I am currently on the traditional homelands of the Piscataway and Nacotchtank tribal nations.

I recognize and acknowledge the ancestors, elders, and relatives/relations past, present and emerging still connected to the land on which we meet today.

Cellular materials

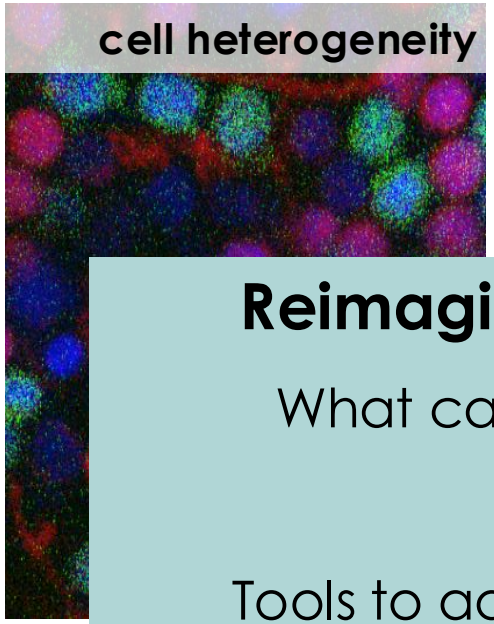
engineering complexity through biomaterial design

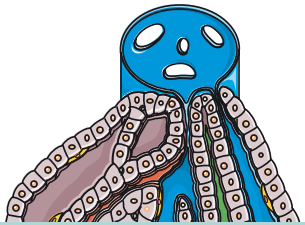
Brendan A.C. Harley

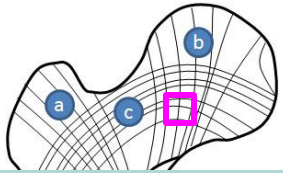
Robert W Schaefer Professor, Dept. of Chemical & Biomolecular Engineering
Program Leader, Cancer Center at Illinois
Co-Director, Center for Gender and Sex in Health
Carl R. Woese Institute for Genomic Biology
University of Illinois at Urbana-Champaign, USA

www.harleylab.org | @Prof_Harley | @profharley.bsky.social

We are inspired by interfaces, transitions, and heterogeneity



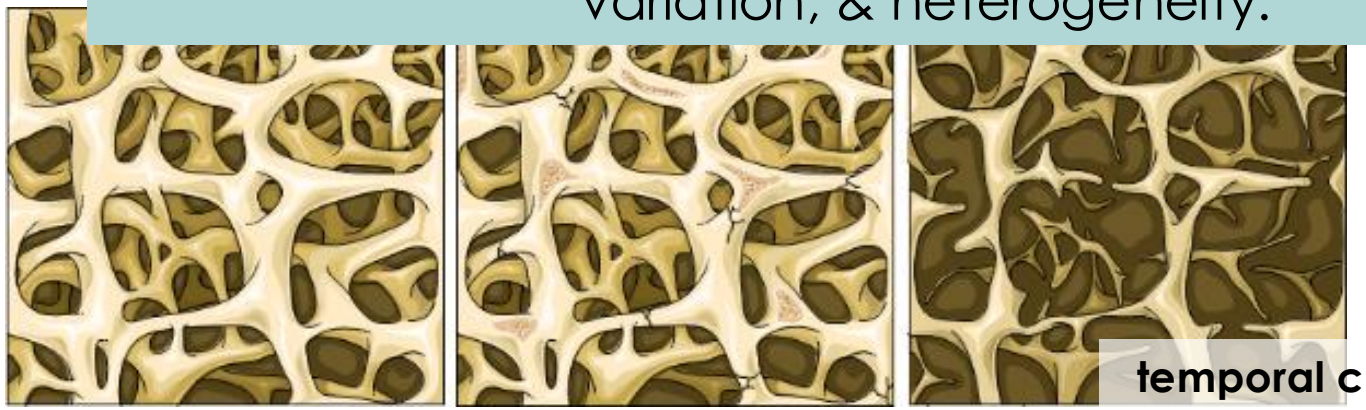


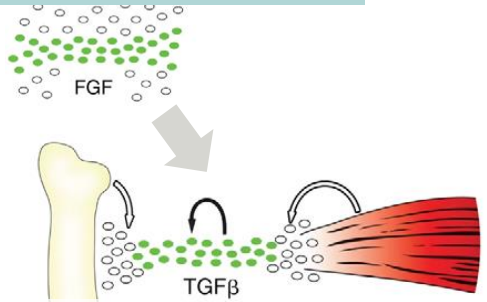


Reimagining biomaterials for the 21st century

What can biomaterials do beyond generalization?

Tools to address questions of health disparities, patient variation, & heterogeneity.





temporal changes

SERVIER

from margin to center**

Precision biomaterials. Complex societal challenges require more than technology solutions. We must account for heterogeneity, plasticity, and social factors.

Making space. Intentional focus on ***centering people*** historically marginalized by our systems and history as well as ***centering projects*** at the margins of current scientific discourse.

Who is left out of the story?

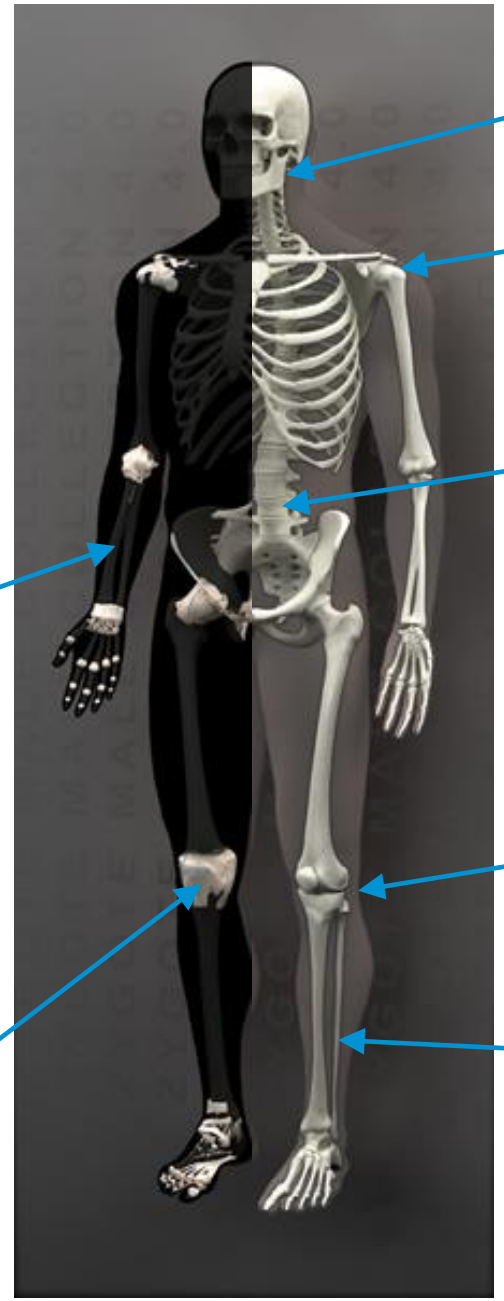
Growth & perspective. The university is a place where we help shape the future of our society. Building and resourcing a vibrant, equitable, and innovative academic ecosystem.

** bell hooks, 1984

Musculoskeletal tissue engineering

what will it take for regenerative therapies to become surgical standard-of-care
modify the tissue engineering triad (biomaterial-cells-morphogens) to consider scalability, hierarchy

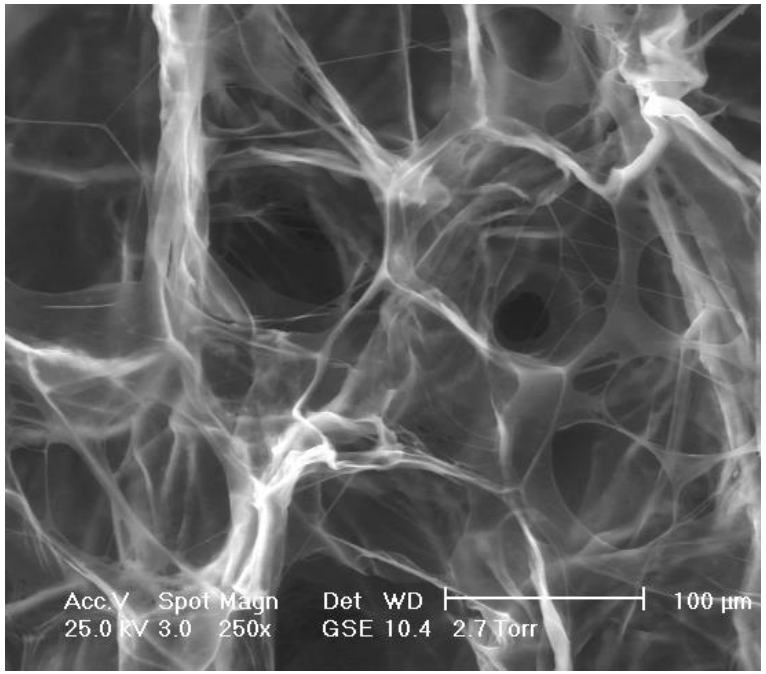
opportunities & challenges
biomaterials as factories of endogenous signals
synthetic circuits & long-range coordination
mechanical reinforcement & surgical practicality
shaping inflammatory response
health disparities & underlying conditions

