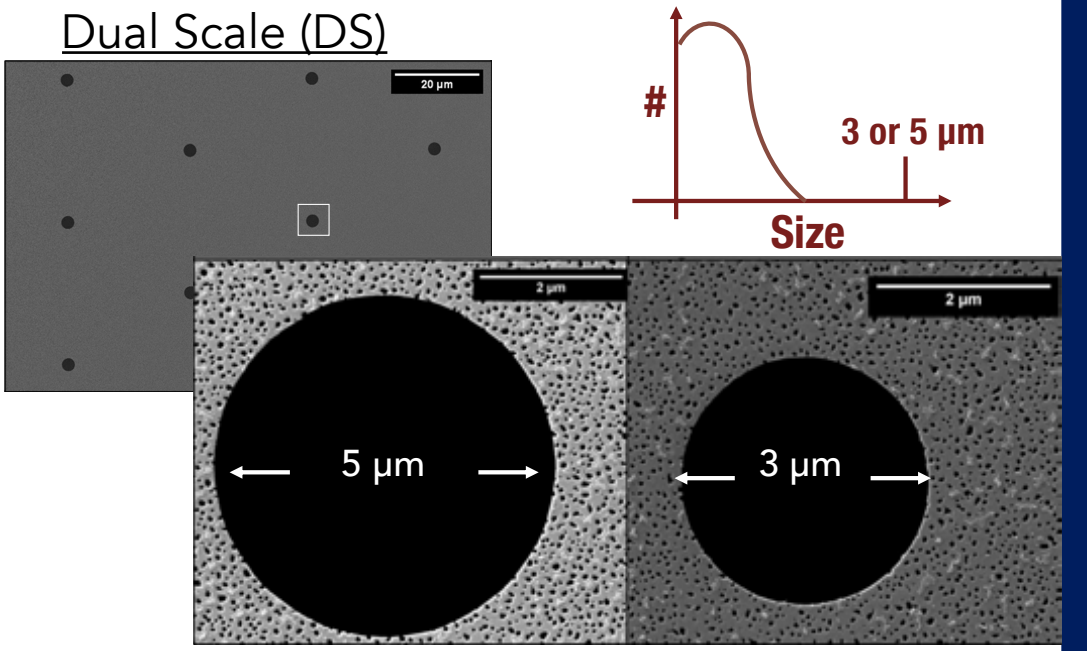
Nanoporous Silicon Nitride (NPN)



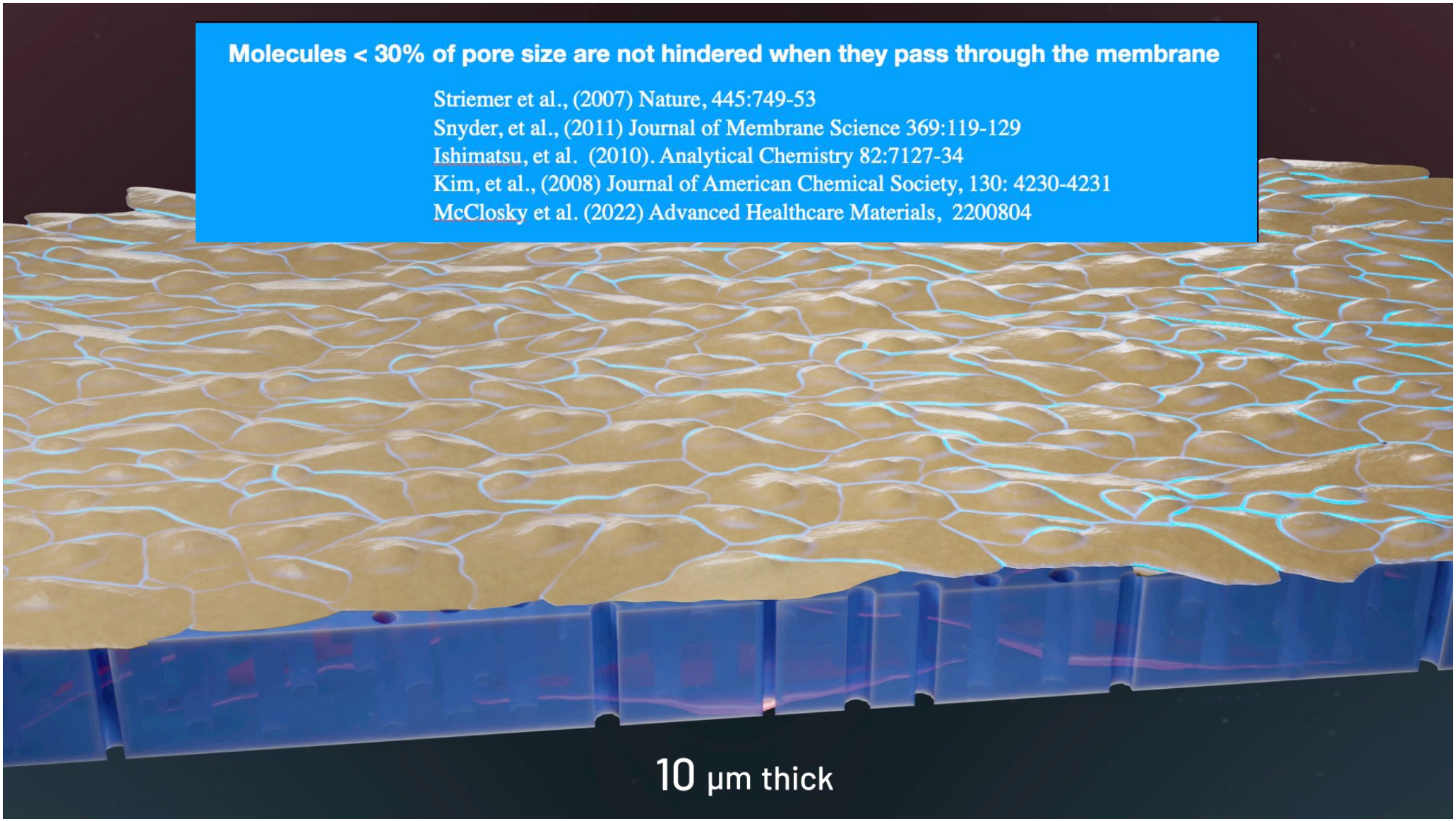


- < 100 nm thick
- ~ 60 nm pores (cytokines, antibodies freely pass)
- 100M pores per membrane
- 15% porosity (~100 nm spacing between nanopores)
- 200,000 nanopores per endothelial/epithelial cell
- Transwell: 10 µm thick; 1M; 0.5 µm pores; 80 pores per cell.

