



# **Advancing Skin-on-a-Chip Models: Integrating Human-Relevant Cellular and Biomechanical Complexity**

**Erbil Abaci, Ph.D.**

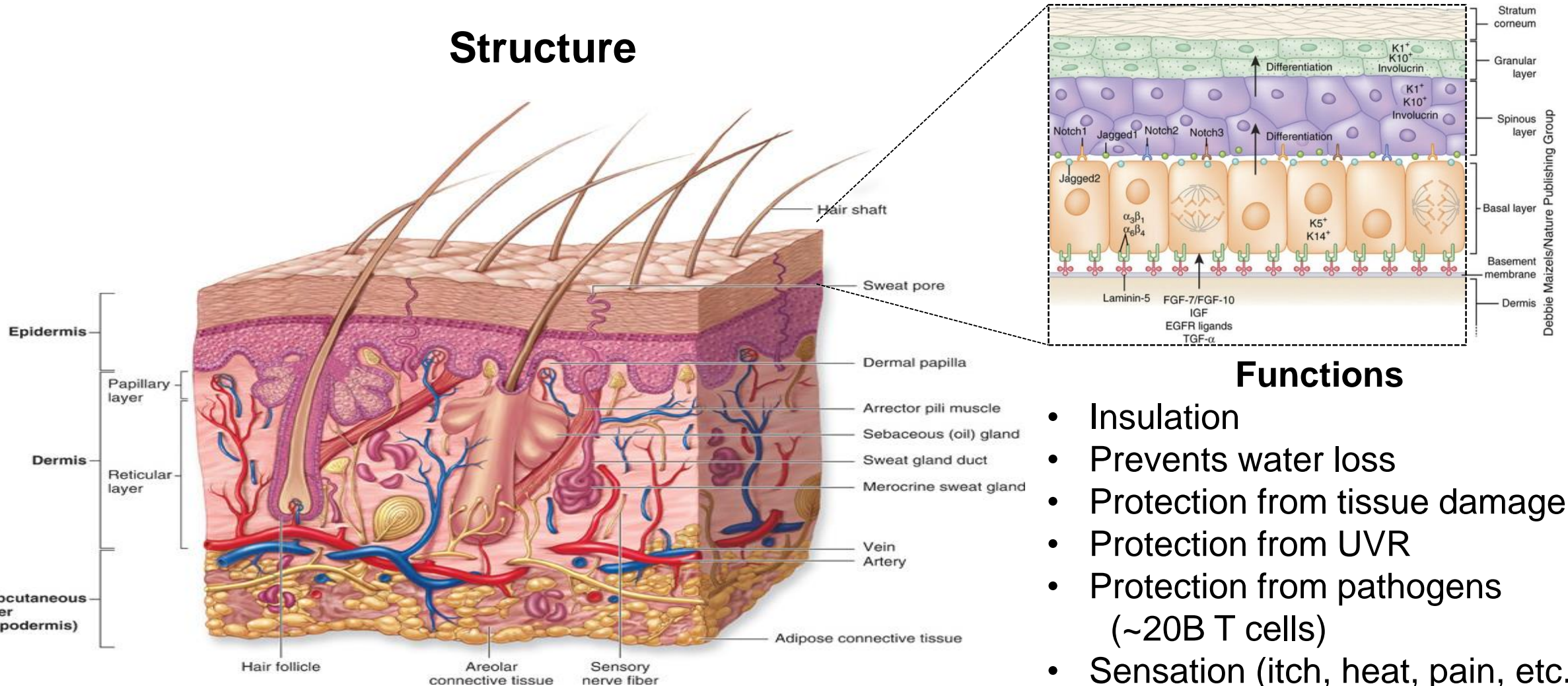
**Assistant Professor,**

**Department of Dermatology and  
Biomedical Engineering  
Columbia University Irving Medical Center, New York**

**12/10/2024, Penn State Uni.**

# Human Skin with Complex Structure and Functions

## Structure



## Functions

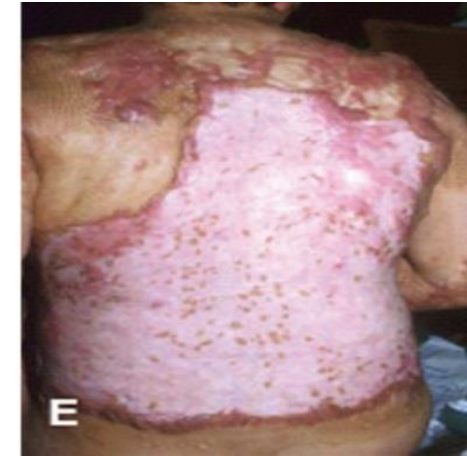
- Insulation
