Regenerative Engineering for Lupus and Uterine Fibroids

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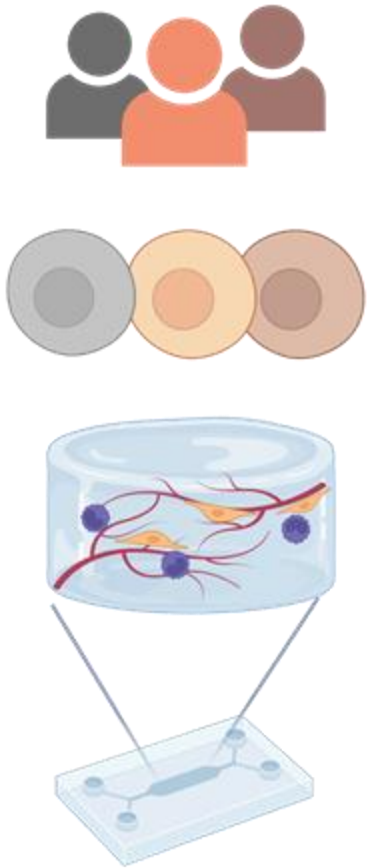
MOORE LAB

The Intersection of Regenerative Medicine and Women's Health: A Workshop
Oct. 2024

Disclosures: None

Innovations to advance translational research

- Conditions observed in the clinic are sometimes challenging to analyze on a single cell or in vivo context
  - Challenge of animal models
- Development of microphysiological systems which enable context of the microenvironment to be considered



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Mission of the Lab:

Engineering biomaterial models to leverage the regenerative potential of the immune system across health inequities

Vision of the Lab:

Developing compassionate innovators equipped to transform biomedical research

Leveraging regenerative medicine to address limitations in fundamental knowledge

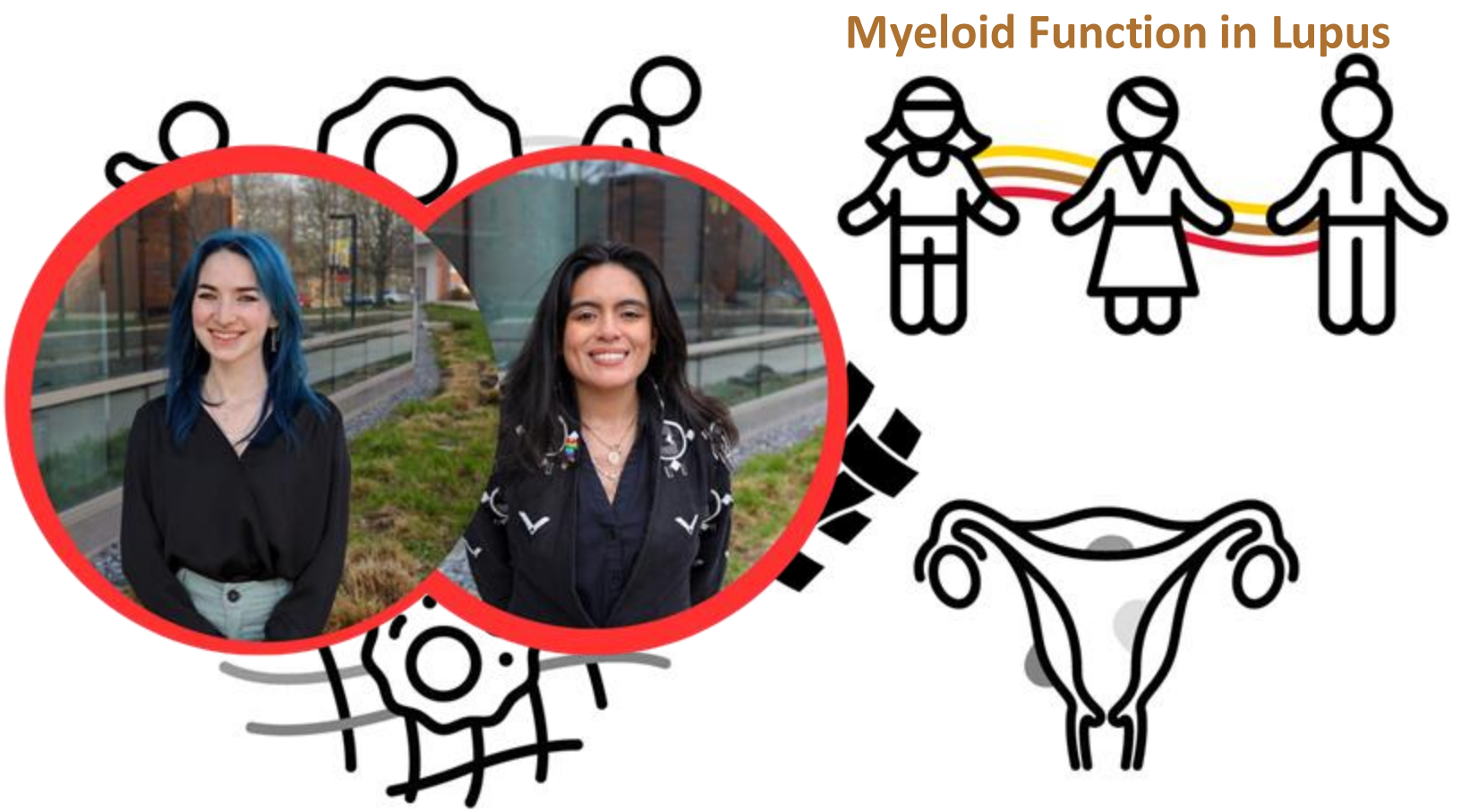
Myeloid Function in Aging

Myeloid Function in Lupus

Myeloid Attenuation + ECM

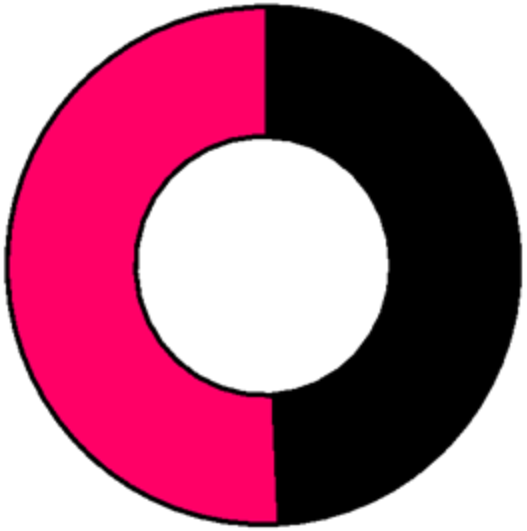
Myeloids in Uterine Fibroids

Preclinical Model of Monocyte Influence on Vascular Plexus in Lupus

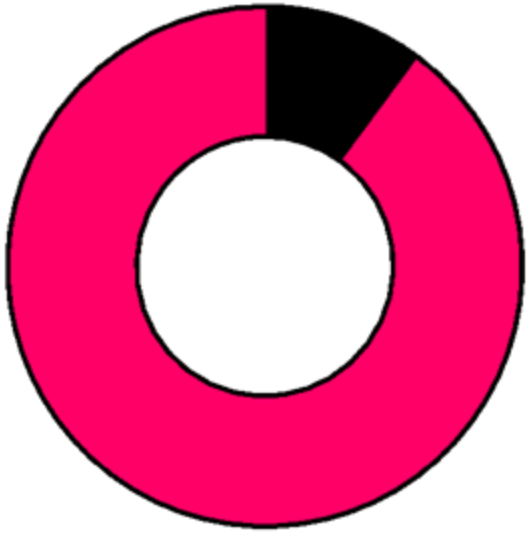


Females make up 90% of SLE patients

U.S. Population



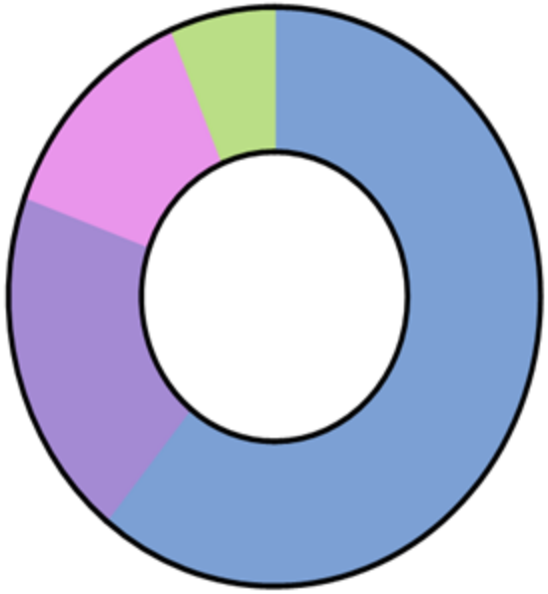
SLE Patients in U.S.