Dual Scale (DS)



- Background material is NPN
- Lithographically patterned micropores
- 1,000 to 10,000 micropores per membrane
- 1-10 micropores per cell
- Leukocytes will transit 3 µm
- Endothelial cells, etc., transit 5 µm


Molecules < 30% of pore size are not hindered when they pass through the membrane
Striemer et al., (2007) Nature, 445:749-53
Snyder, et al., (2011) Journal of Membrane Science 369:119-129
Ishimatsu, et al. (2010). Analytical Chemistry 82:7127-34
Kim, et al., (2008) Journal of American Chemical Society, 130: 4230-4231
McClosky et al. (2022) Advanced Healthcare Materials, 2200804
10 µm thick

Play video

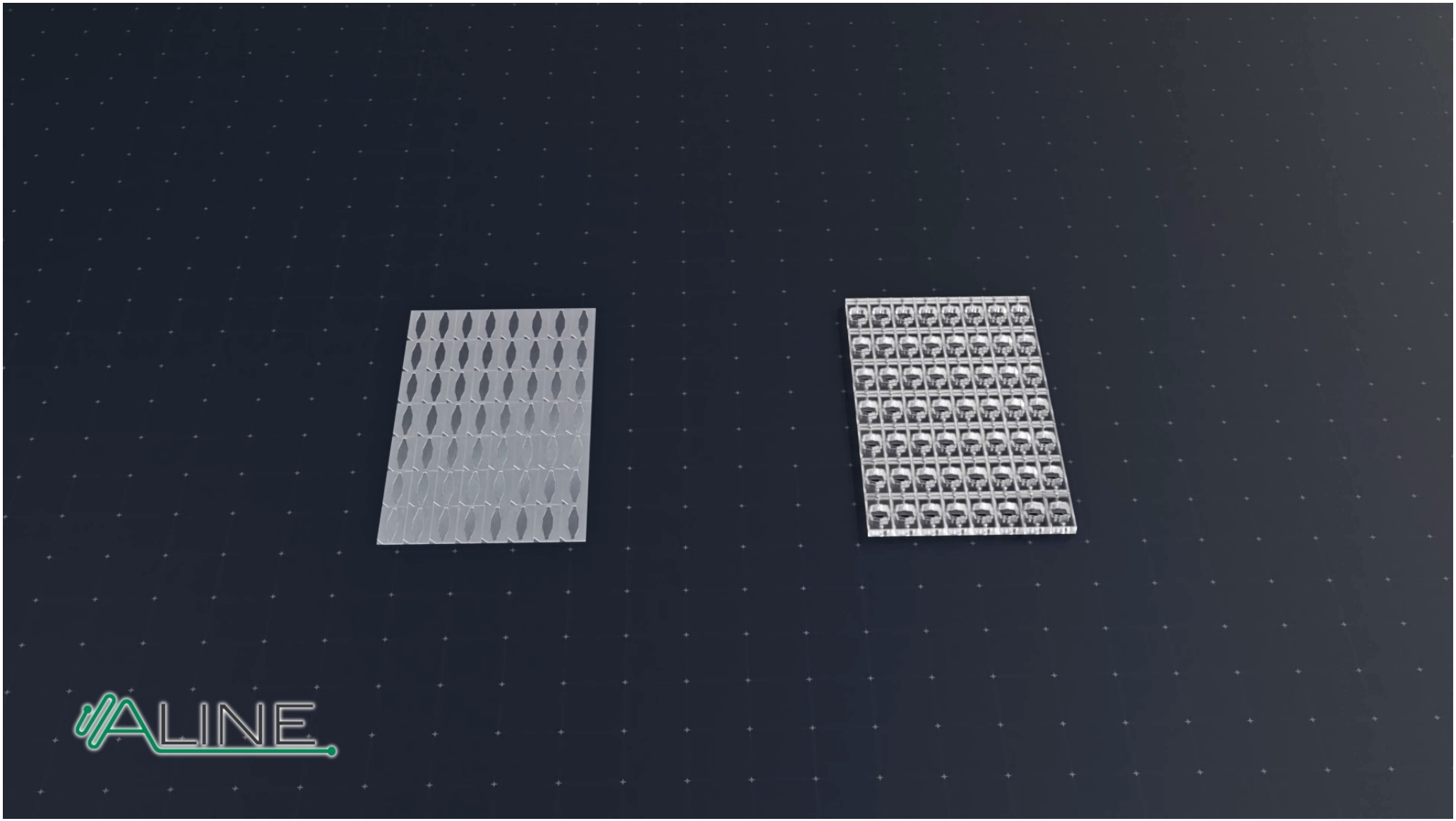
The Modular µSim Tissue Chip Development Platform

µSiM

Vascular barrier modeling

hToC

Vascular barrier with an underlying tissue



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APPLICATION

BRAIN INJURY AS AN OUTCOME OF SYSTEMIC INFLAMMATION: MODELING THE VULNERABLE BRAIN

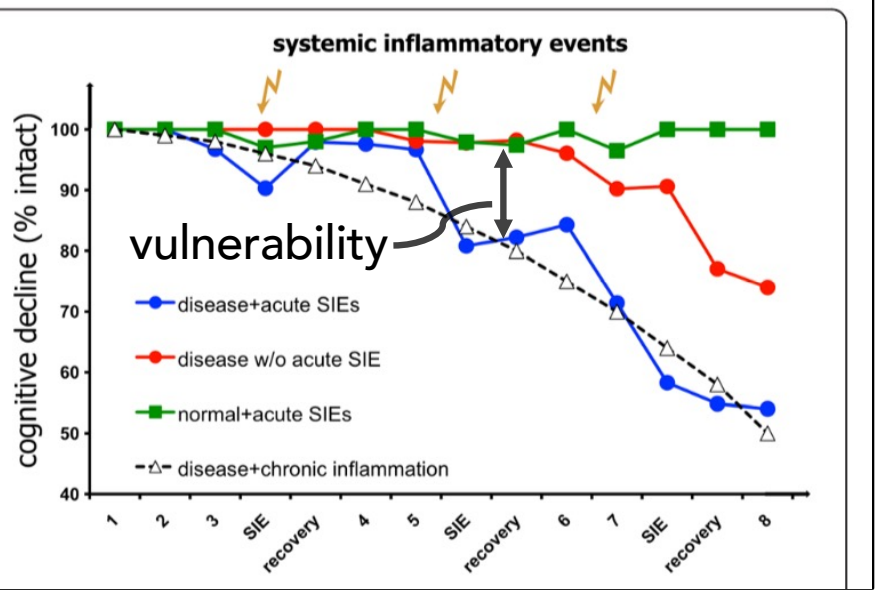
MODELING SYSTEMIC INFLAMMATION LEADING TO BRAIN INJURY

GUIDEPOSTS AND INSPIRATIONS

- "In AD, patients who may have been previously resilient to their underlying neuropathology, commonly experience an abrupt worsening of cognitive impairment after hospitalization for critical illness." - Ben Singer, MD (U. Michigan)

- Many scenarios where 'cytokine storm' accelerates neurodegenerative disease: 1) Sepsis (A. Pietropaoli); 2) surgery in older adults (N. Terrando); 3) acute lung injury (H. Gelbard);); 4) Immunotherapies (CAR T; bispecific mAbs - M. Kim).