- Prevents water loss
- Protection from tissue damage
- Protection from UVR
- Protection from pathogens (~20B T cells)
- Sensation (itch, heat, pain, etc.)
- Temperature regulation (sweating, vessel constriction)

# Applications of Bioengineered 3D Skin

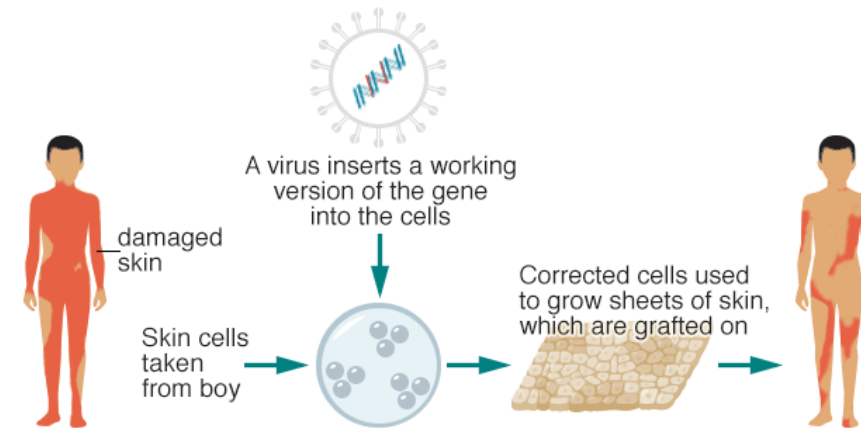
- Clinical application as skin grafts
  - Patients with large wounds (>50% of body surface)
  - Burns and traumatic wounds
  - Genetic diseases, e.g., epidermolysis bullosa