Lim et al. MMWR Morb Mortal Wkly Rep (2019)

African American women disproportionately suffer from SLE

U.S. Population

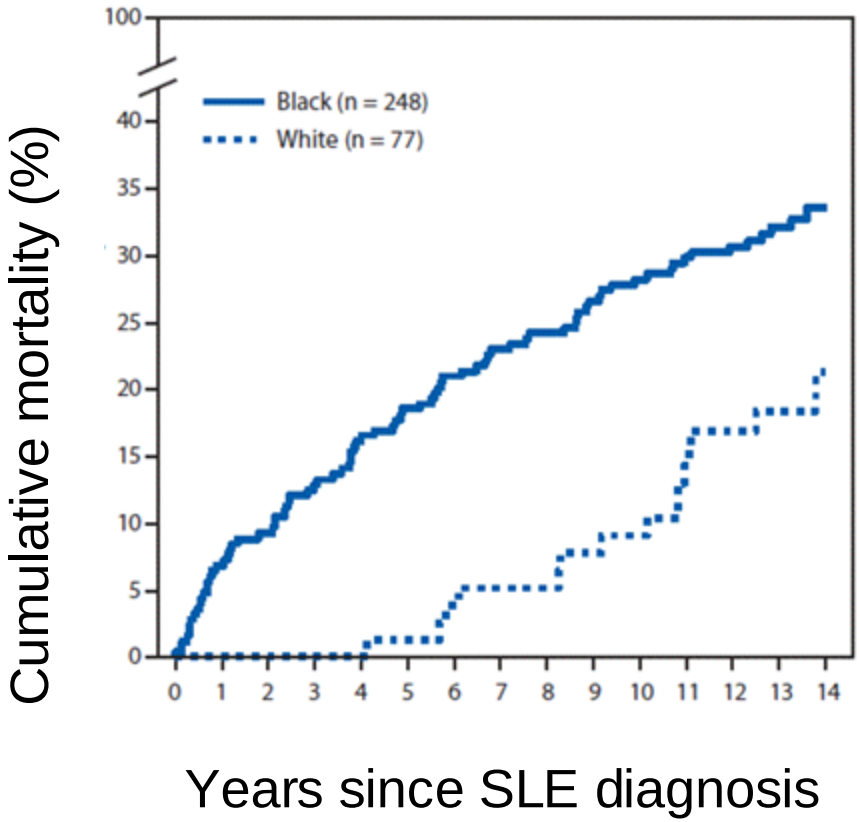


SLE Patients in U.S.

Lim et al. MMWR Morb Mortal Wkly Rep (2019); Fujimura, Soc Stud Sci (2011); Chou, Sci News (2017)

SLE mortality is higher in patients of African ancestry

- Diagnosed earlier in life
- More severe course of disease
- More likely to die at a younger age

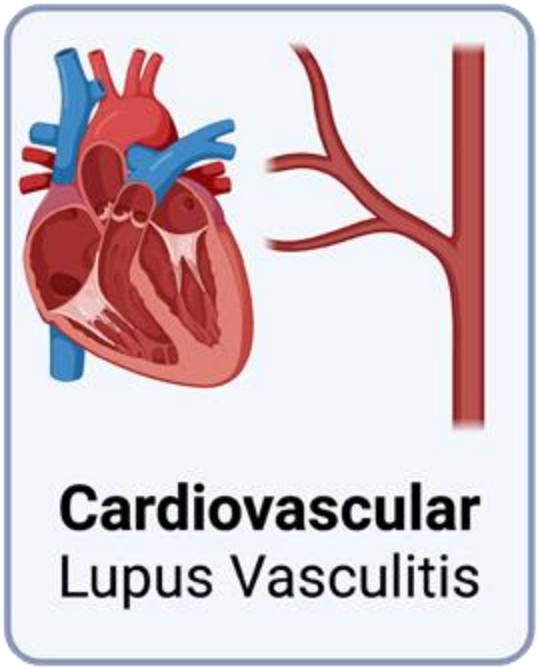


Lim et al. MMWR Morb Mortal Wkly Rep (2019); Fujimura, Soc Stud Sci (2011); Chou, Sci News (2017)

Lupus Vasculitis (LV): A common complication of SLE

LV is defined as SLE associated **inflammation of vasculature**

LV can result in other types of cardiovascular disease

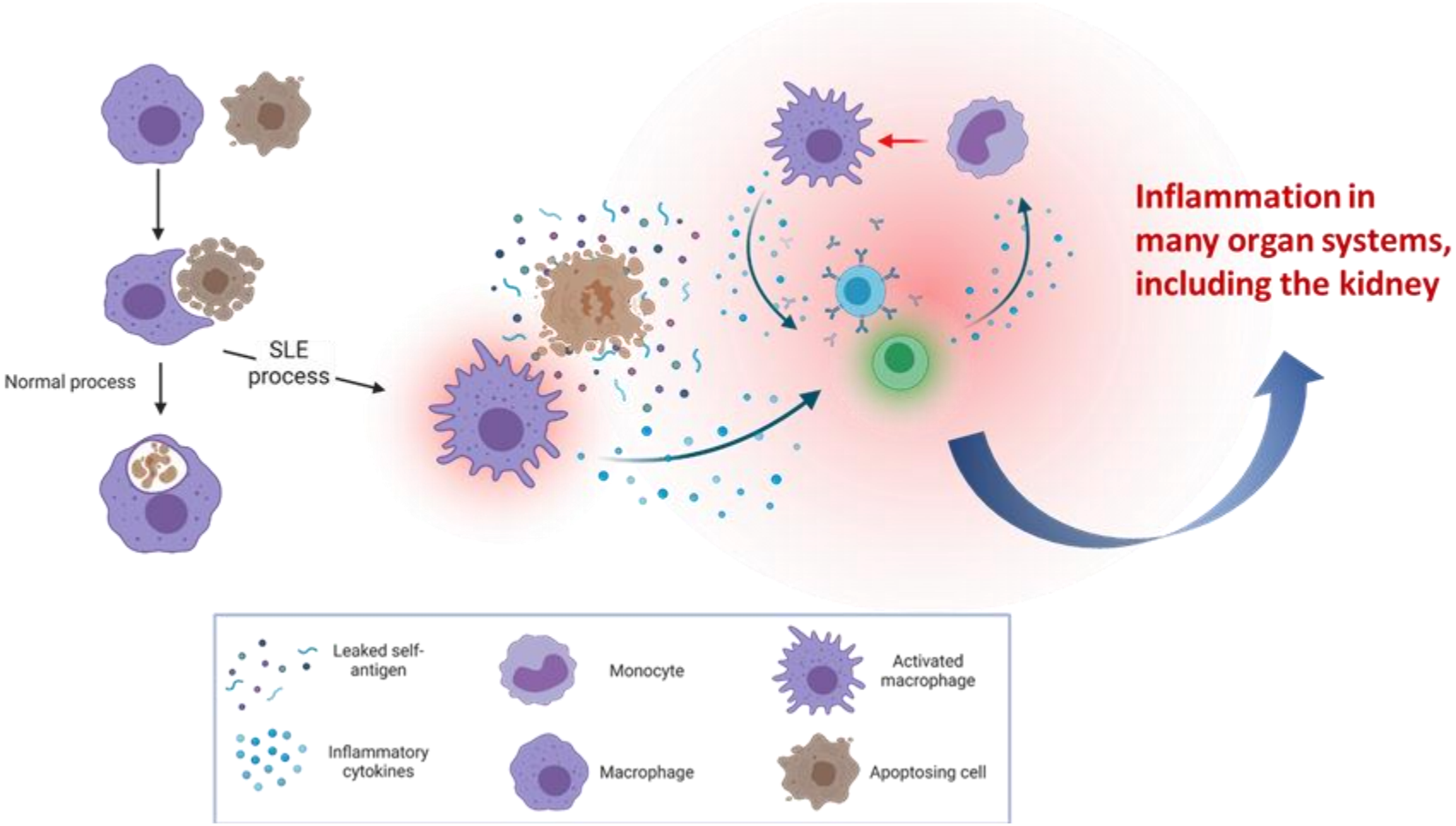


LV can damage other tissues/organ systems

LV can affect small, medium, or large vessels

Image created with Biorender.com

Role of Monocytes in SLE



Dema B, *Antibodies* (2016); Dörner T, *Lancet* (2019); Tian J, *ARD* (2023); Lim S, *Morb. Mortal. Wkly. Rep.* (2019); Izmirly PM, *A&R* (2021) Li Y, Arch Immunol Ther Exp (2010)

Image made with BioRender

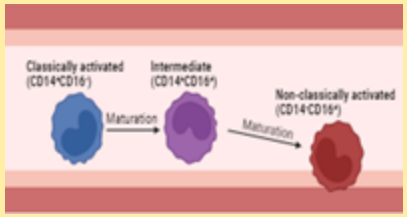
Employ Microphysiological Platforms to Characterize Monocytes from SLE Patients

Specific effects of alterations in monocytes from SLE patients remain under-studied

Question 1

Is monocyte expression of genes and cell markers altered in SLE patients?