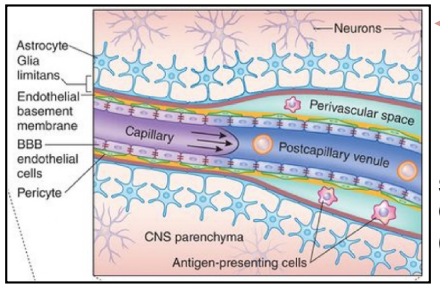
Cunningham and Hennessy *Alzheimer's Research & Therapy* (2015) 7:33



Leukocytes as an agent of brain injury …

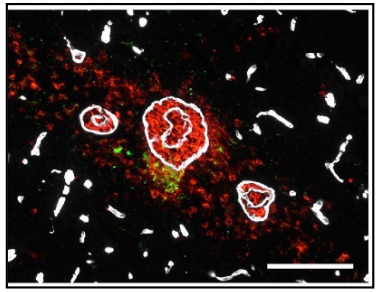
Trzeciak, et al. J Immunol, 2019. 203(11):2979-2989.
Andonegui, et al. (2018). JCI Insight 3(9): e99364.

Leukocytes enter the brain at the post-capillary venule … which is two barriers in series



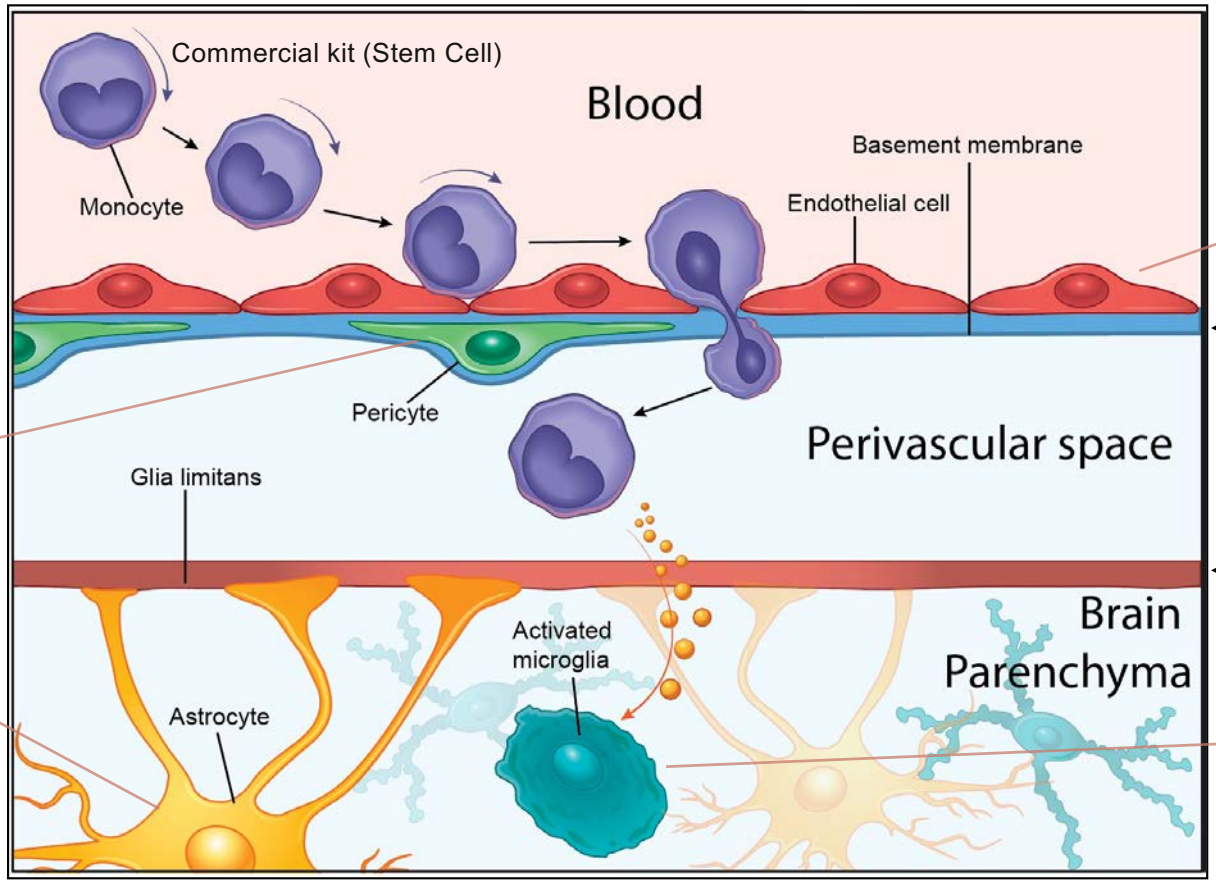
Engelhardt, B., et al., 2017. Nat Immunol, 18: 123-31.

Song, C. et al., Cell Rep 10(7) (2015) 1040-54.



So our task is to build 'healthy' and 'vulnerable' models of the post-capillary neurovascular unit (pcNVU)

DIFFERENTIATION OF iPSCS for the μSiM - pcNVU

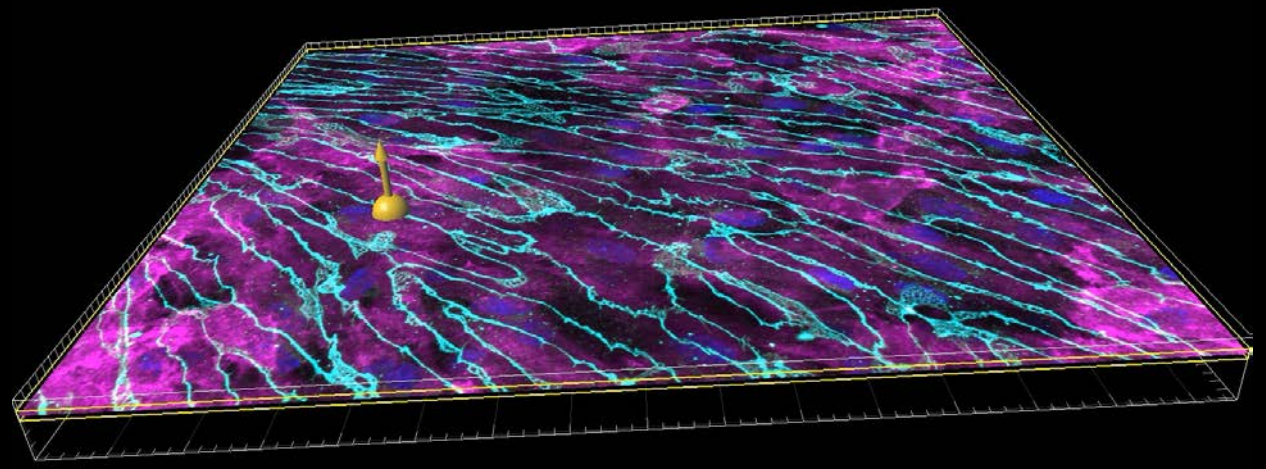


[1] A. McQuade, Mol Neurodegener 13(1) (2018) 67 [2] B.D. Gastfriend, Curr Protoc 1(1) (2021) e21 [3] H. Nishihara, B.D. Faseb. J. 34(12) (2020) 16693-16715