Day 28



Day 479



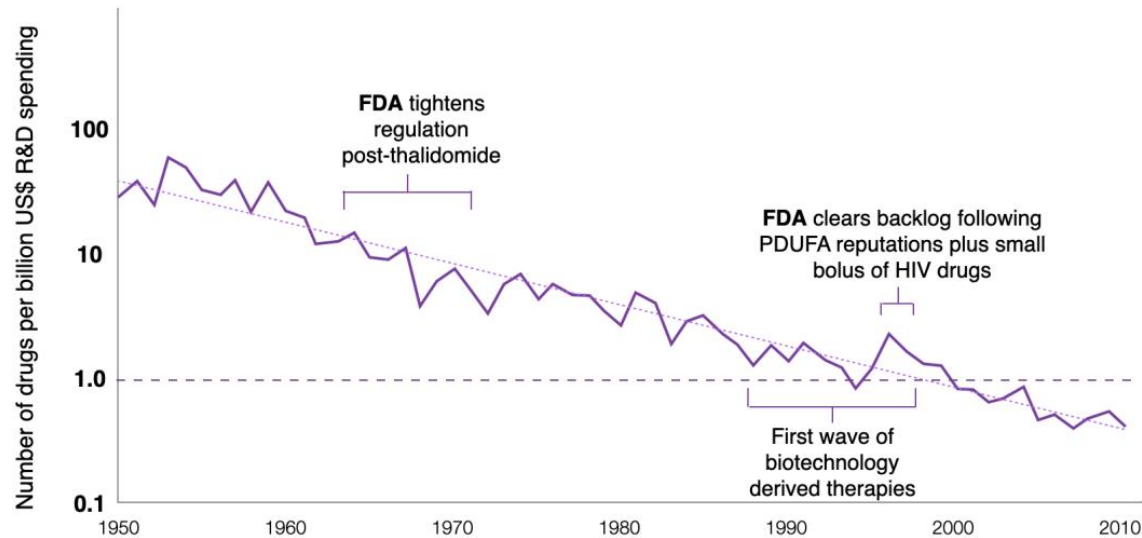
Source: Nature

Boyce ST, et al. *J Trauma*. 2006;60(4):821-9. Hirsh. *Nature*. 2017

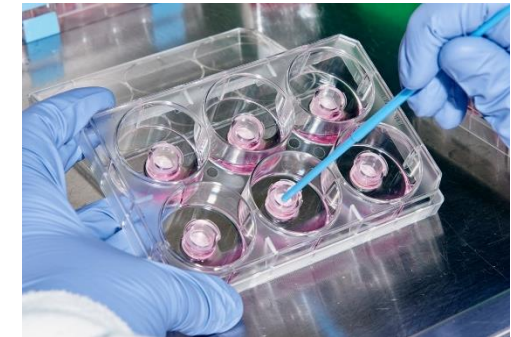


# Applications of Bioengineered 3D Skin

**95% of drugs that work in animal tests fail in human trials!**



**Eroom's Law:** The cost of developing a new drug roughly doubles every nine years (inflation-adjusted)



- Since 2023, US Food and Drug Administration (FDA) no longer requires testing of drugs on animals prior to clinical trials

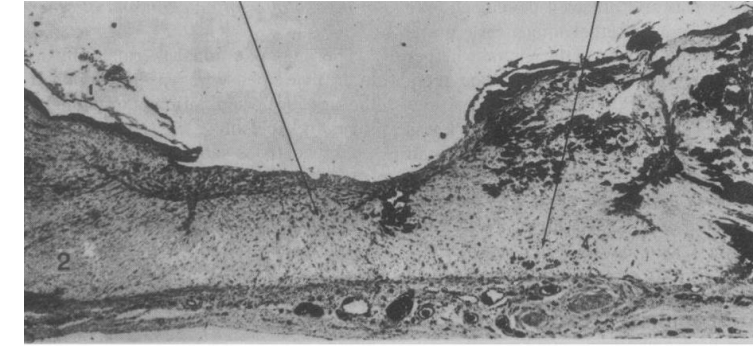
Scannell JW, et al. *Nat Rev Drug Discov.* 2012;11(3):191-200.

[prime.peta.org](http://prime.peta.org)

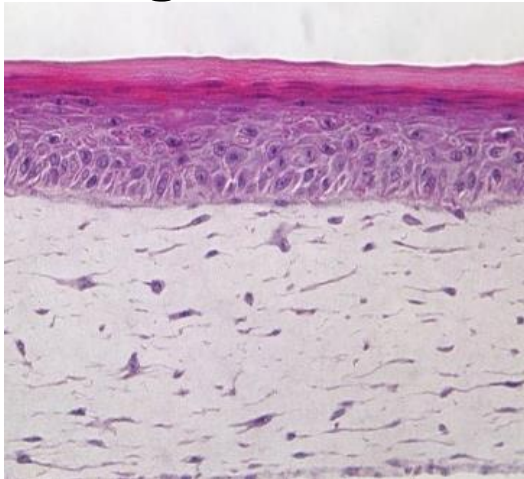
[wired.com](http://wired.com)

# Skin is the First “Bioengineered Organ”

- Howard Green and James Rheinwald isolated and cultured keratinocytes *in vitro* from a skin biopsy
- Eugene Bell engineered the first full-thickness skin equivalent