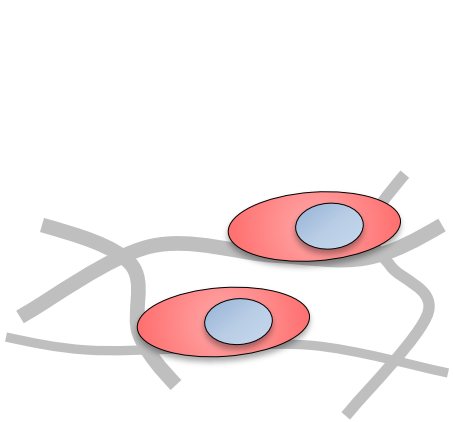


Source: 3DScience.com

Modifying a collagen scaffold to promotes lineage trajectories

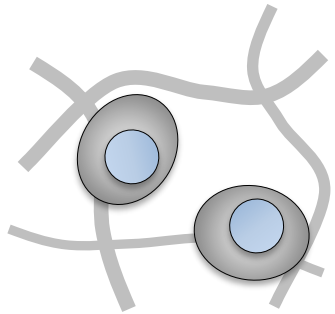
selective alterations to microstructural features of a collagen biomaterial to promote musculoskeletal differentiation



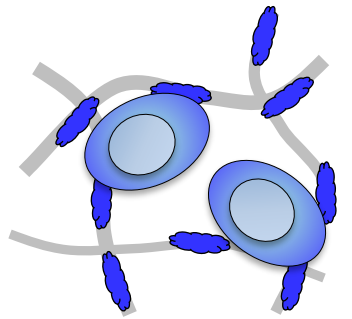


anisotropic

Harley et al., *J Biomed Mater Res,* 2010a,b
Caliari and Harley, *Biomaterials* 2011
Caliari et al., *J Mech Behav Biomed Mater* 2012
Gonnerman et al., *Biomaterials* 2012
Caliari and Harley, *Tiss Eng A* 2013
Hortensius et al., *Biomaterials* 2013
Caliari et al., *Adv Healthc Mater* 2014
Caliari and Harley, *Tiss Eng A* 2014
Grier et al., *J Mech Behav Biomed Mater* 2017
Grier et al., *Connect Tiss Res* 2019
Sun Han Chang et al., *Sci Adv* 2021



isotropic



mineralized

Weisgerber +, *J Mech Behav Biomed Mater 2013*
Weisgerber +, *Biomat Sci* 2015
Ren et al., *Biomaterials* 2015
Lee et al., *J Craniofac Surg* 2015
Ren et al., *Biomaterials* 2016
Weisgerber et al., *J Mech Behav Biomed Mater* 2016
Ren et al., *Adv Healthc Mater* 2016
Zhou et al., *Adv Healthc Mater* 2017
Weisgerber et al., *Tissue Eng A* 2018
Ren et al., *Sci Adv* 2019
Dewey et al., *RSC Adv* 2020
Tiffany et al., *RSC Adv* 2020
Zhou et al., *Macromolec Biosci* 2021
Dewey at al., *Materialia* 2021

Mineralized collagen scaffolds can shape multicellular crosstalk

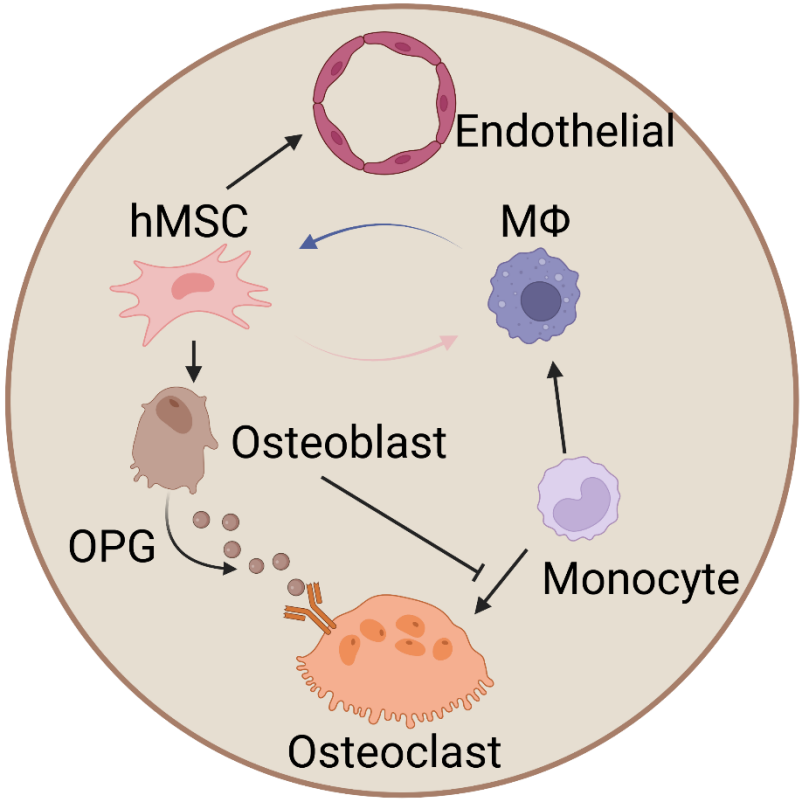
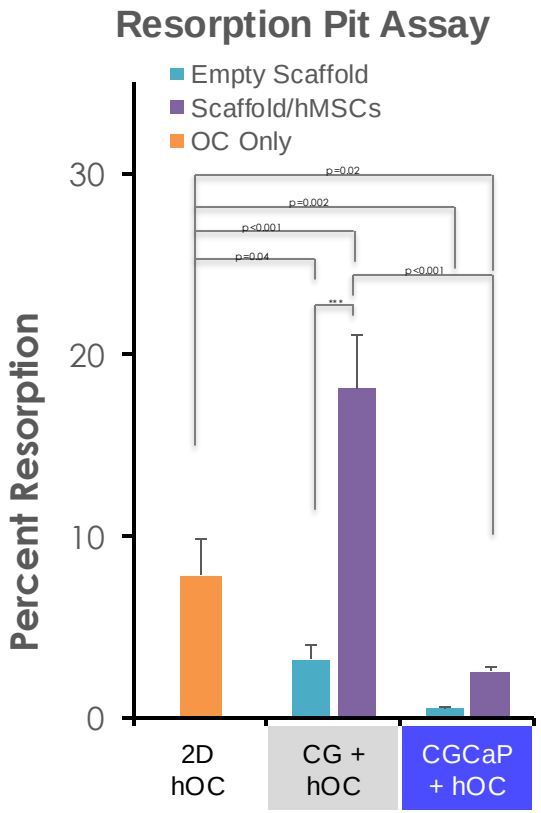