BMECS / PERICYTE CO-CULTURES ON EITHER SIDE OF AN 'INVISIBLE' NANOMEMBRANE

BMECs (VE-cadherin)

Pericytes (PDGFRb)



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COMPOSITION OF THE BASEMENT MEMBRANE

BMECs

Pericytes

Laminin

Fibronectin

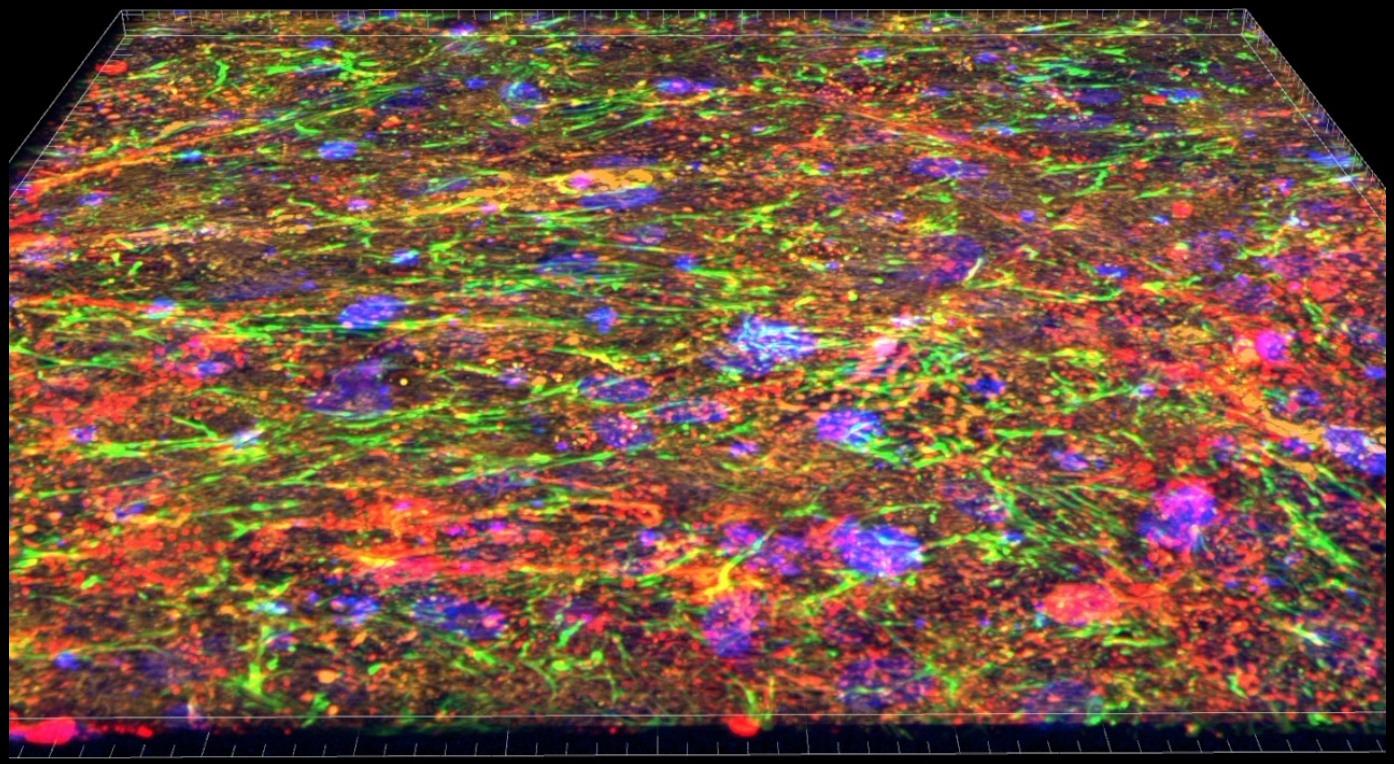
Col IV

Hoechst

Laminin is diffuse and planar

Fibronectin is fibrous with more toward the membrane

Col IV is fibrous far furthest from the membrane and globular elsewhere



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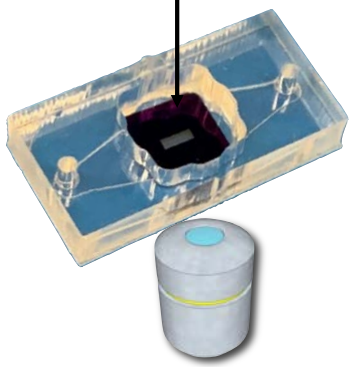
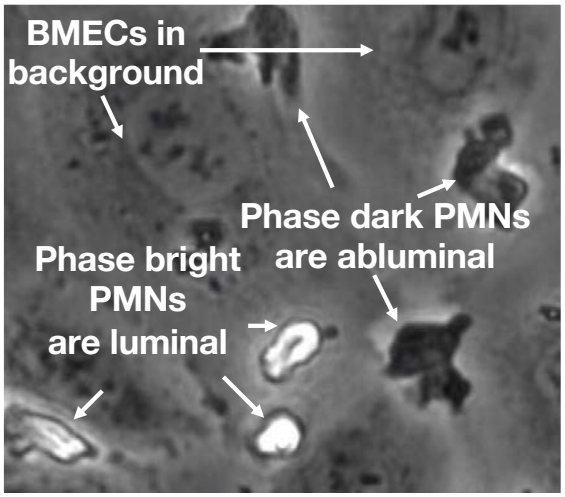
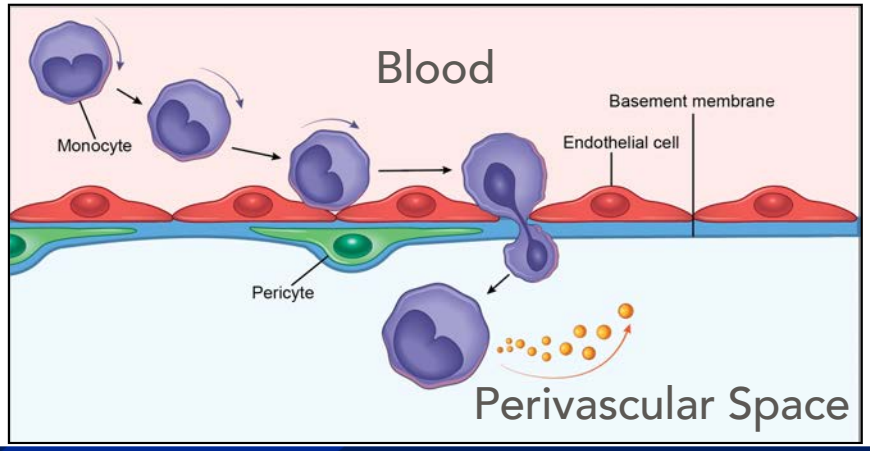
Neutrophil Trafficking Across an Inflamed Blood Brain Barrier