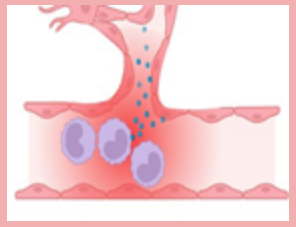
Polarization states and gene expression



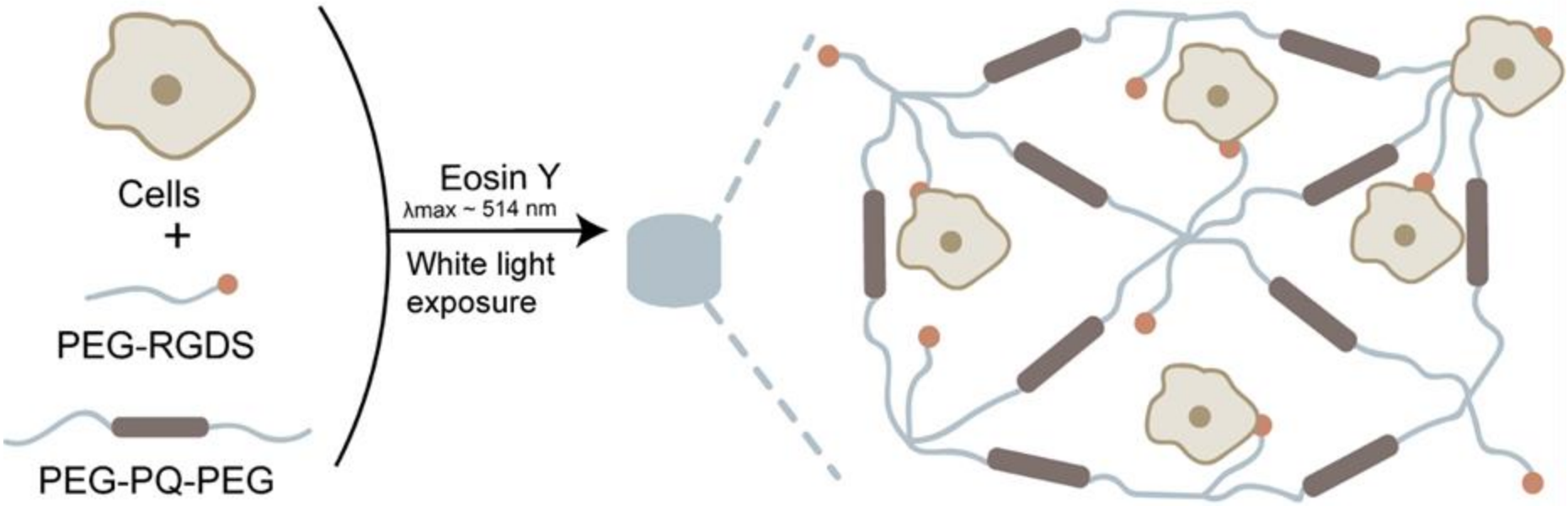
Question 2

Do monocytes from SLE patients alter microvessel connectivity in 3D vessel formation assay?

In vitro effects of monocytes on segment connectivity



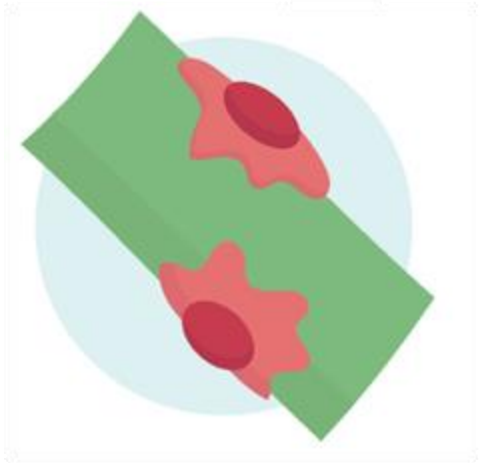
Microphysiological systems to study diseases

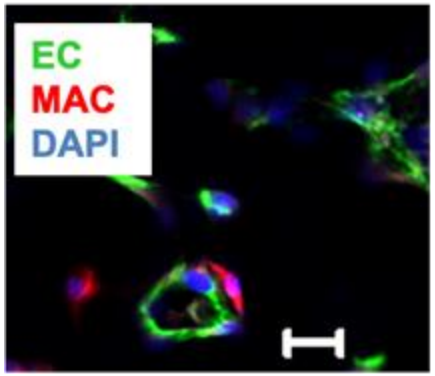


PEG- poly(ethylene glycol)
RDGS/PQ- ECM derived peptides

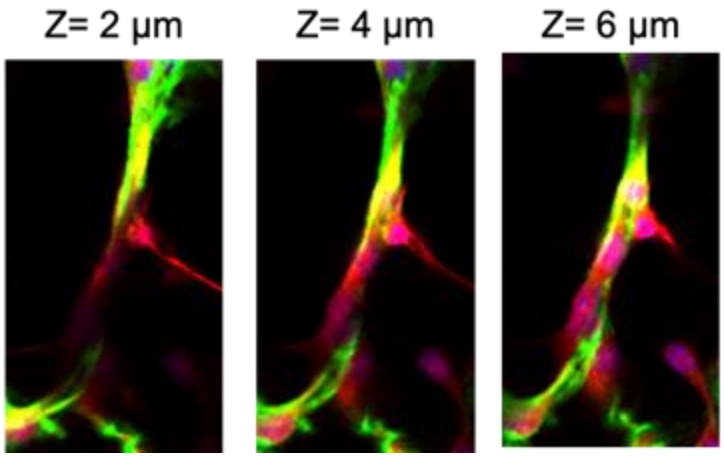
Our microphysiological platforms can replicate immune cell functions