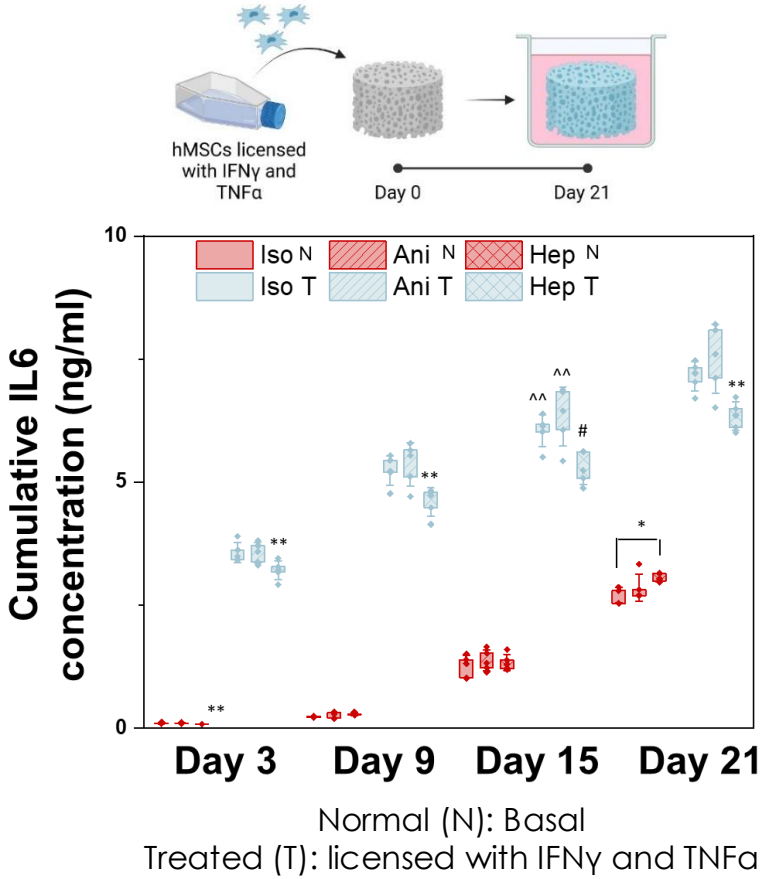
Figure made with BIORENDER

MSCs inhibit osteoclastogenesis



increased OPG production: reduced hOC activity

immunosuppressive capacity of hMSCs



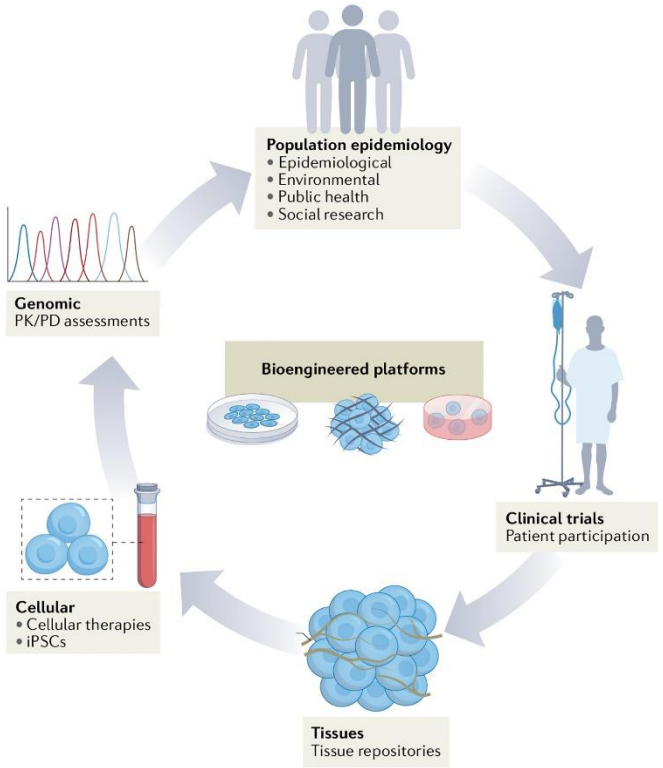
Normal (N): Basal
Treated (T): licensed with IFNγ and TNFα

hMSC IL6 secretion reduced in presence of macrophages (THP-1)

Collaborator: *J. Lee (UCLA/VA), T. Fan (U. Illinois)*

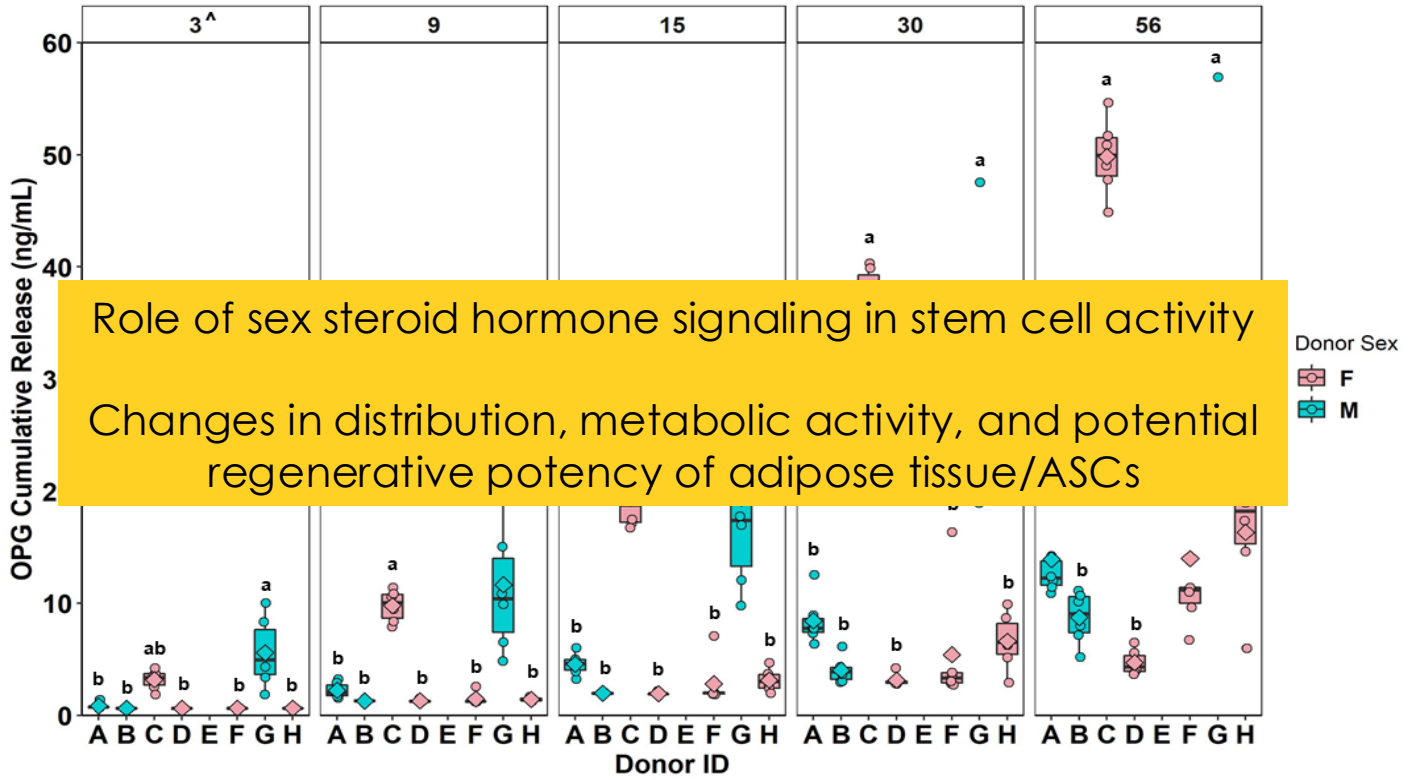
Mineralized collagen scaffolds to understand donor variability

Who is left out?
donor variability | ancestry (biology, genetics, sociocultural factory) | sex



James et al., *Adv. H. Mat.,* 2021 | Shah *et al.*, Am J Physiol Cell Phsyiol., 2014 | Guerrero *et al.*, Scientific Reports, 2018 | Kyeong Lee, BMB Rep., 2018 | Moore et al., Nat. Rev Mater, 2021

ASCs from male donors are more metabolically active for the entire culture period



Role of sex steroid hormone signaling in stem cell activity

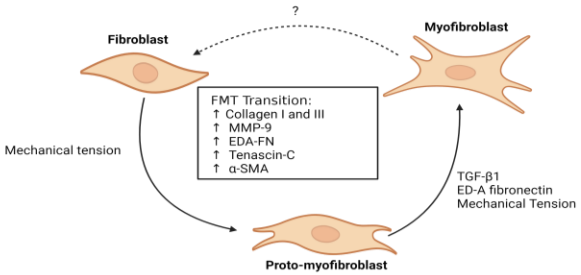
Changes in distribution, metabolic activity, and potential regenerative potency of adipose tissue/ASCs

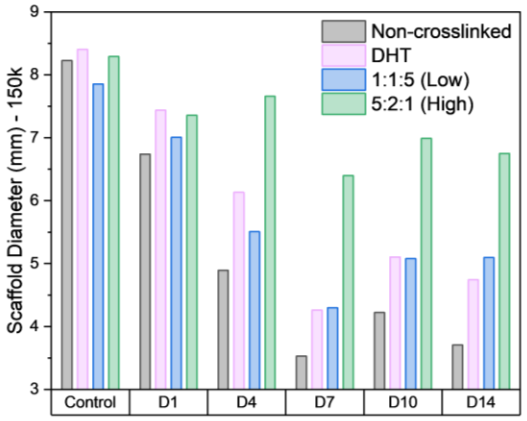
ASCs from female donors have higher ALP activity than male donors beginning at Day 15

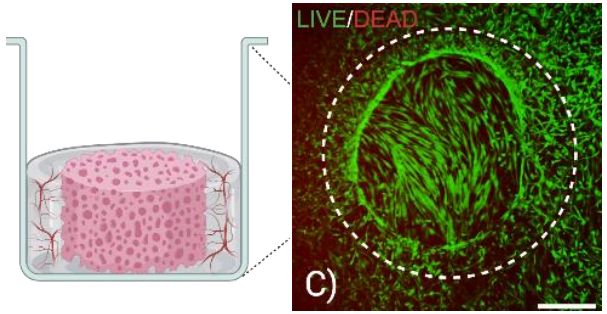
Scaffolds seeded with ASCs from female donors contained increased Ca and P content

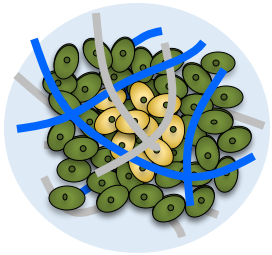
Emerging opportunities in musculoskeletal tissue engineering

ehlers-danlos syndrome | donor variability | sex steroid hormones | amniotic membrane