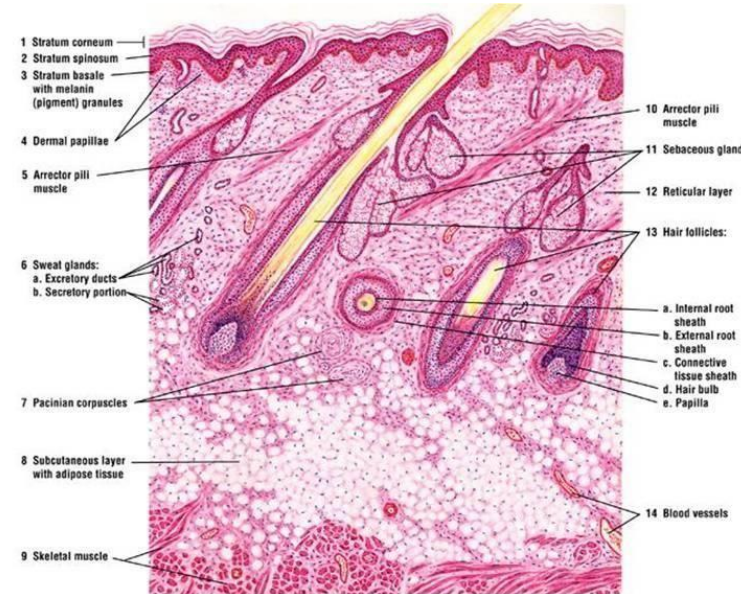
## Bioengineered 3D Skin



Fibroblasts  
Keratinocytes

VS

## Human Skin

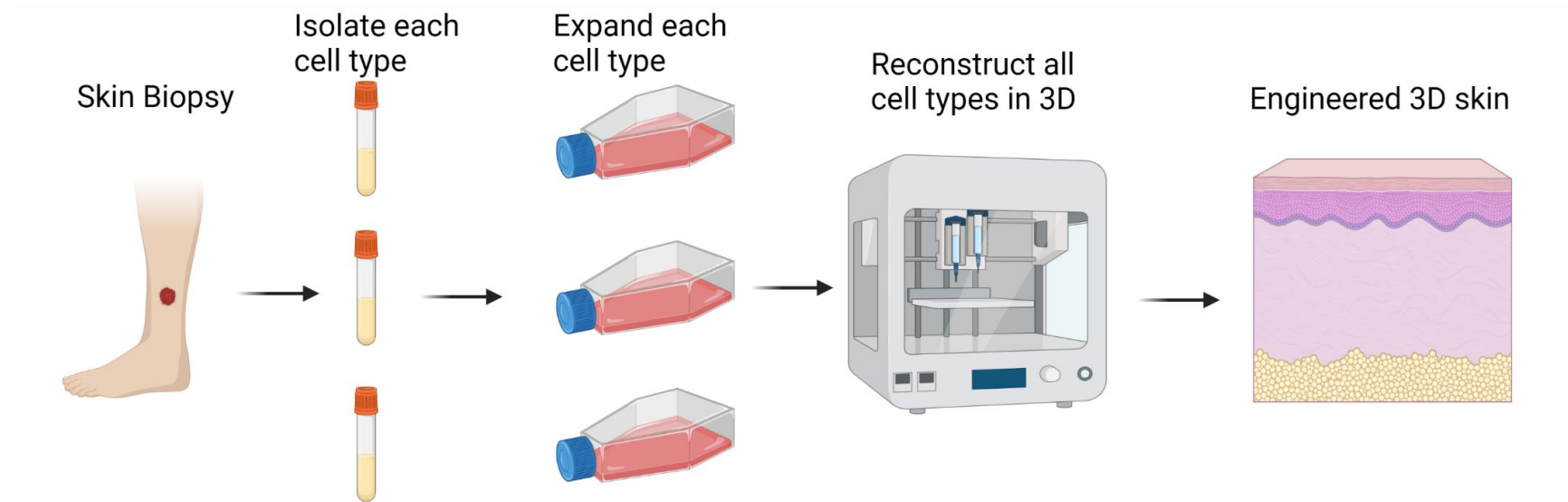


>50 cell types

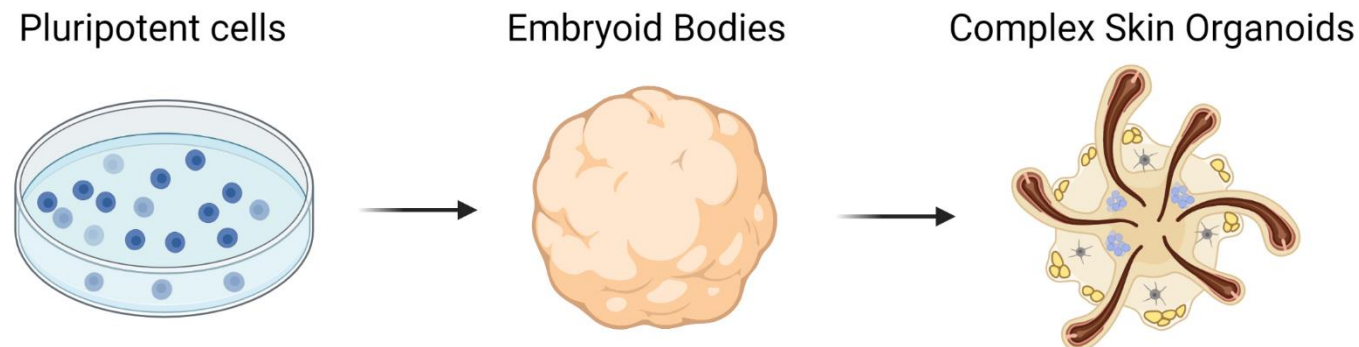
- Pigmentation
- Hypodermis
- Vasculature
- Appendages
- Innervation
- Immune Cells

# Skin Tissue Engineering Approaches

- Reverse engineering (reconstructed tissues)



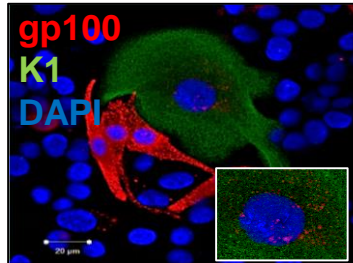