Close Alignment

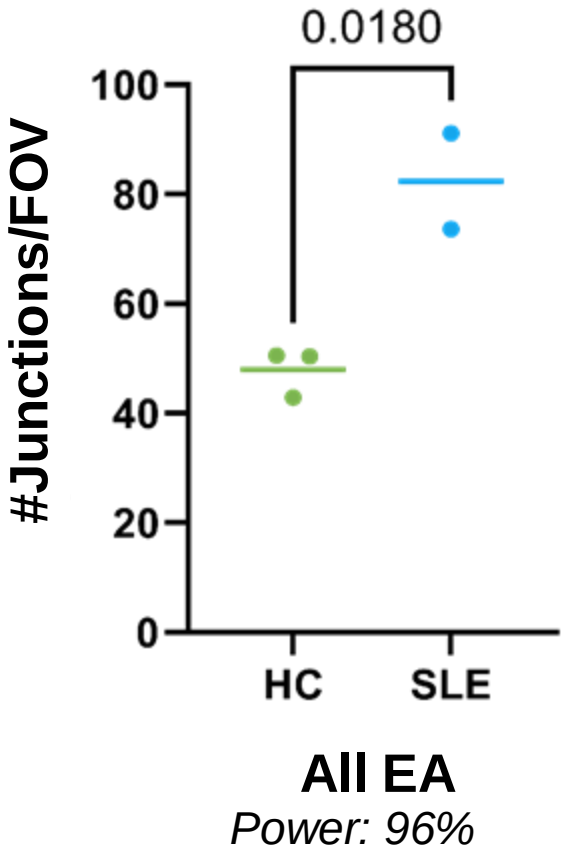


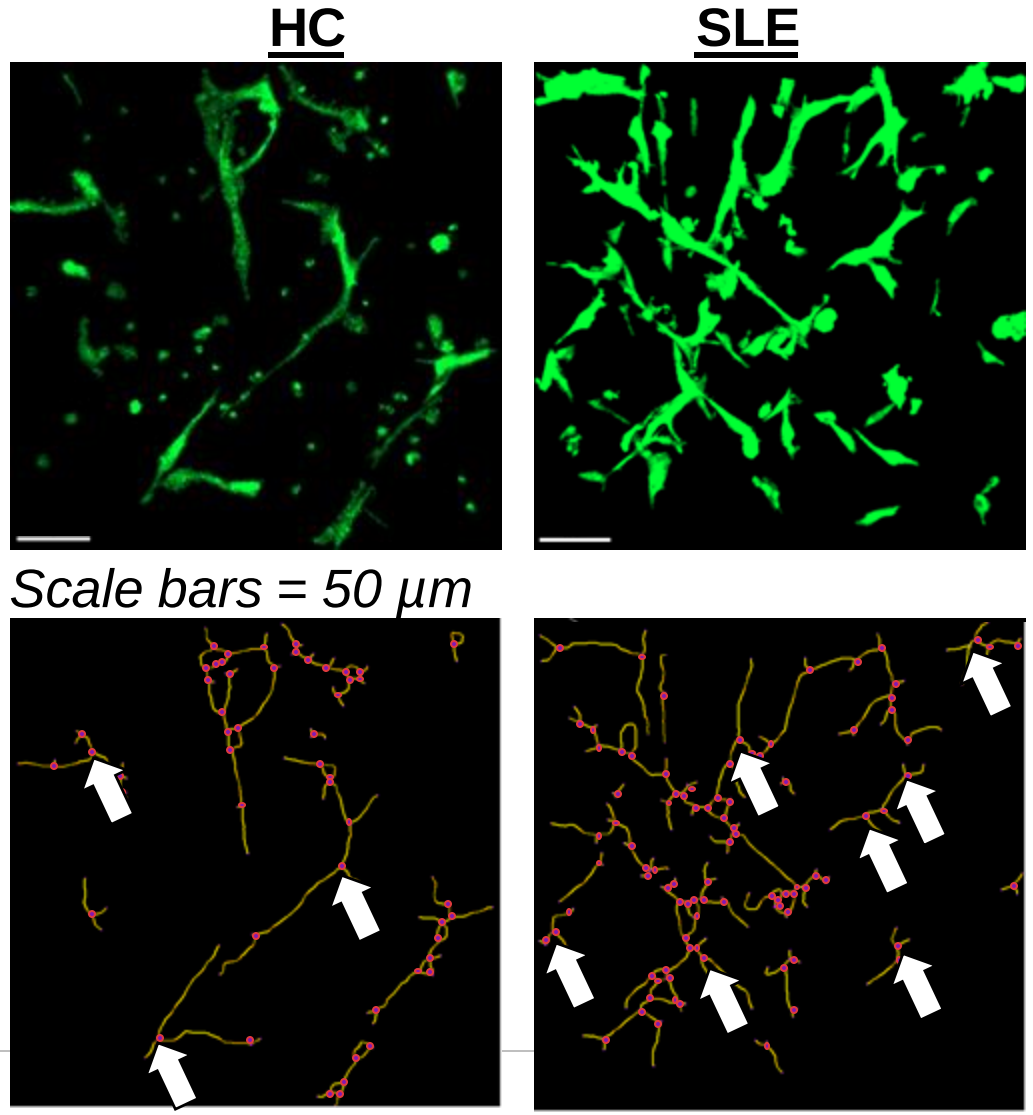


Bridging



SLE increases the number of junctions and endpoints of endothelial segments

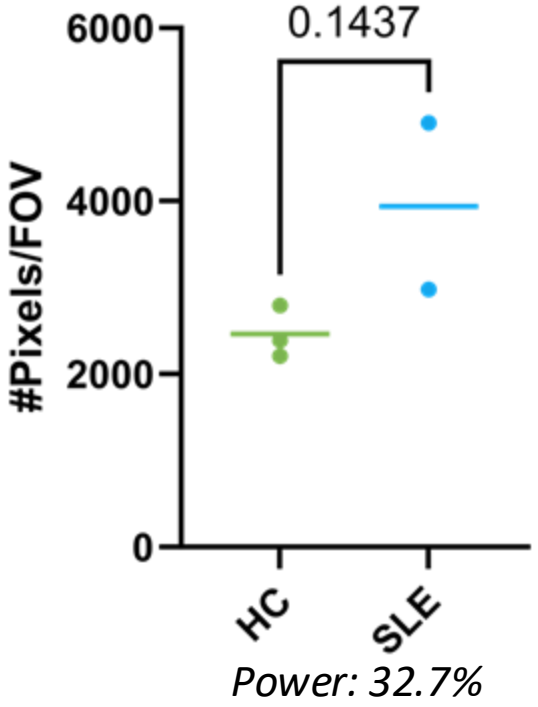




Monocytes from SLE Patients Affect Metrics Related to Branching

Developed a preclinical model to assess SLE myeloid cell influence on microvessel structure

Power: 91.6%

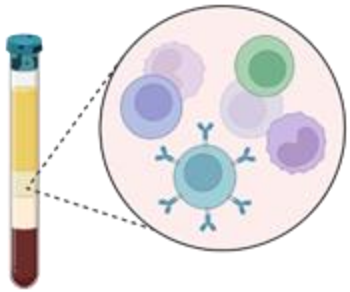


Power: 32.7%

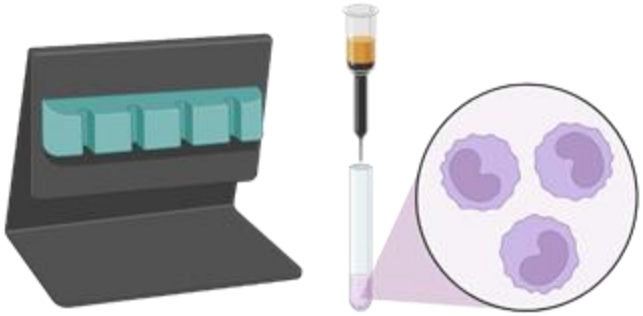
SLE increases the number of junctions and endpoints of microvessel segments