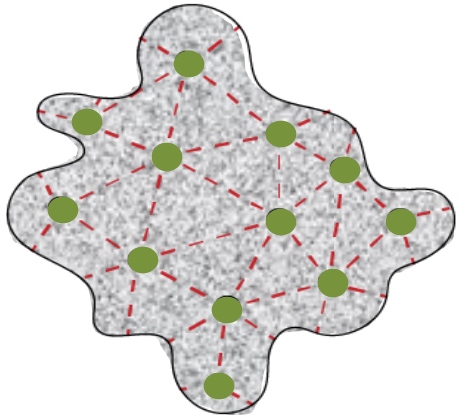


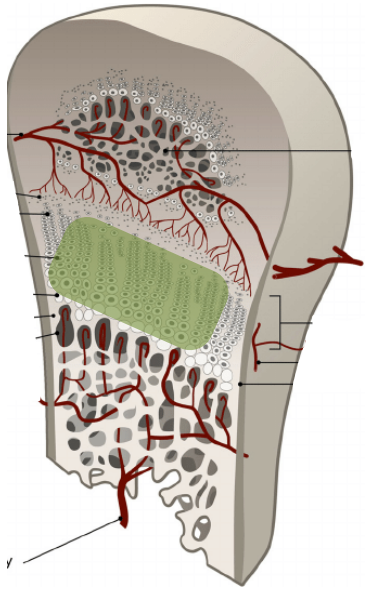




endogenous factory of biomolecules, vesicles, & cells | synthetic cells | wound models | spatial/temporal sequencing

synthetic growth plate | scalable solutions based on assembloids





Collaborators: *C. Laukaitis (Illinois); K. Spiller (Drexel); N. Willett & B. Guldberg (Oregon); N. Hickock (TJU); M. Killian (Michigan)*

The endometrium is a dynamic mucosal tissue that lines the uterus and undergoes remodeling over the course of a menstrual cycle

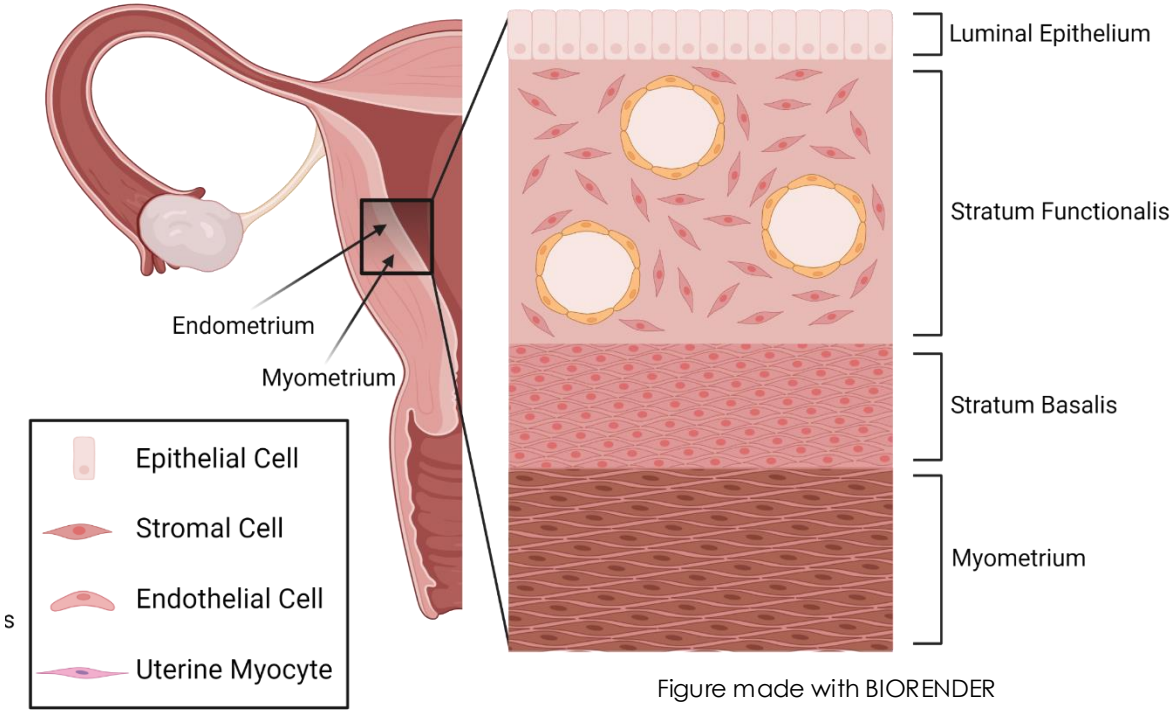


Figure made with BIORENDER

Multi-fold health challenges

Preeclampsia hypertensive disorder (2-8%, globally). Insufficient trophoblast invasion leading to poor placentation is believed to be a significant driver.

Endometriosis poorly understood role of legion activity (stress, inflammatory status, stigma, pain).

Endometrial cancer progression, therapeutic intervention.

Broader gender/sex considerations

Health disparities | race/ethnicity | intersectional identities

psychosocial stressors and hormone set-points

trans/non-binary | intersex health concerns

reflexive bioengineering via critical studies collaborations

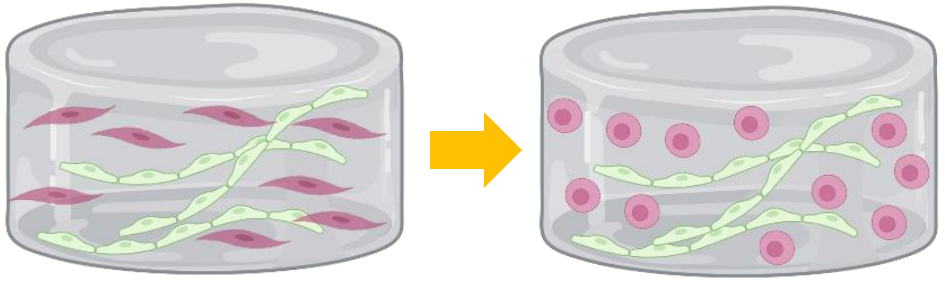
Collaborators: *K. Clancy, R. Nowak, G. Underhill (Illinois); G Dveksler (USUHS); M. Oyen (WUStL)*

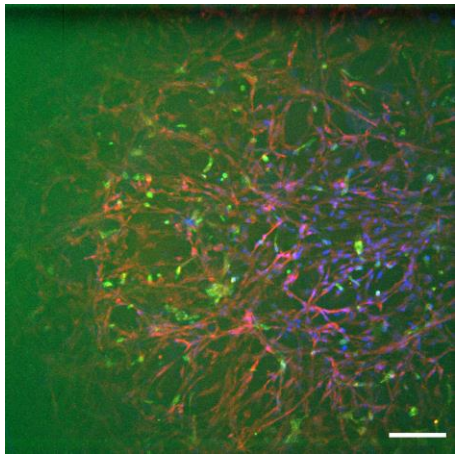
Aplin, The Endometrium, 2008 | Cha et al., *Nat Med*, 2012 | GBD 2015 Maternal Mortality Collaborators, *The Lancet*, 2016

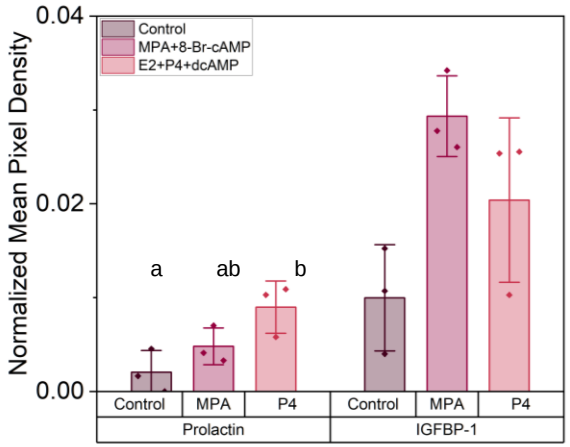
Decidualized endometrial models and matrix-induced chirality

Need: Decidualization and trophoblast activity

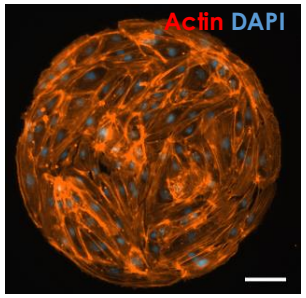
Human Endometrial Microvascular Endothelial Cells (HEMECs)
Human Endometrial Stromal Cells (HESCs)



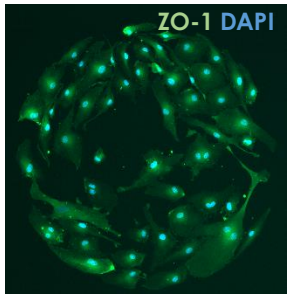




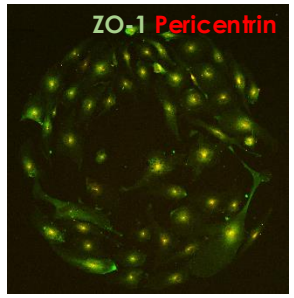
Design rules: Chirality and endometrial endothelial cells