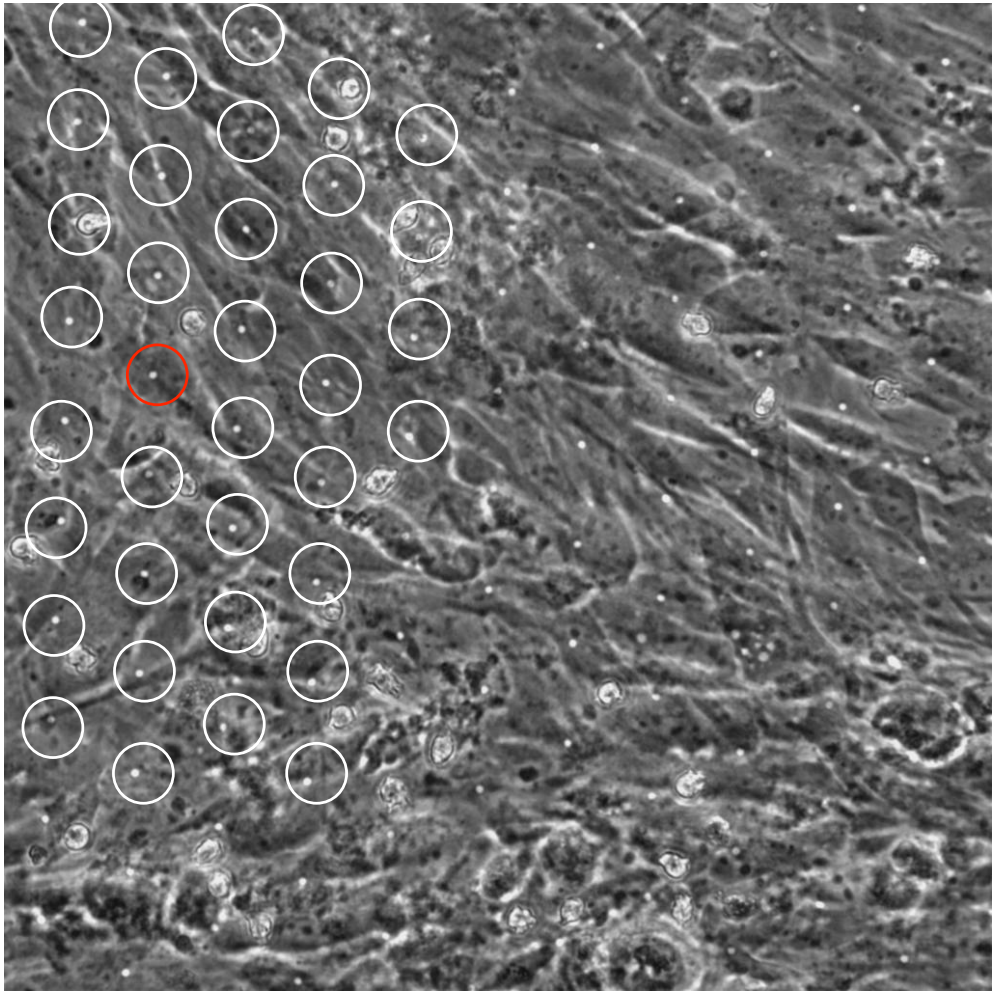
PMNs on top of BBB





Phase contrast imaging @ 40X





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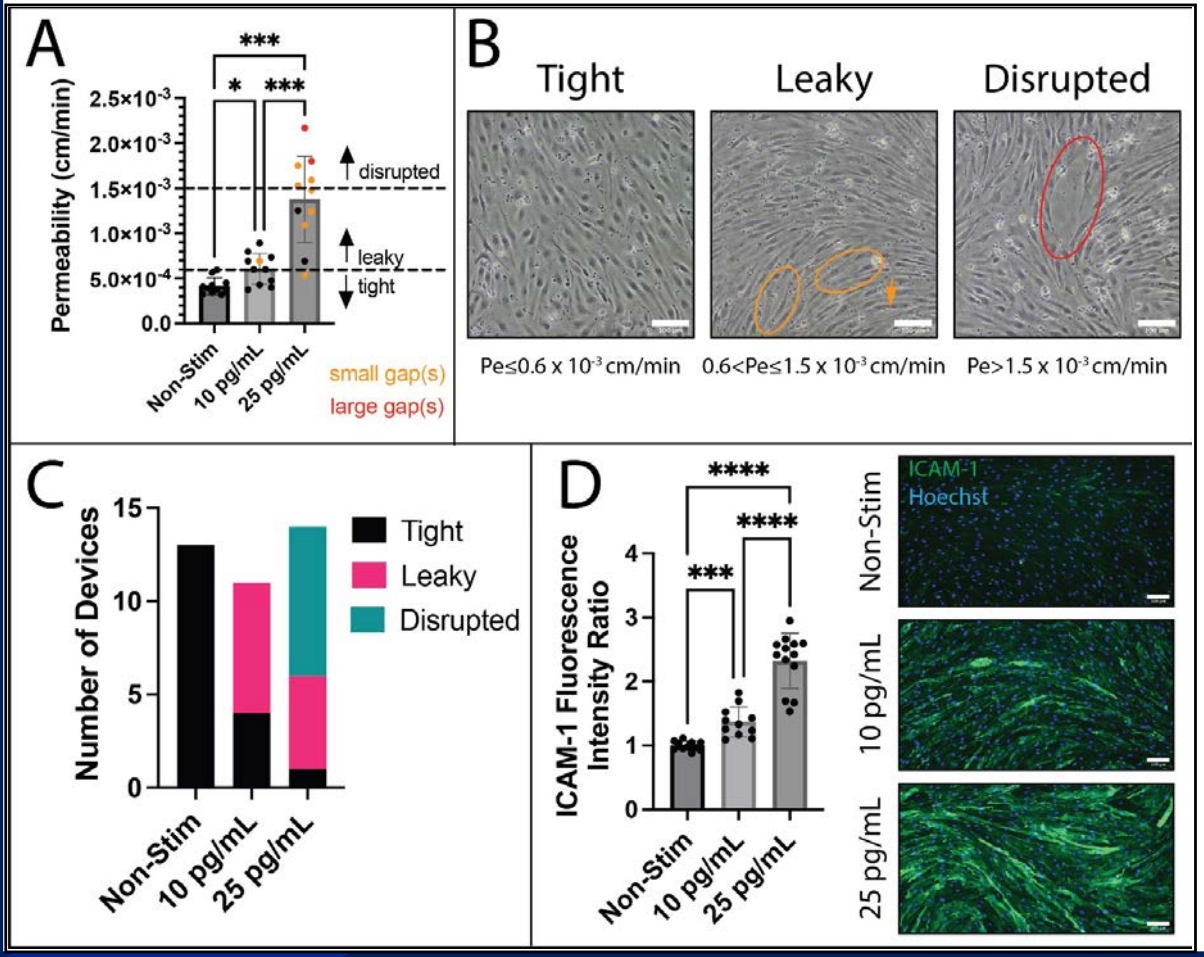
BBB RESPONSE TO 'CYTOMIX' (EQUIMOLAR IL-1β; TNF-α; INFγ)