Translating impact for personalized profiling

Collect 40 mL peripheral blood



Peripheral blood mononuclear cells

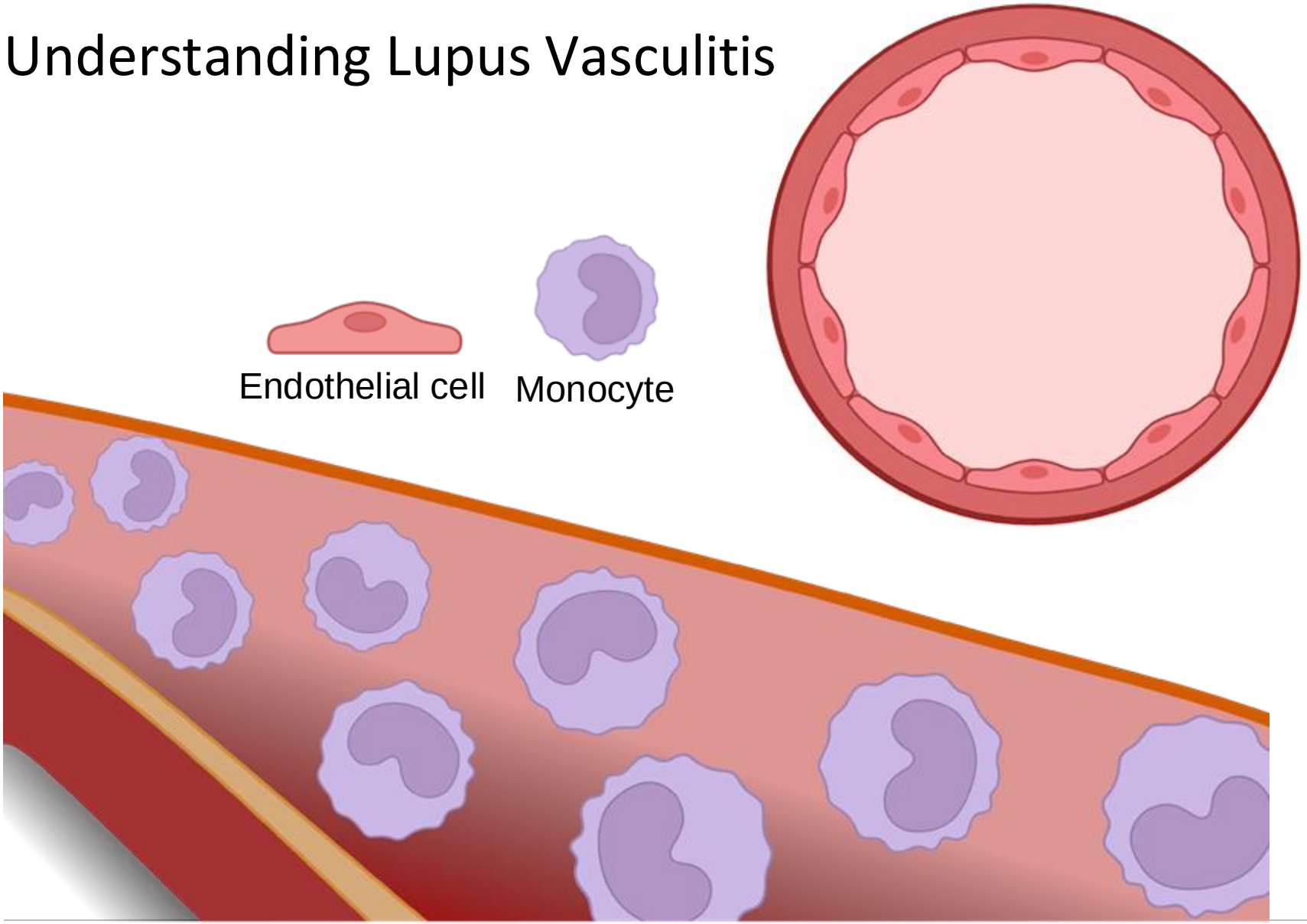


Negative magnetic isolation of monocytes

Partnership with JHU Lupus Center, Dr. Michelle Petri

Image made with BioRender

Understanding Lupus Vasculitis



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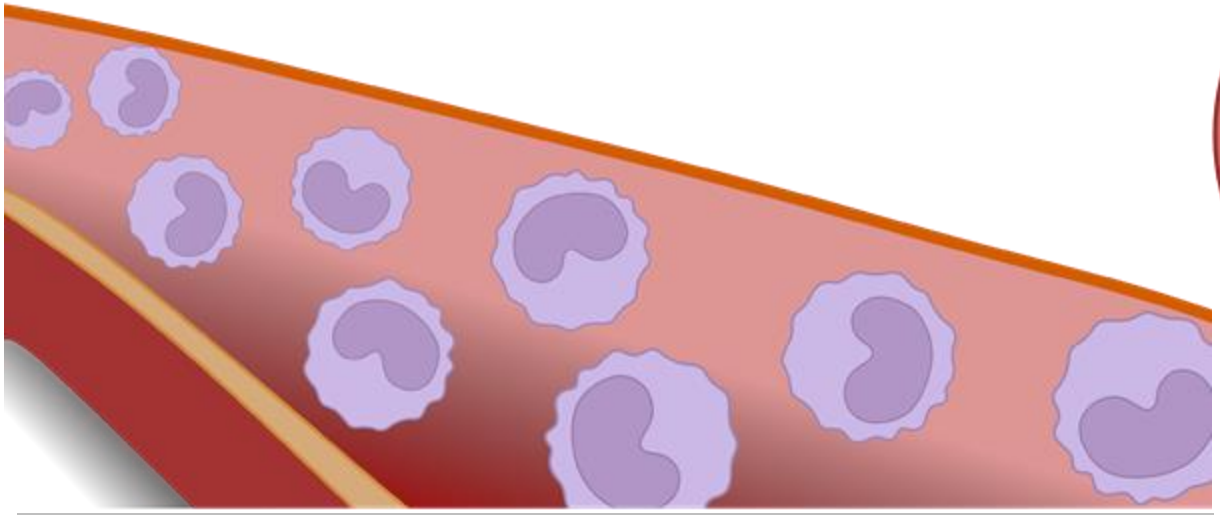
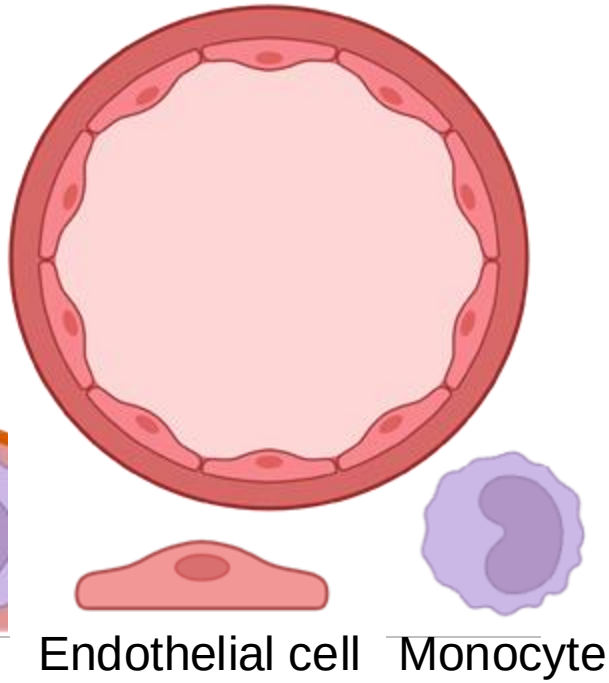
Understanding Lupus Vasculitis

SLE general inflammation → Endothelial Activation → Aberrant monocyte-endothelial cell interactions → Endothelial cell Inflammation → Inflammation of vasculature → Lupus Vasculitis





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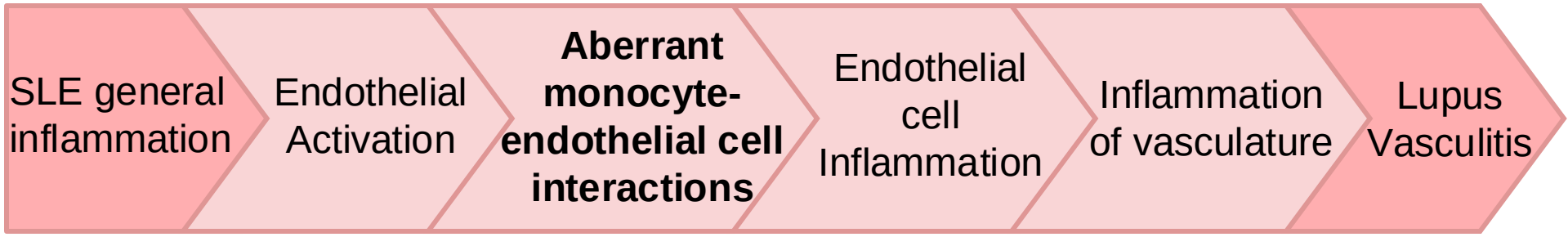
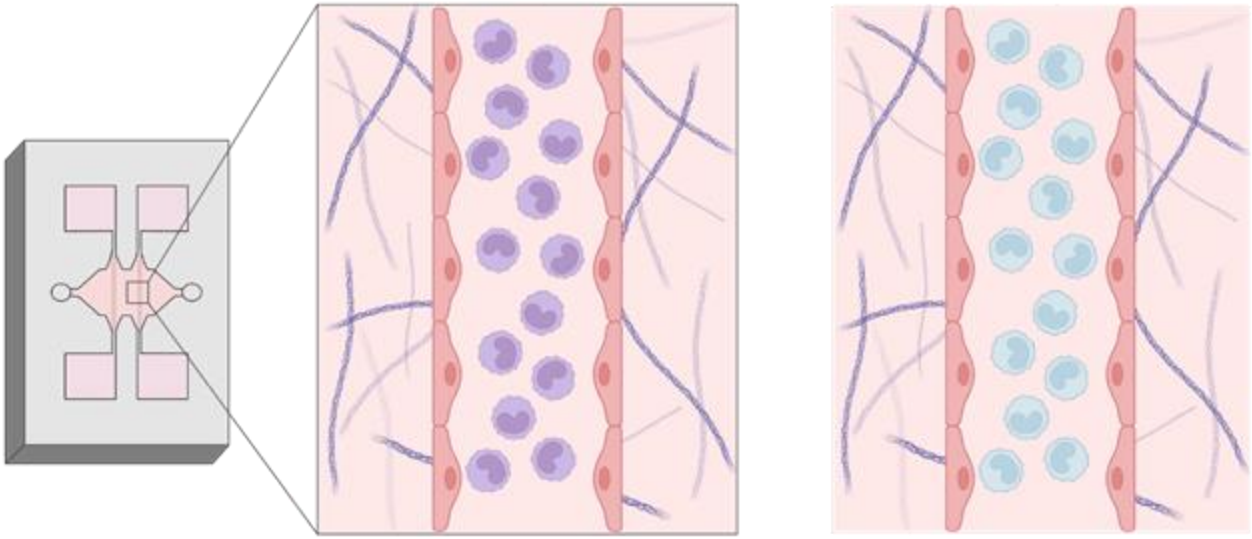
What causes Lupus Vasculitis?