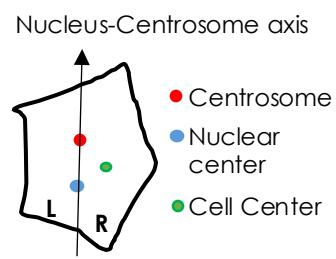


Stress Fiber Alignment

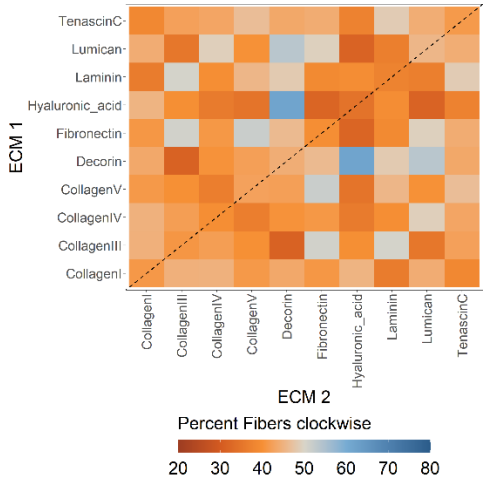


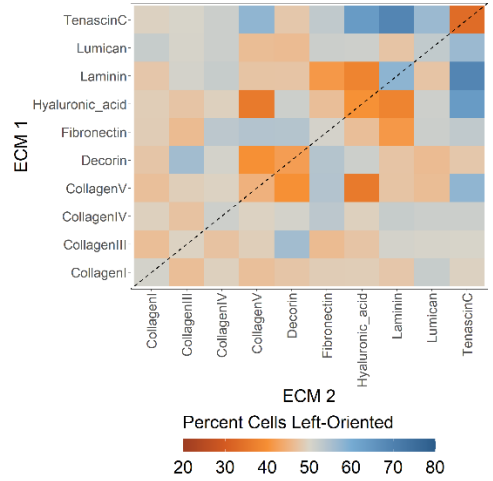
Cell boundary-based cell alignment





Nucleus-centrosome based LR alignment

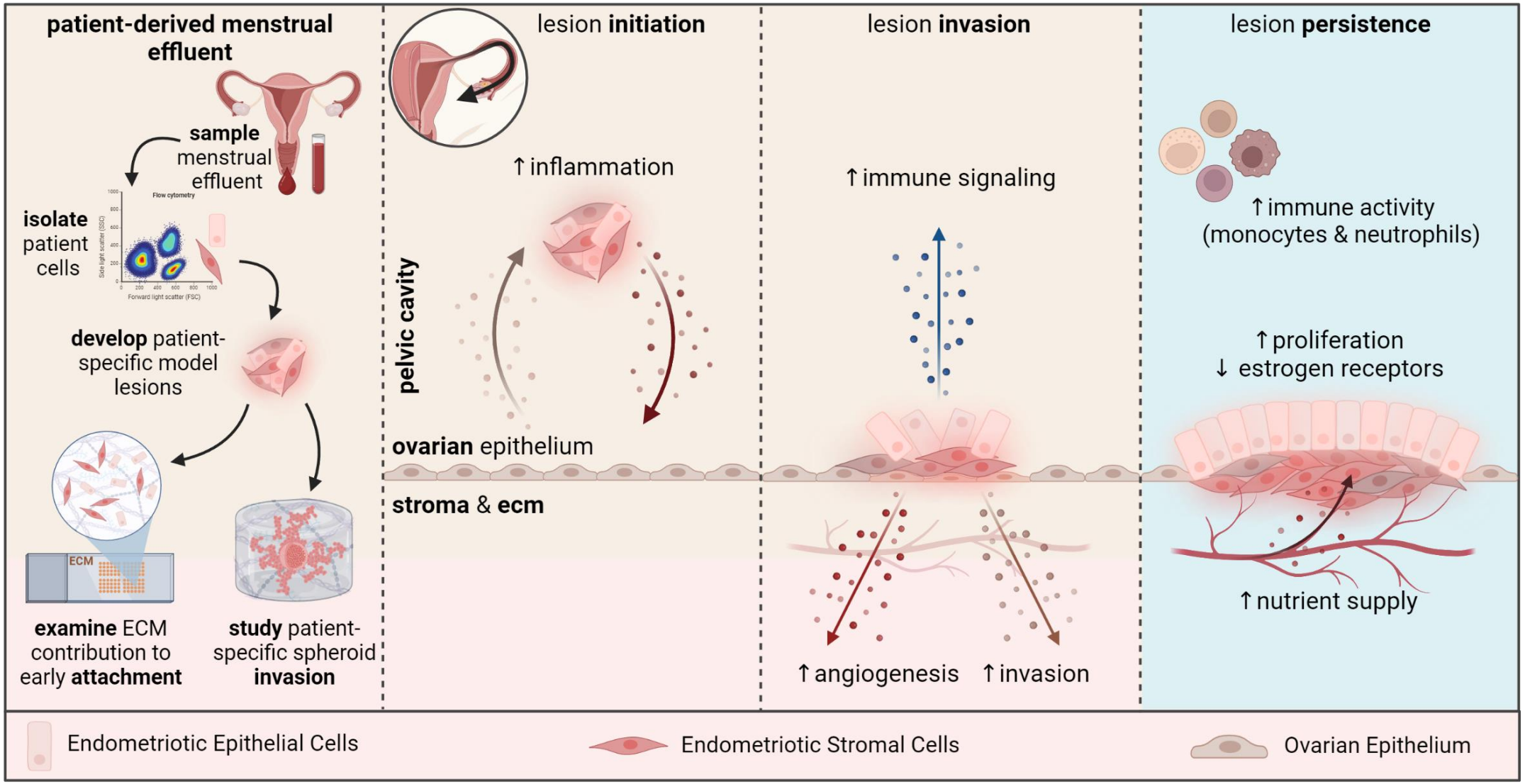




Collaborators: *K. Clancy, G. Underhill, R. Nowak (Illinois)*

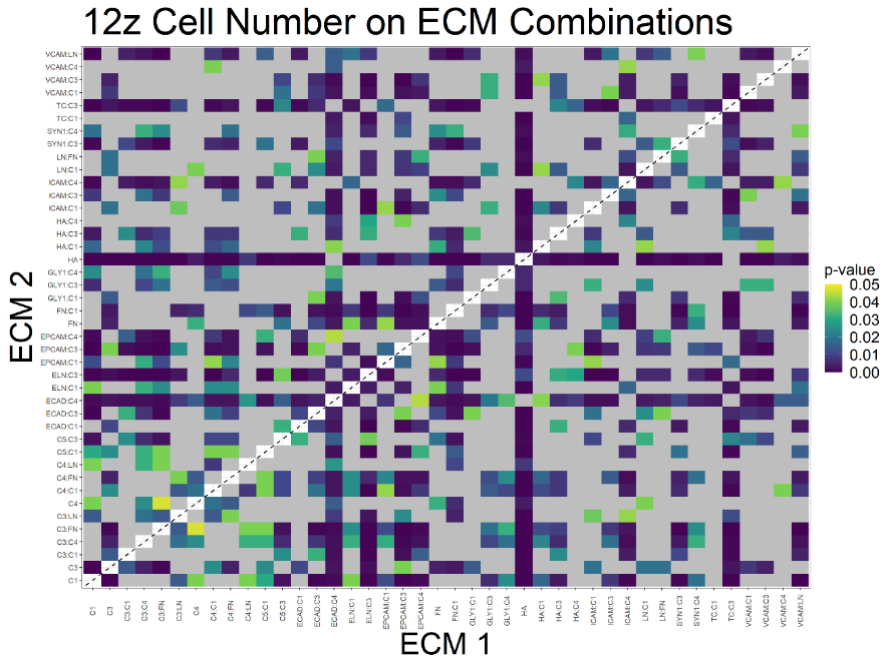
Zambuto et al., *Interface Focus*, 2019 | Zambuto et al., *ACS Biomater Sci*, 2022 | Zambuto et al., *npj Women's Health*, 2024 | Zambuto et al., *Adv. Healthc. Mater.*, 2024

Endometrioma: ovarian lesion microenvironment



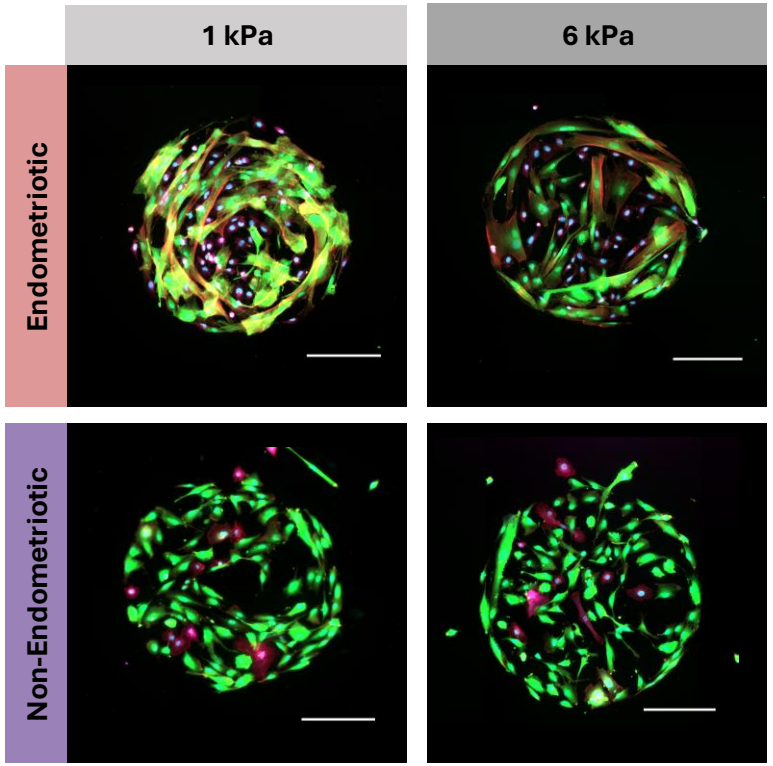
Collaborators: *K. Clancy, G. Underhill, R. Nowak (Illinois)*