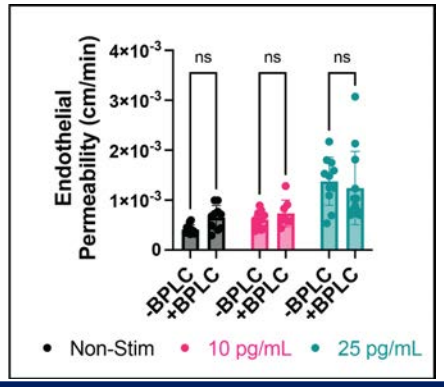
McCloskey and Ahmad et al., 2024 Biomaterials Research 28:0081

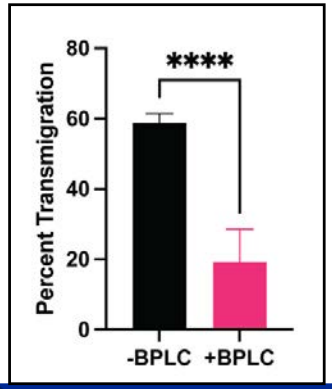


Orhun, G., et al. (2019). "Association Between Inflammatory Markers and Cognitive Outcome in Patients with Acute Brain Dysfunction Due to Sepsis." Arch Neuropsychiatry **56**(1): 63-70.

Table 2. Comparison of serum immunological and neurodegenerative parameter levels of sepsis-induced brain dysfunction patients with delirium and coma

Biomarkers	Patients with delirium (n=64)	Patients with coma (n=18)	p value
IL-1β (pg/mL)	17.3±10.9	9.7±6.8	0.277
IL-8 (pg/mL)	120.3±37.3	268.4±100.8	0.090
IL-6 (pg/mL)	43.9±6.8	90.9±21.3	**0.023**
IL-10 (pg/mL)	8.5±4.1	24.9±9.7	0.066
IFN-γ (pg/mL)	6.2±1.8	11.0±6.5	0.243
TNF-α (pg/mL)	32.1±6.0	58.6±14.1	**0.048**
IL-17 (pg/mL)	2.9±0.9	12.6±8.6	0.136
IL-12 (pg/mL)	9.1±1.1	16.6±2.6	**0.007**



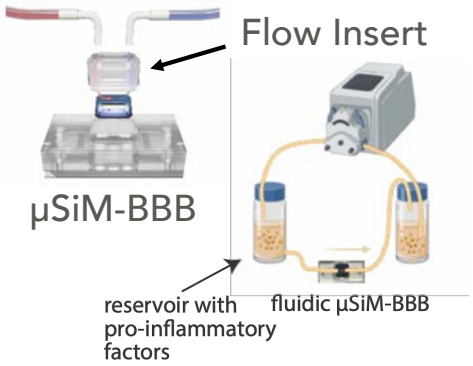


SHEAR CONDITIONING PROMOTES MICROVASCULAR ENDOTHELIAL BARRIER RESILIENCE IN A HUMAN BBB-ON-A-CHIP MODEL OF SYSTEMIC INFLAMMATION LEADING TO ASTROGLIOSIS

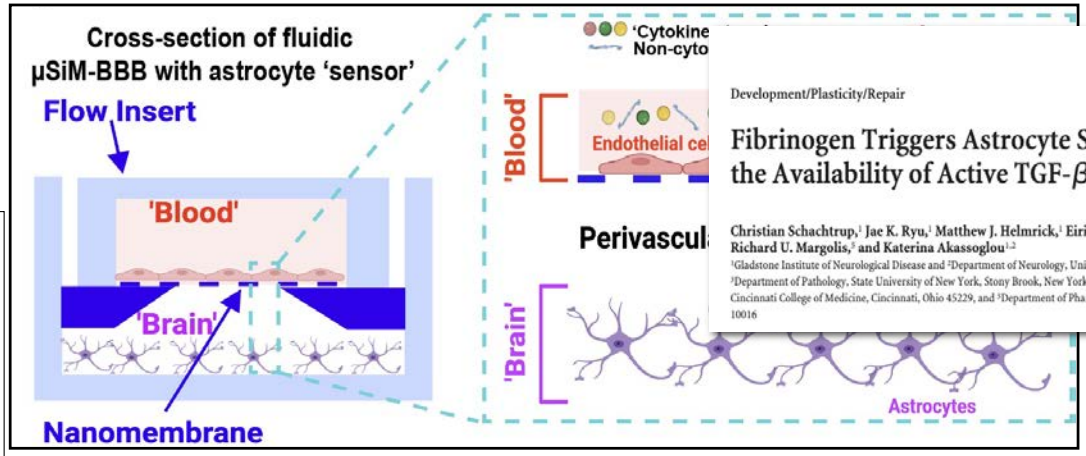
First Successful Transduction of Systemic Inflammation into Neuroinflammation in the μSiM-BBB

Kaihua (Chloe) Chen

Chen et al. (2025)
Adv Sci e08271



- Shear conditioning of BMECs for 48 hours improves barrier function and dampens several inflammatory responses
- ± Introduction of pro-inflammatory factors after conditioning
- Measurement of barrier function and astroglyosis marker (GFAP)



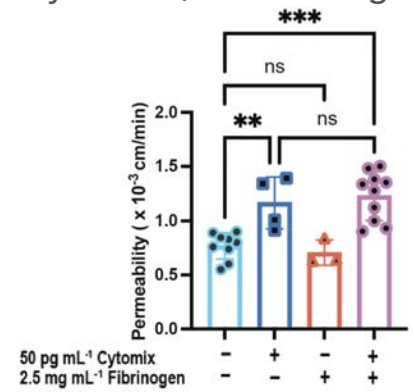
The Journal of Neuroscience, April 28, 2010 • 30(17):5843–5854 • 5843