There are limited in vitro models of Lupus Vasculitis

Introduce a microfluidic device to observe monocyte-endothelial cell interactions



Monocytes
Endothelial Cell
Hydrogel

Dr. Evangelia Bellas

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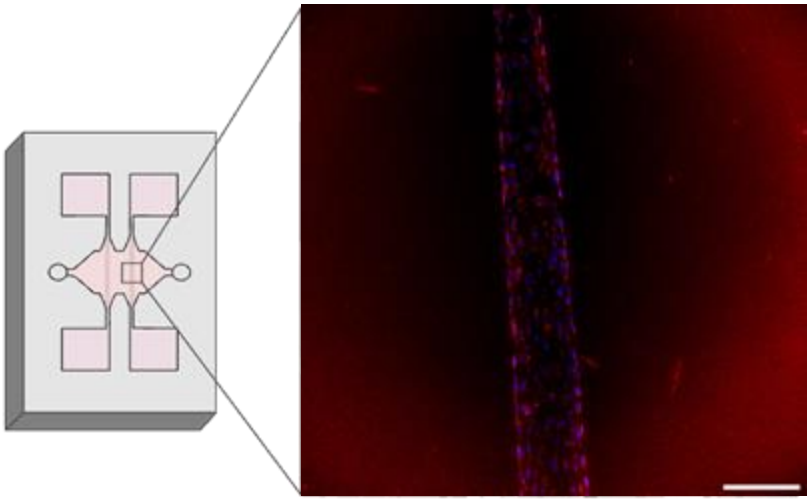
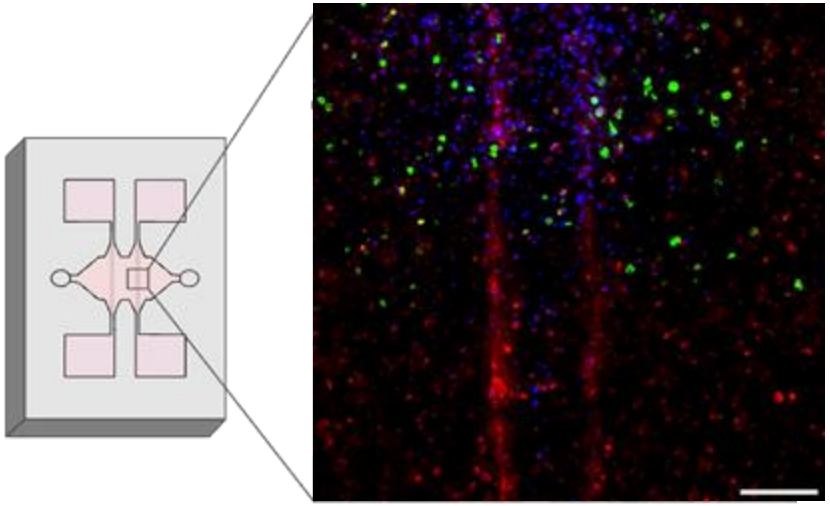
Image made with BioRender

Assessing monocyte behavior with endothelial cells as a function of disease state





Development of a microfluidic system to assess SLE myeloid cell
endothelial cell function

Dr. Evangelia Bellas

Understanding uterine fibroid growth through regenerative medicine tools

Uterine Fibroids

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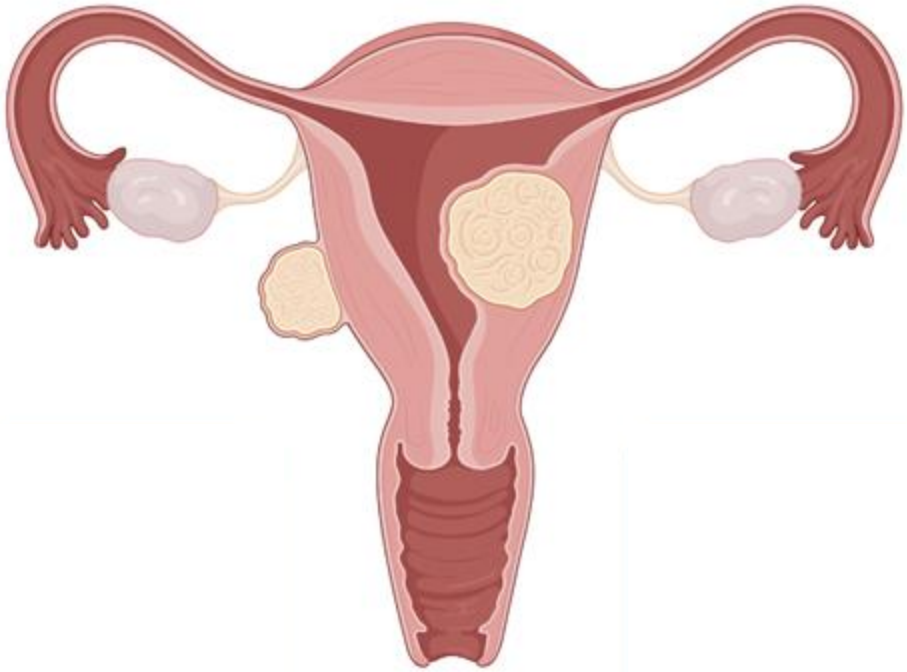
Uterine fibroids are the most common gynecological tumor and arise in the myometrium.

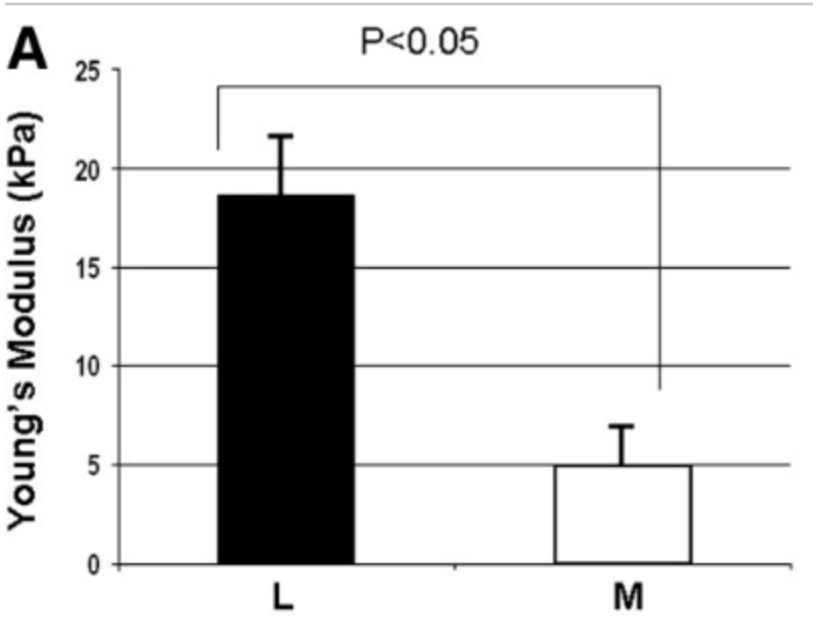


Al-Hendy A, et al. (2017) Semin Reprod. Day Baird D, et al.(2003) Am J Obs Gynecol. Drayer S, et al. (2015). J Gyn & Obst. De La Cruz MS. (2017) Am Fam Phys. Madueke-Laveaux OS, et al. (2021). J Clin Med.

Image made with BioRender

What is known about uterine fibroids?

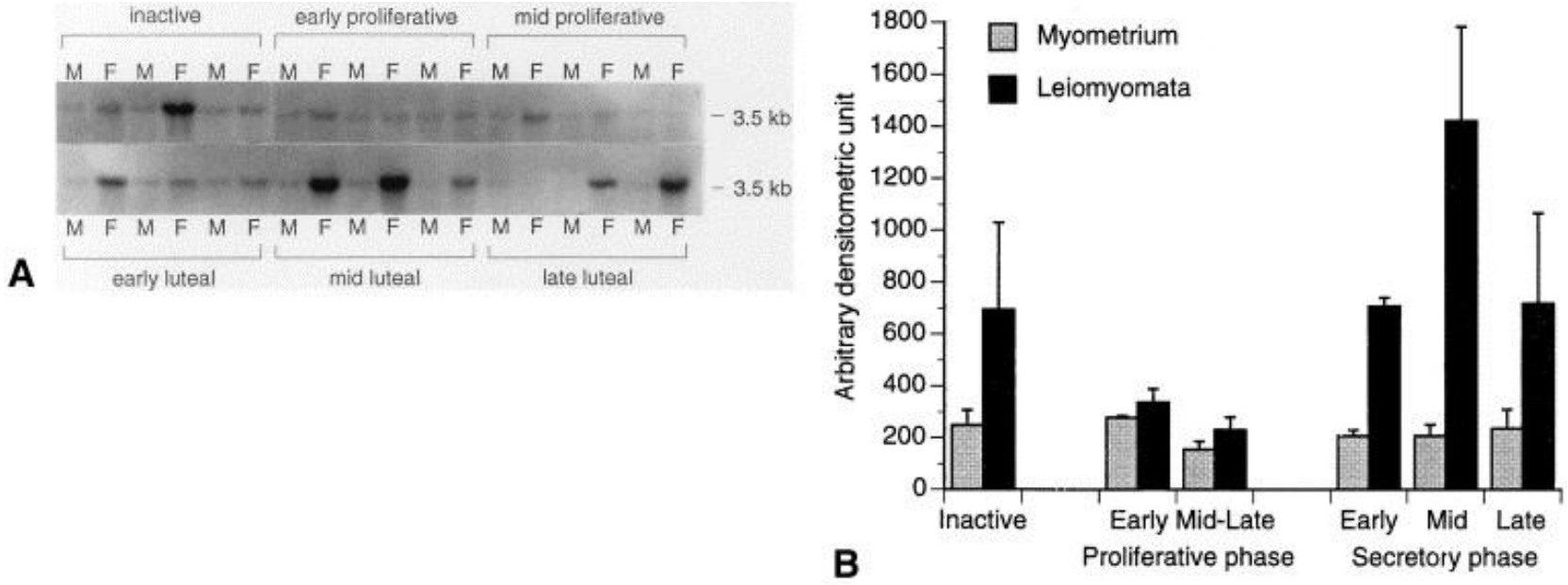
- Fibroids (L) are 2-3 x stiffer than myometrial (M) tissue



Rogers R, et al. (2008). Am J of Obstetrics and Gynecology.