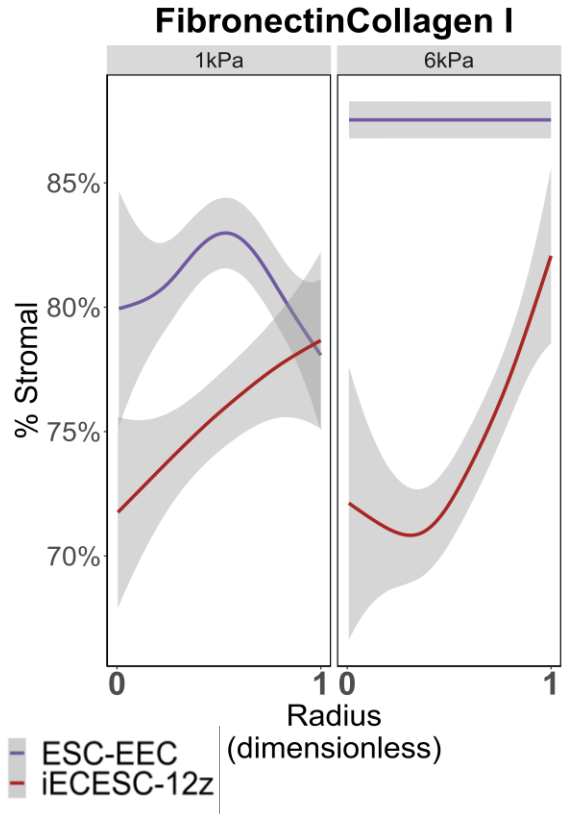
Matrix signals strongly influence endometriotic adhesion & patterning



Matrix combinations strongly influence 12z (endometriotic) epithelial adhesion vs. healthy hEECs.

Stiffness and ECM explains more of the variance in 12z attachment vs. EEC,



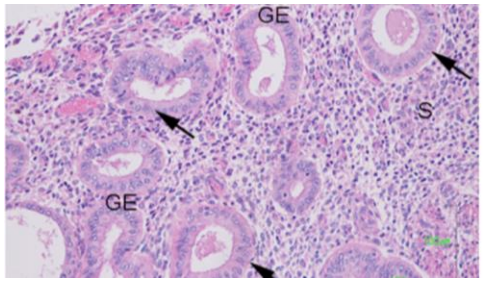


Increased adhesion of endometriotic epithelial and stromal cells cohorts on ovarian-specific matrix environment; co-culture increases endometriotic stromal cell actin expression

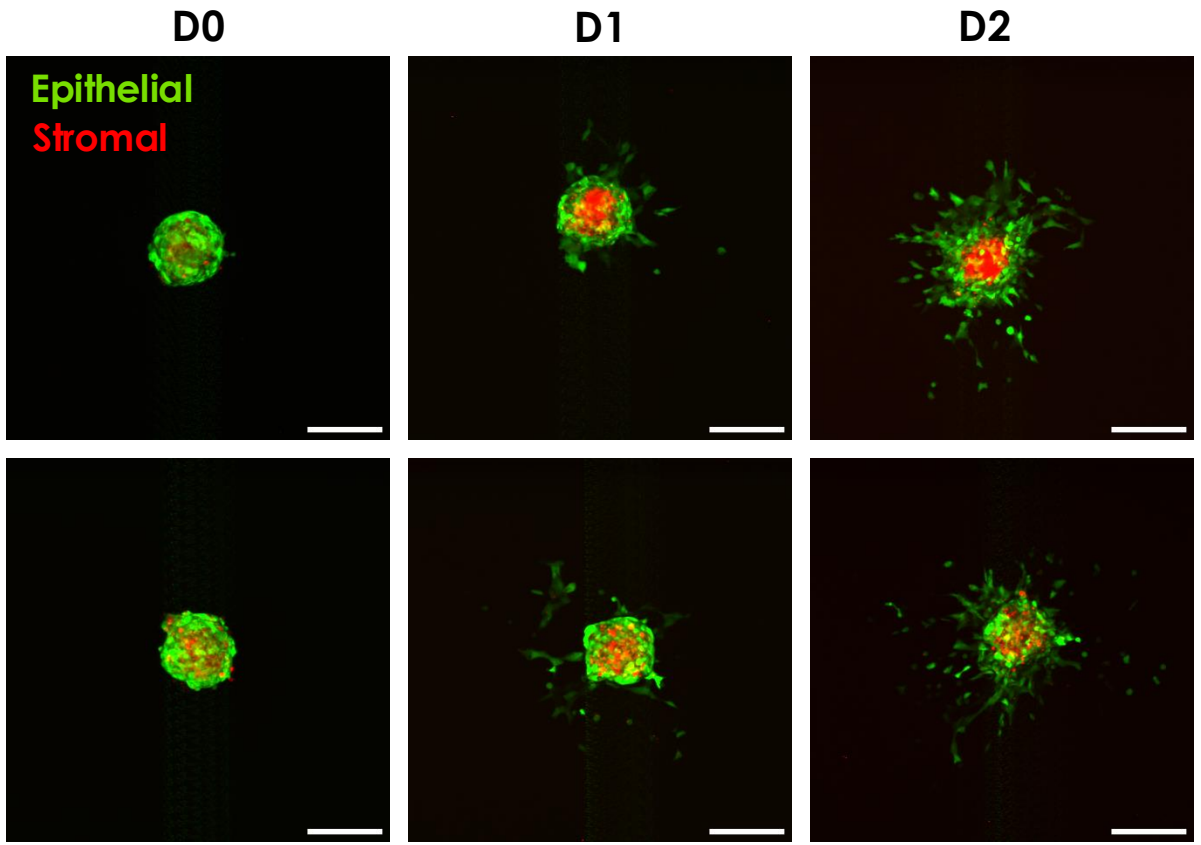
Define patterns of endometrioma invasion via multicellular spheroids

Ratios 0:100, 75:25, 50:50, 25:75, & 100:0 (**epithelial to stromal**)

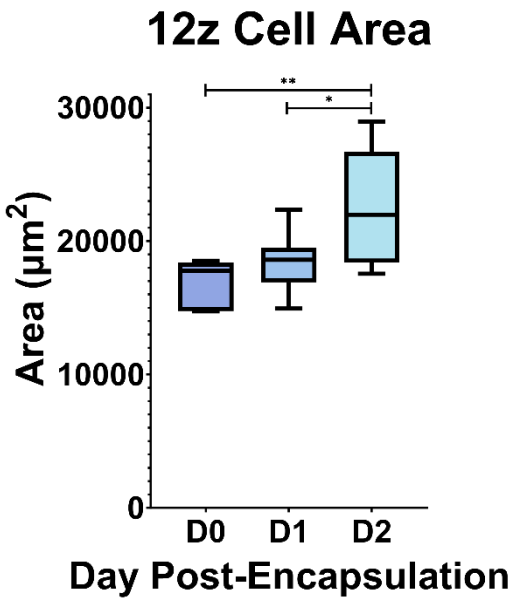
Increased outgrowth was observed with the **25:75** ratio.



Franco-Murillo. Y. *Reprod Sci.* (2015)



Epithelial: pLL-EF1a-RFP-T2A-Blast Lenti-Labeler (SystemBiosciences)



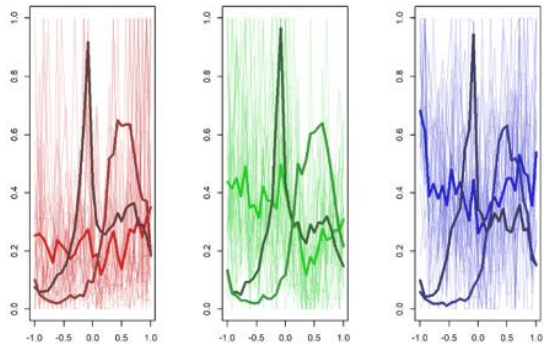
Endometriotic epithelial & stromal cells self-assemble into multi-layered spheroids with an epithelial shell

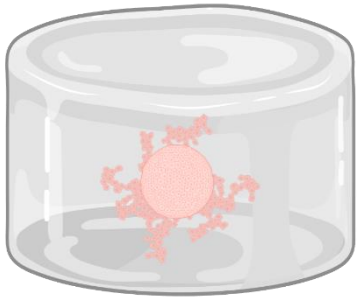
Endometriotic epithelial cells shown significant invasive phenotype

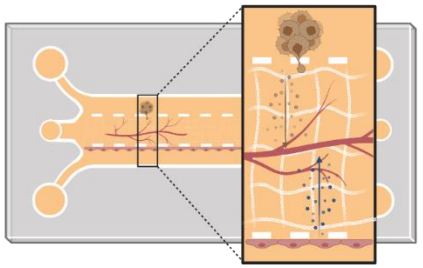
Future: Decidualized endometrial models & menstrual effluent inputs