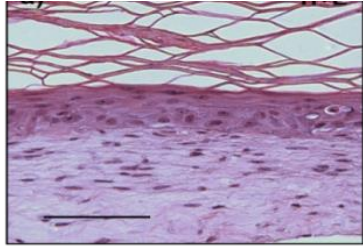
- Forward engineering (pluripotent cell-derived organoids)





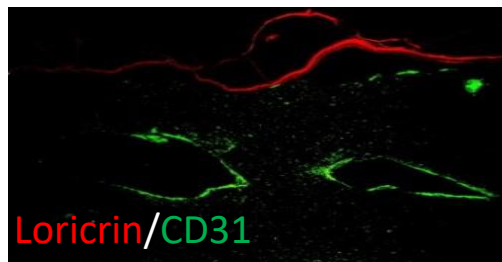
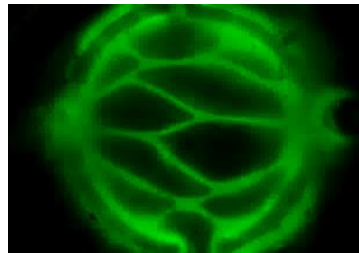
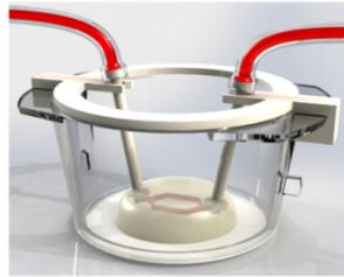
# Toward a Complex Human Skin

## Pigmentation



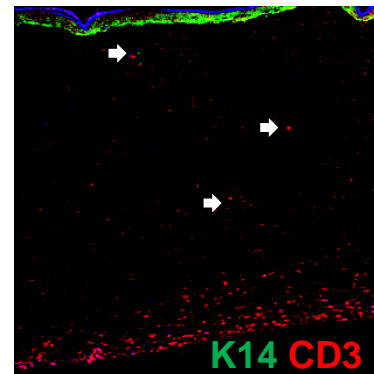
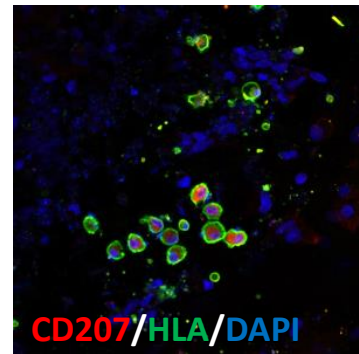
Gledhill et al. *PlosOne*.  
2014