What is known about uterine fibroids?

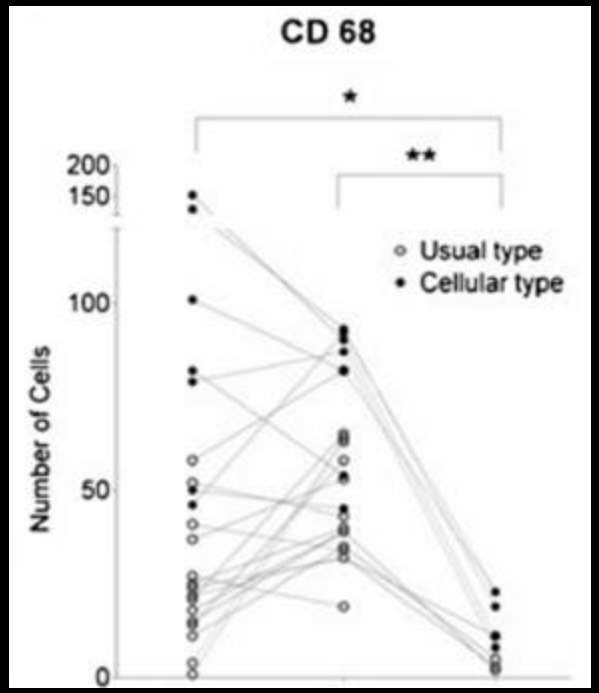
- Fibroids are 2-3 x stiffer than myometrial tissue
- TGF-β3 is up to 5x higher in fibroids than myometrium



Arici, et al. *Reproductive Bio* (2000).

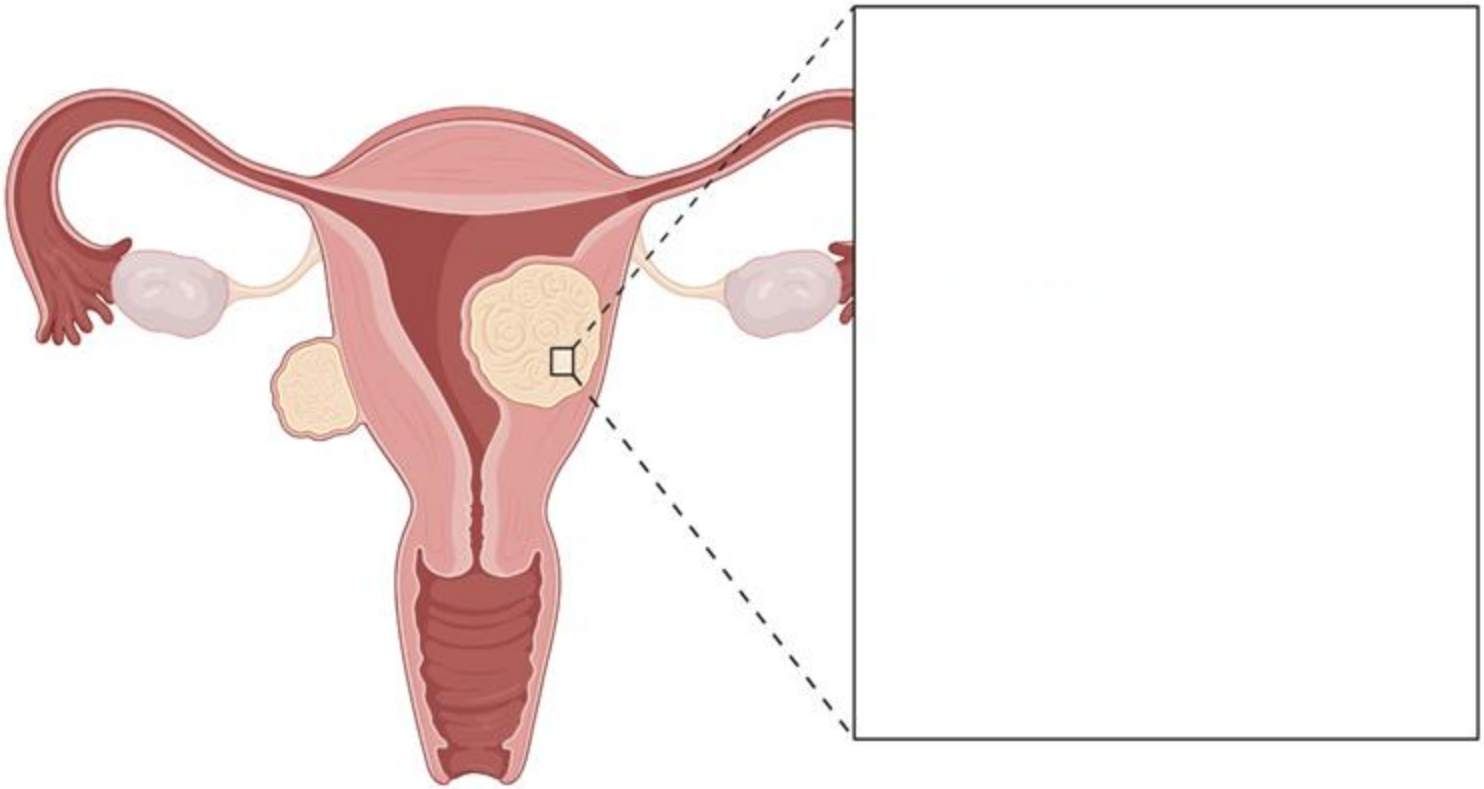
What is known about uterine fibroids?

- Fibroids are 2-3 x stiffer than myometrial tissue
- TGF-β3 is up to 5x higher in fibroids than myometrium
- Macrophages are higher in density in fibroids compared to distant healthy tissue



Modified from Protic O, et al. (2016). Cell and Tissue Res.

Fibroids are composed of cells and extracellular matrix (ECM) proteins



Zannotti A, et al. (2021) *Cells*.

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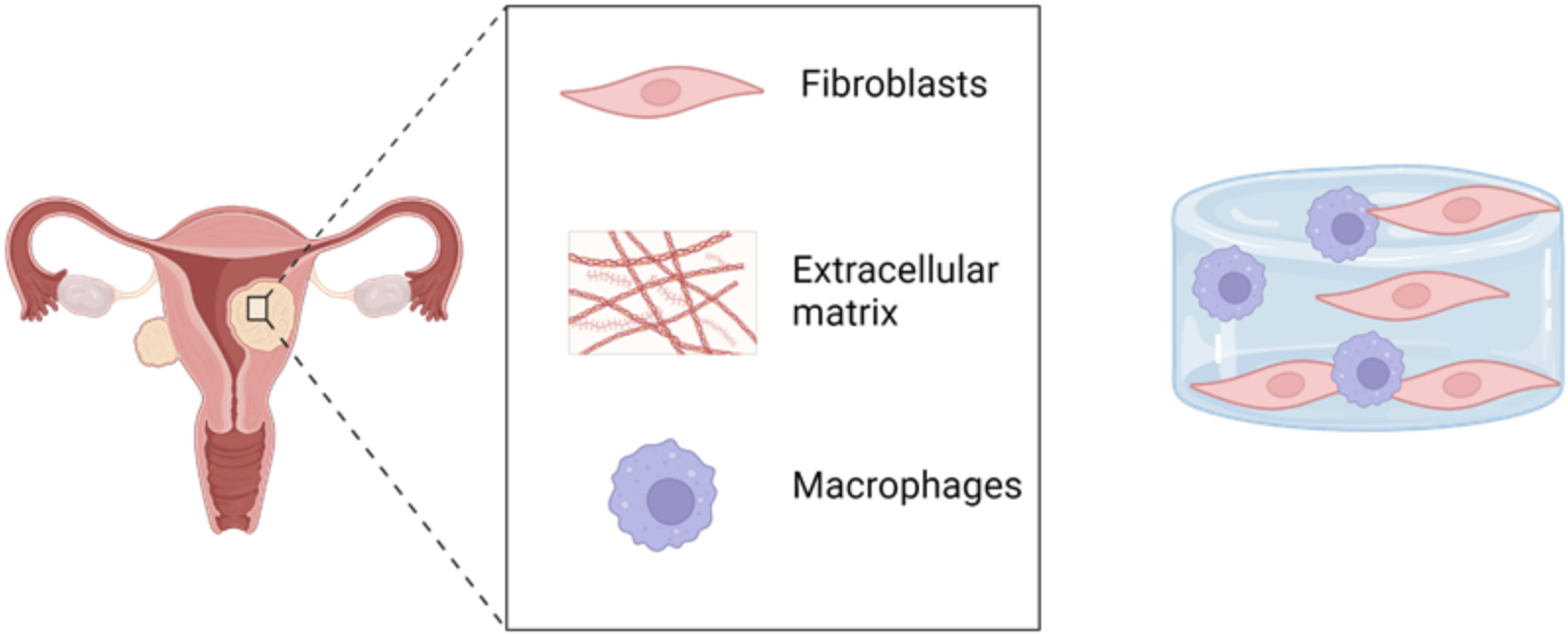
Image made with BioRender