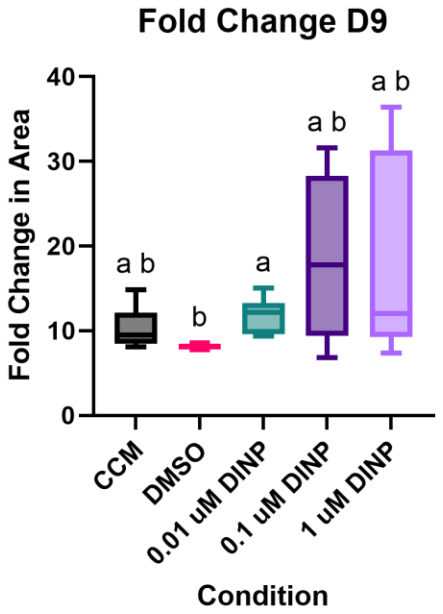
Emerging opportunities to create decidualized endometrial/endometrioma models using menstrual effluent

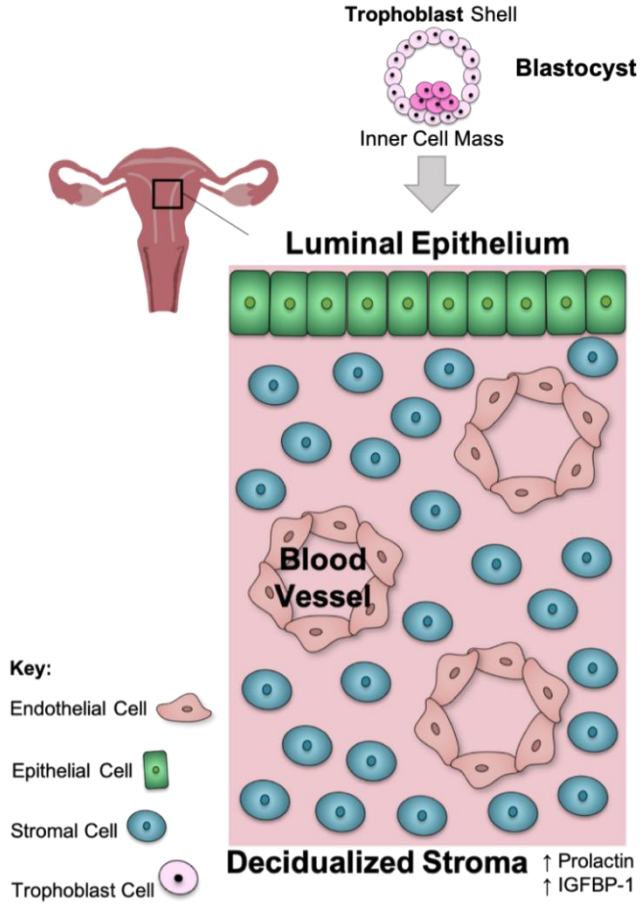
Overlap between hypothalamic-pituitary-adrenal & hypothalamic-pituitary-ovarian axes: *cortisol and phthalates influencing trophoblast vs. endometriotic cell invasion*











Collaborators: *K. Clancy, G. Underhill, R. Nowak (Illinois)*

Gender/sex. initiatives that move beyond women's health

Gender/sex: Sex is a multifactorial phenomenon that relates to hormones, gonads, chromosomes, and more. And gender is a personal and social construction relating to identity, expression, and lived experiences of inequality.

CGSH: develop shared understanding of gender/sex; how gender/sex relates to social determinants of health; intersecting lived experiences around race, ethnicity, class, and disability.

Donor variability

Is there biological reality? Strategies to consider degree of similarity/difference. Do biomaterial solutions need to account for this variability?

Biology is not binary

Need a more capacious definition (vs. Western binary)

Who is excluded when using a narrow definition of women's health?

Transgender men who retain uterus/endometrium. Transgender women: increased risk of lupus, breast cancer. Intersex patients.

HARLEYLAB
UNIVERSITY OF ILLINOIS

Alumni
Dr. Tori Barnhouse (PhD)
Prof. Steven Caliari (PhD)
Dr. Emily Chen (PhD)
Dr. Ji Sun Choi (PhD)
Prof. Marley Dewey (PhD)
Dr. Seema Ehsan (postdoc)
Dr. Nate Gabrielson (postdoc)
Prof. Aidan Gilchrist (PhD)
Dr. Bill Grier (PhD)
Dr. Rebecca Hortensius (PhD)
Dr. Bhushan Mahadik (PhD)
Dr. Laura Mozdzen (PhD)
Prof. Mai Ngo (PhD)
Dr. Jackie Pence (PhD)
Dr. Julio Serrano (PD)
Dr. Raul Sun Han Chang (PhD)
Dr. Aleczandria Tiffany (PhD)
Dr. Dan Weisgerber (PhD)
Prof. Samantha Zambuto (PhD)
Dr. Aliki Kolliopoulos (PhD)
Dr. Tamaki Yokohama-Tamaki
Emily Gonnerman (MS)
Yoanna Ivanova (MS)
Willencia Louis-Charles

Facilities
Carl R. Woese Institute for Genomic Biology
Cancer Center at Illinois

ILLINOIS

Collaborators
Ryan Bailey (Michigan)
Rohit Bhargava (Illinois)
Kate Clancy (Illinois)
Brian Cunningham (Illinois)
Gabriela Dveksler (USUHS)
Tim Fan (Illinois)
Virginia Ferguson (Colorado)
Andrés García (Ga Tech)
H. Rex Gaskins (Illinois)
Paul Hergenrother (Illinois)
Scott Hollister (Ga Tech)
Princess Imoukhuede (U. Wash.)
Roger Kamm (MIT)
Megan Killian (Michigan)
Mary Kraft (Illinois)
Justine Lee (UCLA/VA)
Yi Lu (Illinois/UT Austin)
Romana Nowak (Illinois)
Michelle Oyen (WUStL)
Nicholas Peppas (Texas-Austin)
Heidi Phillips (Illinois)
Rebecca Riggins (Georgetown)
Simon Rogers (Illinois)
Jann Sarkaria (Mayo)
Ramille Shah (Dim. Inx)
Kara Spiller (Drexel)
Gregory Underhill (Illinois)
Amy Wagoner Johnson (Illinois)
Hua Wang (Illinois)
Matt Wheeler (Illinois)
Muhammad Zaman (BU)

NIH
R01 CA256481
R01 DE030491
R01 AR077858
2R01 DK099528
R01 DE029234
R01 AR078892
R01 CA279195
R21 DK131751

NSF
MRI DMR 1726634
CAREER 1254738
EAGER 1547811
DMR 1105300

GRFP

PROTECT PROJECT SUSTAIN

W81XWH-16-1-0566
U.S. Army Medical Research & Materiel Command

MAYO CLINIC & ILLINOIS ALLIANCE For Technology-Based Healthcare

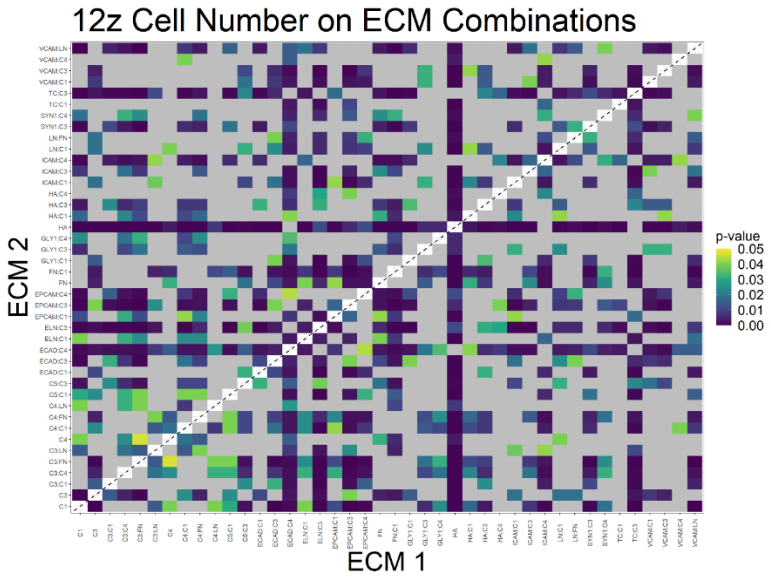
ILLINI 4000 Fighting Cancer on Two Wheels

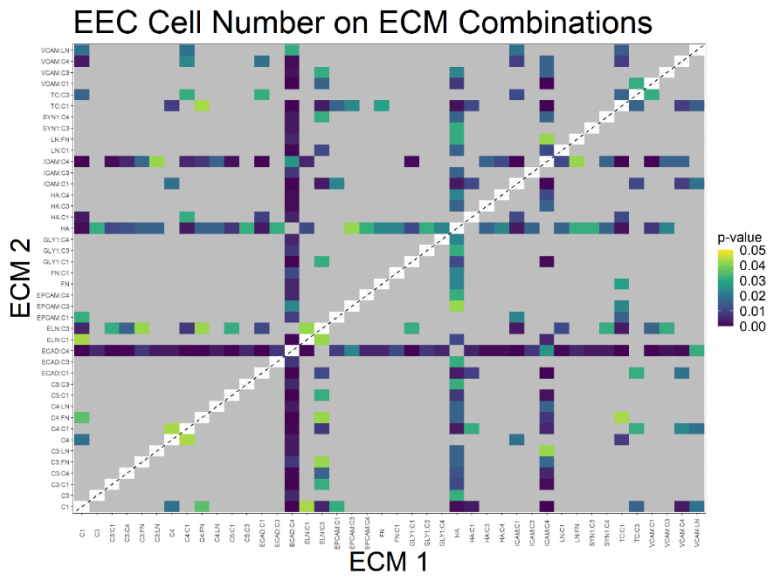
AO Foundation

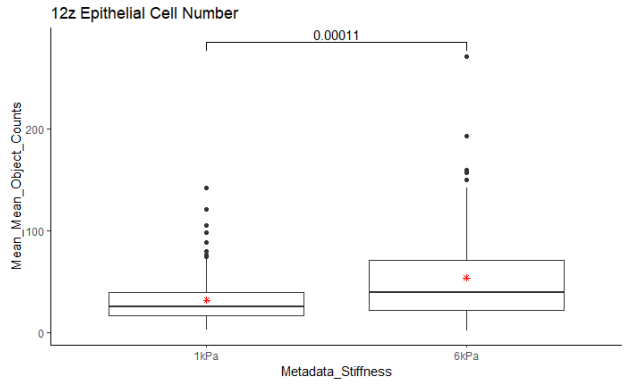
American Cancer Society

Matrix signals strongly influence endometriotic epithelial attachment

Human Endometriotic Epithelial-like Cells (12z) vs, Endometrial Epithelial cells(EEC)