Development/Plasticity/Repair

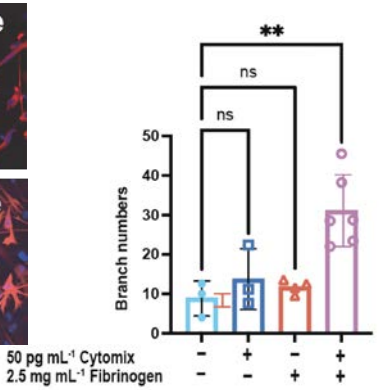
Fibrinogen Triggers Astrocyte Scar Formation by Promoting the Availability of Active TGF-β after Vascular Damage

Christian Schachtrup,[1] Jae K. Ryu,[1] Matthew J. Helmrick,[1] Eirini Vagena,[1] Dennis K. Galanakis,[3] Jay L. Degen,[4] Richard U. Margolis,[5] and Katerina Akassoglou[1,2]
[1]Gladstone Institute of Neurological Disease and [2]Department of Neurology, University of California, San Francisco, San Francisco, California 94158, [3]Department of Pathology, State University of New York, Stony Brook, New York 11794, [4]Children's Hospital Research Foundation and the University of Cincinnati College of Medicine, Cincinnati, Ohio 45229, and [5]Department of Pharmacology, New York University Medical Center, New York, New York 10016

Barrier function affected by cytokines, not fibrinogen



Astrocytes are activated by fibrinogen *after* BBB breakdown



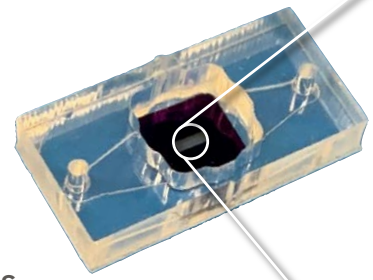
Fibrinogen in Brain Injury and Neurodegeneration (Akassoglou Lab)

- Dean T, Mendiola AS, Yan Z, Meza-Acevedo R, Akassoglou K. Fibrin promotes oxidative stress and neuronal loss in traumatic brain injury via innate immune activation. *Acta Neuropathol*. 2024.
- Petersen MA, Ryu JK, Akassoglou K. Fibrinogen in neurological diseases: mechanisms, imaging and therapeutics. *Nat Rev Neurosci*. 2018;19(5):283-301.
- Schachtrup C, Ryu JK, Meyermann R, et al. Fibrinogen inhibits neurite outgrowth via β3 integrin-mediated transactivation of the EGF receptor. *Proc Natl Acad Sci USA*. 2007;104(26):11814-11819.
- Wood H. Fibrinogen links vascular pathology to cognitive decline. *Nat Rev Neurol*. 2019;15:187.
- Davalos D, Ryu JK, Merlini M, et al. Fibrin-targeting immunotherapy protects against neuroinflammation and neurodegeneration. *Nat Immunol*. 2018;19(12):1315-1323

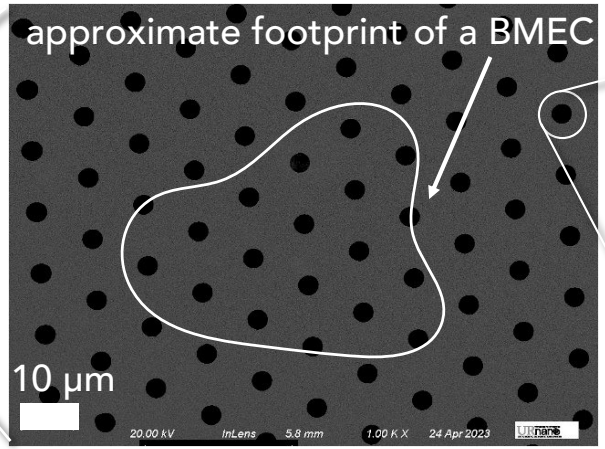
THE VULNERABLE BRAIN … 2) BY ENGINEERING THE ENVIRONMENT

Michelle Trempel

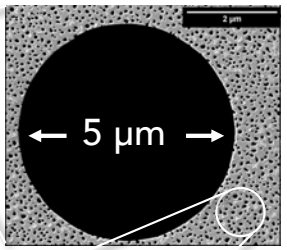
- Basement membrane degradation, pericytes 'loss' and a 'leaky' BBB are hallmarks of the aging, vulnerable brain.
- Can we engineer a defective basement membrane to generate this phenotype?

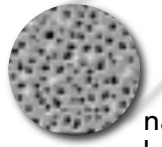


The µSiM



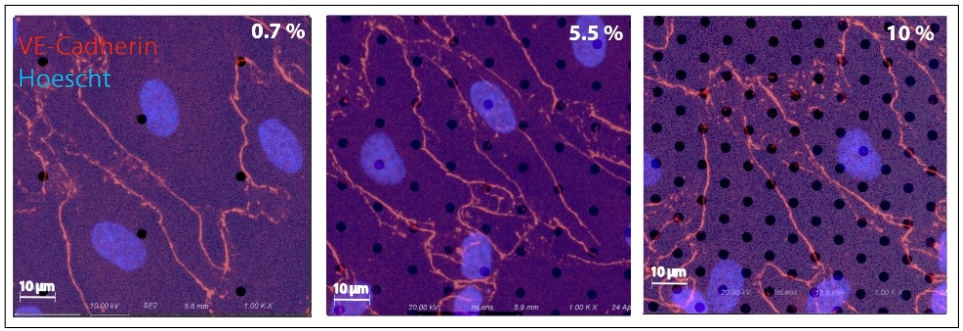
microporous defects





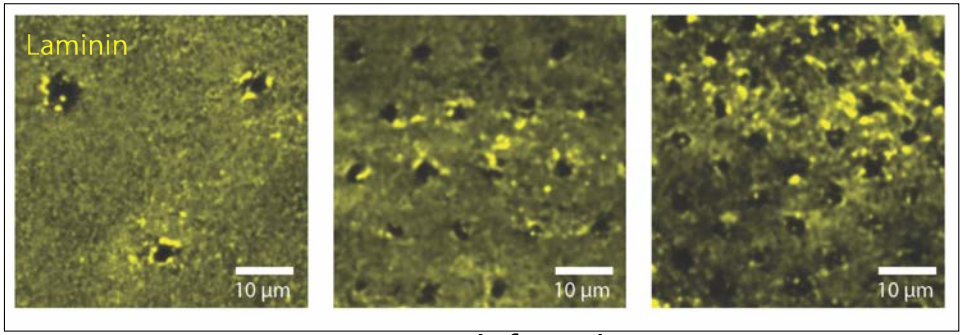
nanoporous background

1. Banks,. et al. Nat Aging 1, 243–254 (2021).
2. Berthiaume, et al., Nat Commun 13(1) (2022) 5912.
3. Farkas and Luiten, Prog Neurobiol 64(6) (2001) 575-611.
4. Ceafalan, et al. J Cell Mol Med 23(2) (2019) 819-827.
5. Nehra, et al., Fluids Barriers CNS 21(1) (2024) 29.