A microphysiological system mimicking the uterine fibroid environment



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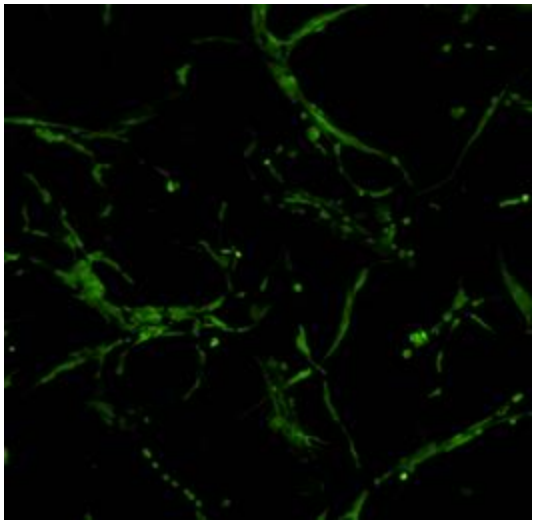
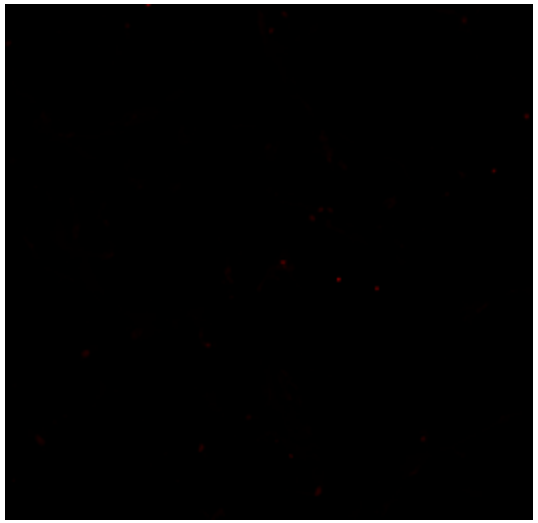
Primary human uterine fibroblasts are viable in our microphysiological system.

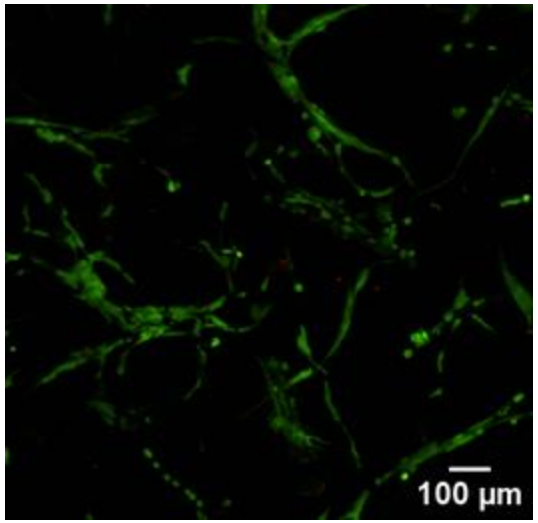
Live



Dead

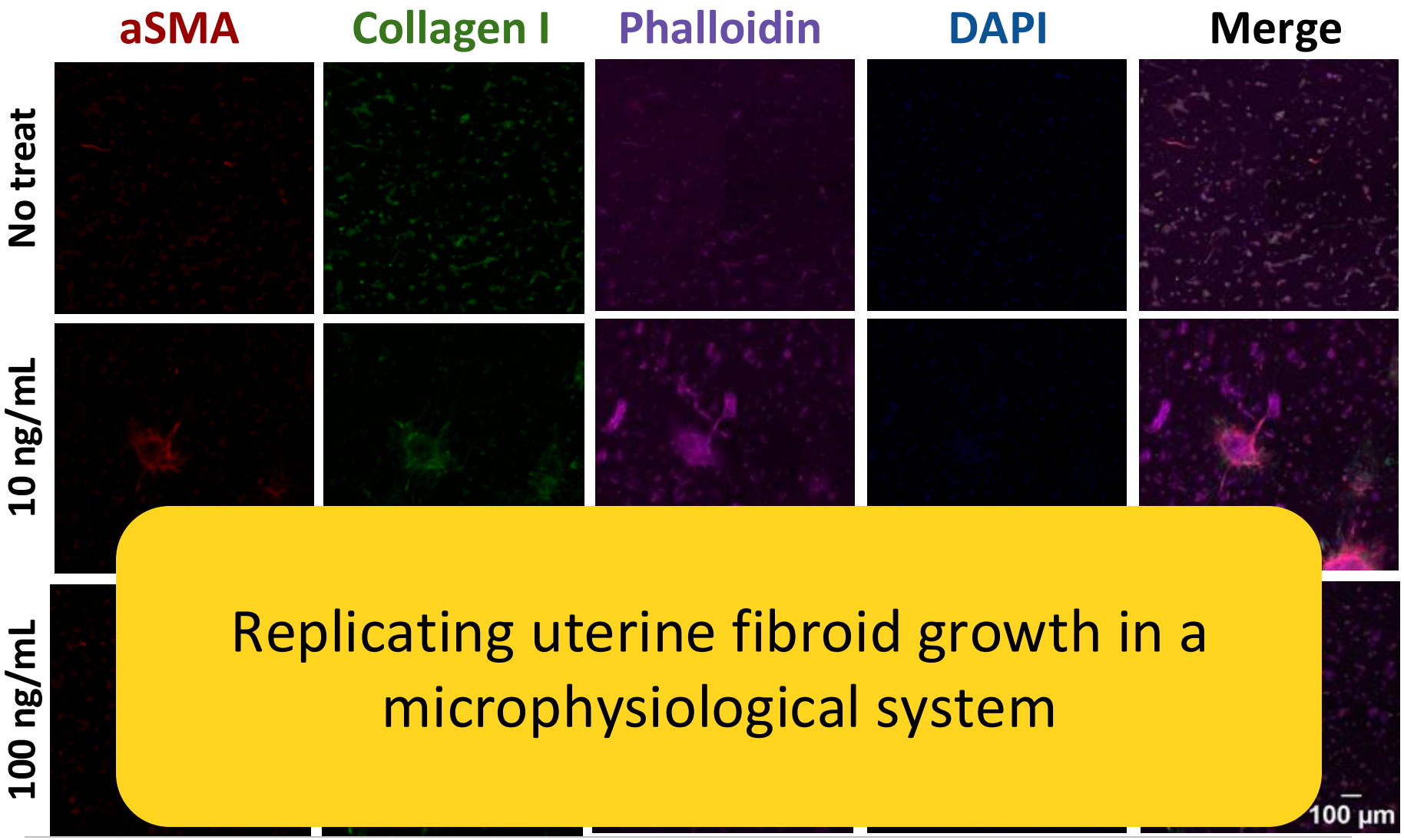


Merge



Live Cells - Calcein-AM
Dead Cells - Et-homodimer

Screening Uterine Fibroblast Response to TGF-B3



Replicating uterine fibroid growth in a microphysiological system

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Holistic framework around precision medicine

- Recruiting patients with specific consideration for self-identified ancestry
- **Consideration of disease and who is burdened by that disease**
- Vendor availability allows us to investigate previously understudied associated dysfunction
- <u>Question: WHO you study and WHY?</u>

https://go.umd.edu/MooreLab

Thank you for the opportunity to share some of our work!

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@DrErikaMoore

Acknowledgements

Trainees who currently POWER the lab

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- Michele Dill
- Lara Larson
- Ally Moses

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- NIH EFRI
- NSF CAREER
- Lupus Research Alliance
- NIH/NINDS R01
- 3M
- NIH/NCATS KL2

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- Connie Mulligan (UF)
- Michelle Petri (JHU)
- Kaitlin Fogg (OSU)

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