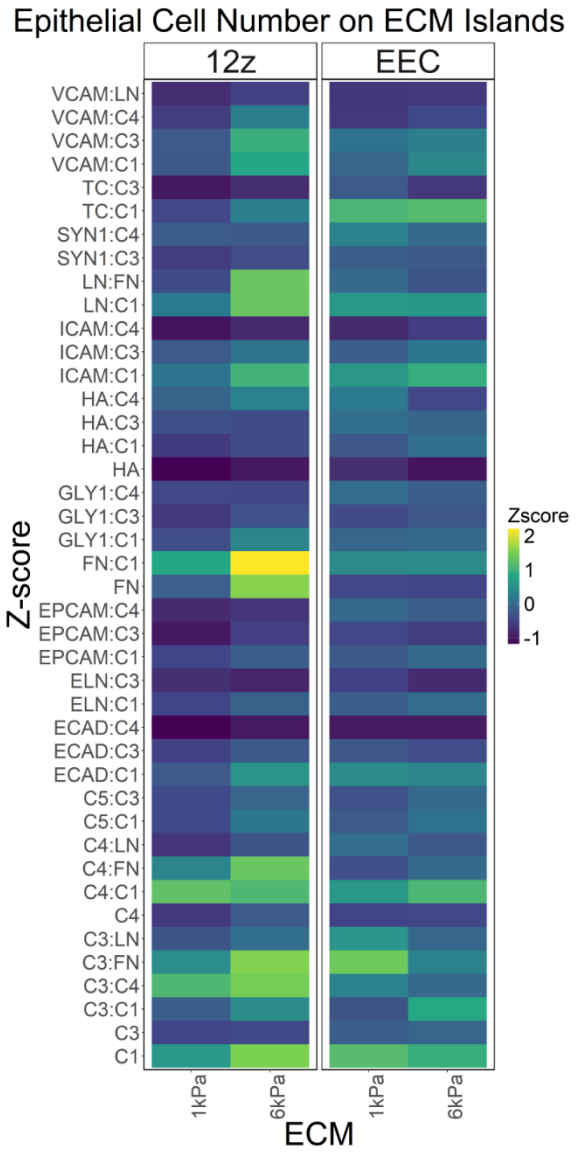




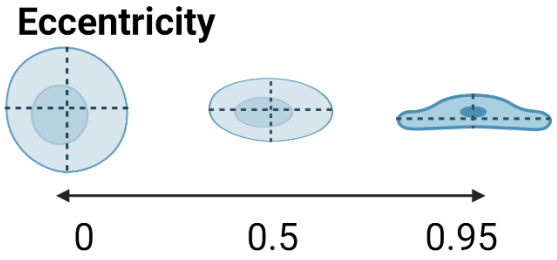
Non-parametric Wilcoxon test: matrix combinations strongly influence 12z (endometriotic) attachment vs. healthy hEECs.

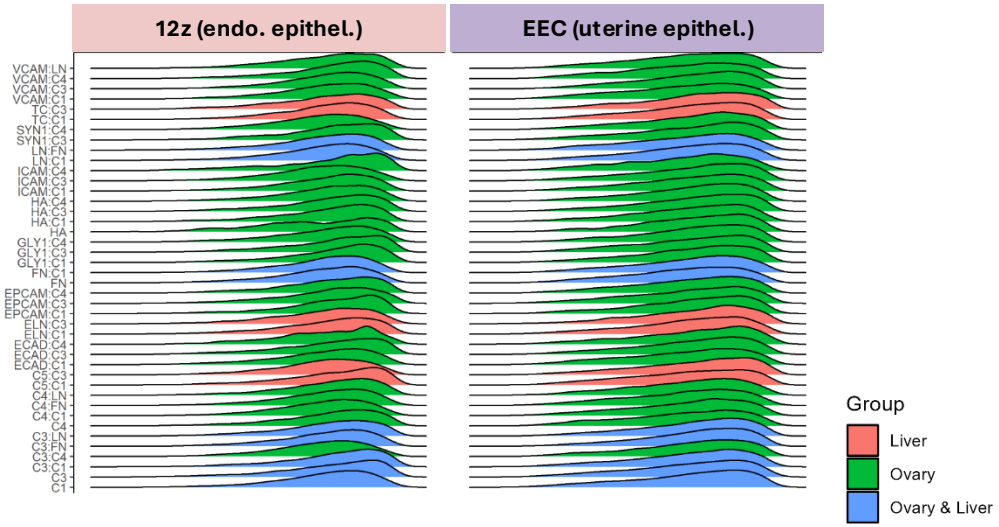
Stiffness significantly influences 12z endometriotic epithelial attachment (6 kPa > 1 kPa).

Linear mixed-effects model (lmer/R): stiffness and ECM explains more of the variance in 12z attachment vs. EEC (variation explained by biological replicates)

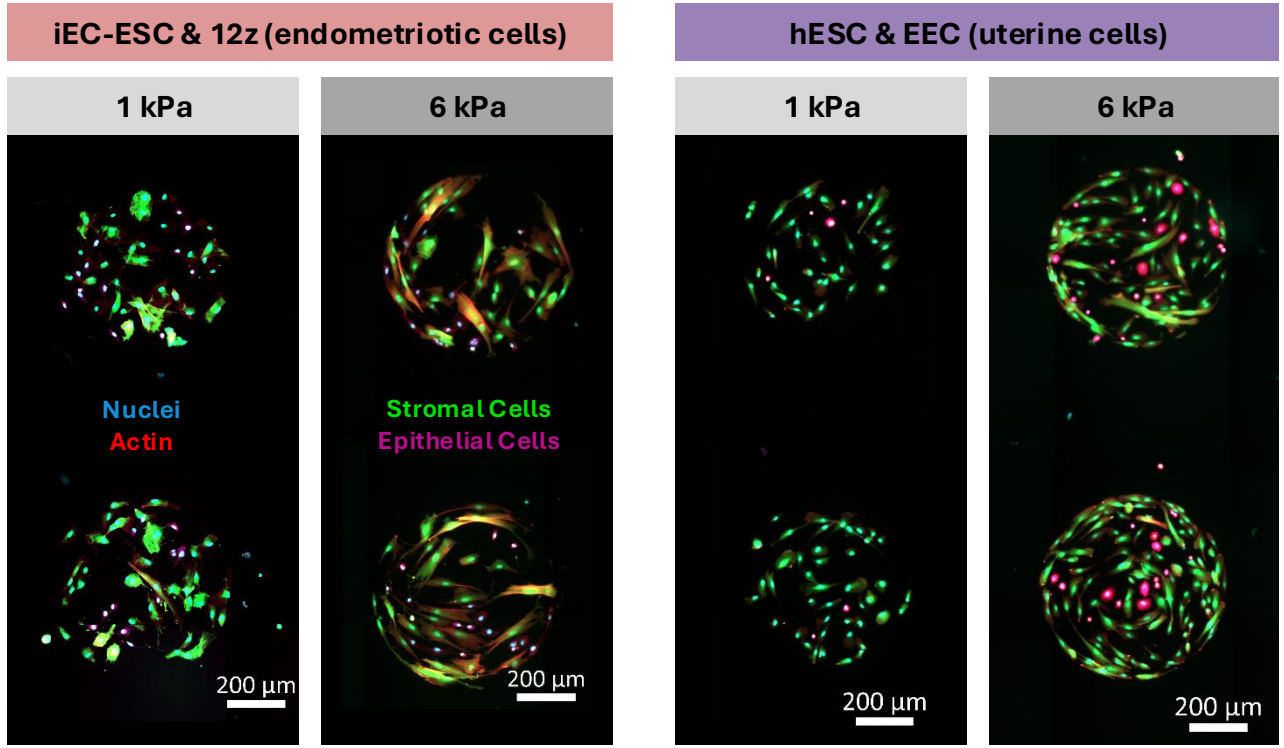


Ongoing: patterns of cell eccentricity and multicellular interactions





ECM composition significantly affects eccentricity while stiffness (6 vs 1kPa) did not



Increased adhesion of endometriotic epithelial and stromal cells cohorts on ovarian-specific matrix environment (COLIV-SYN1); co-culture increases endometriotic stromal cell actin expression