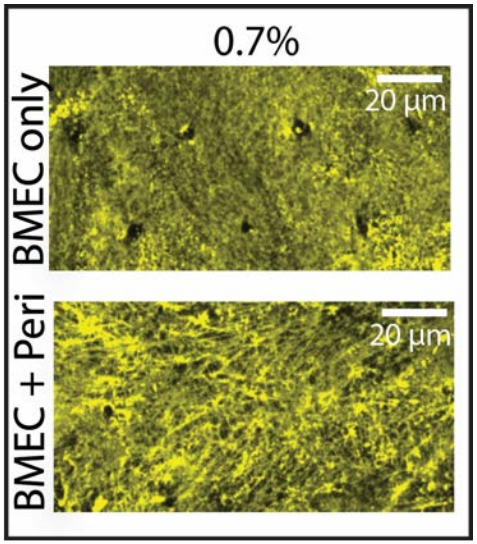
increasing defect density

BMEC Monoculture



increasing defect density

PERICYTES REPAIR ENGINEERED DEFECTS IN THE BASEMENT MEMBRANE TO RESTORE BARRIER FUNCTION IN AN IN VITRO MODEL OF THE BLOOD-BRAIN BARRIER

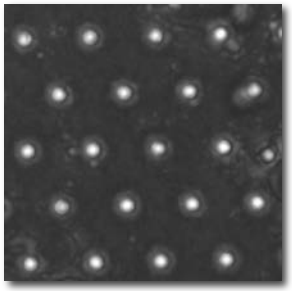


Pericyte 'repair'

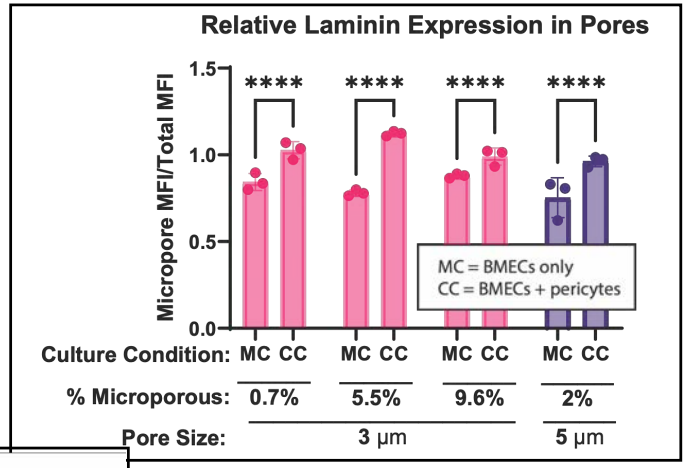
With pericytes …

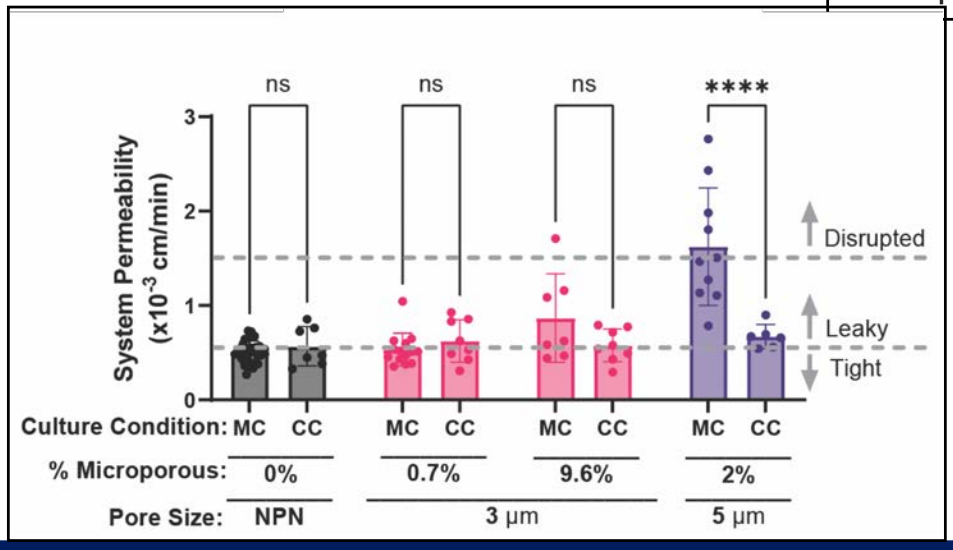
- Holes get smaller and often disappear
- Laminin becomes fibrous rather than smooth

DIC Image shows micropore locations as bright spots



generate mask from DIC image





Thoughts on pericytes and the 'vulnerable brain' …

- Pericytes are not 'needed' for baseline barrier function in the µSiM-BBB unless the basement membrane is defective
- Loss of pericytes is seen in neurodegenerative disease and aging-associated leaky BBB (AD, PD, ALS, MS)

NANOMEMBRANE RESEARCH GROUP

Current Trainees

Michael Klaczko, PhD (Viruses and Bacteria)
Sam Walker (EV-based Diagnostics)
Victor Zhang (Tendon-on-a-Chip - Matrix and iPSCs)
Isabelle Linares (Fluidic Tendon-on-a-Chip)
Michelle Trempel (Delirium Chip)
Kevin Ling (Outer Retinal Barrier Chip)
Savin Liu (Diagnostics)
Alexis Felder (Aging)
Emily Reitz (TBA)
Arvind Srivatsava (OLCN chip; e-beam lithography)
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R61/R33 HL154249; RF1AG079138; UG3/UH3 TR003281

Alumni

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Jess Snyder (Diffusion, EO)
Barrett Nehilla (Cell Culture)
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Maryna Kavalenka (Gas Flow)
Joe Qi (pnc-Si on SiN)
Josh Winans (NPN, Fouling)
Bob Carter (RIT; Lift-off)
Tucker Burgin (Dialysis & ECMO)
Karl Smith (Dead End Filtration, Fouling)
Tejas Khire (Vascular Models'; μSiM v1)
Jirachai Getpreecharsawas (Electrokinetics)
Henry Chung (Microfluidics; μSiM v1)
Kayli Hill (Dialysis)
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Aslan Dehghani (RIT, Exosome Capture)
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Chloe Chen (Fluidics in brain chips)
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Thank you!