## Vascularization



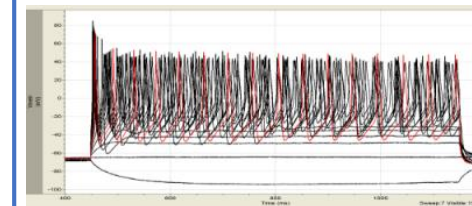
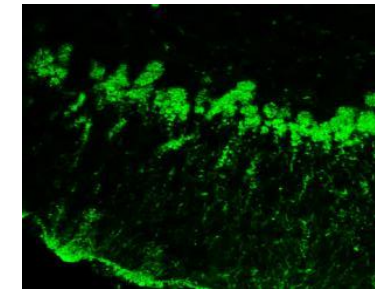
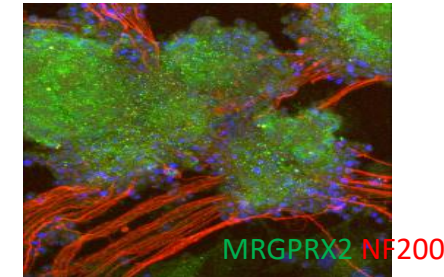
Abaci HE, et al.  
*Adv Healthc Mat*.  
2016;5(14):1800-7.

## Immunity



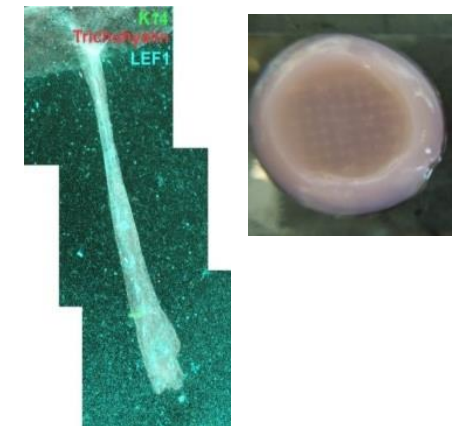
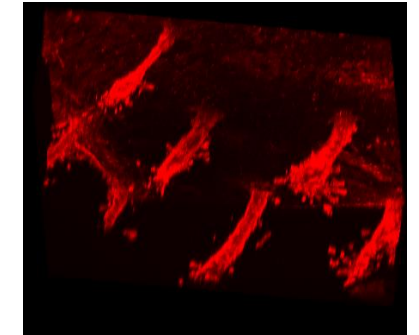
Abaci/Jung U et al.  
*Scientific Reports*. 2019

## Innervation



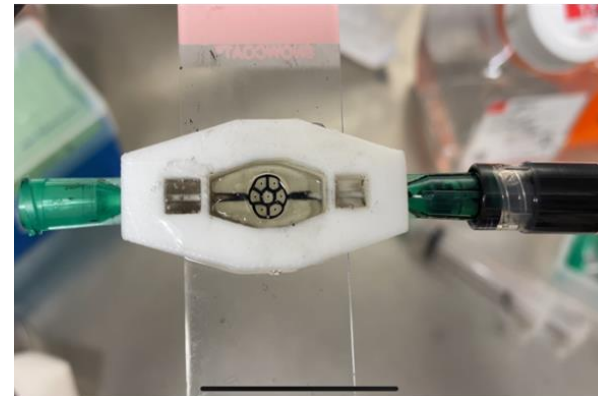
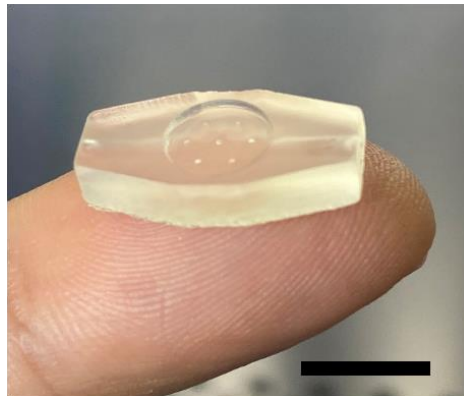
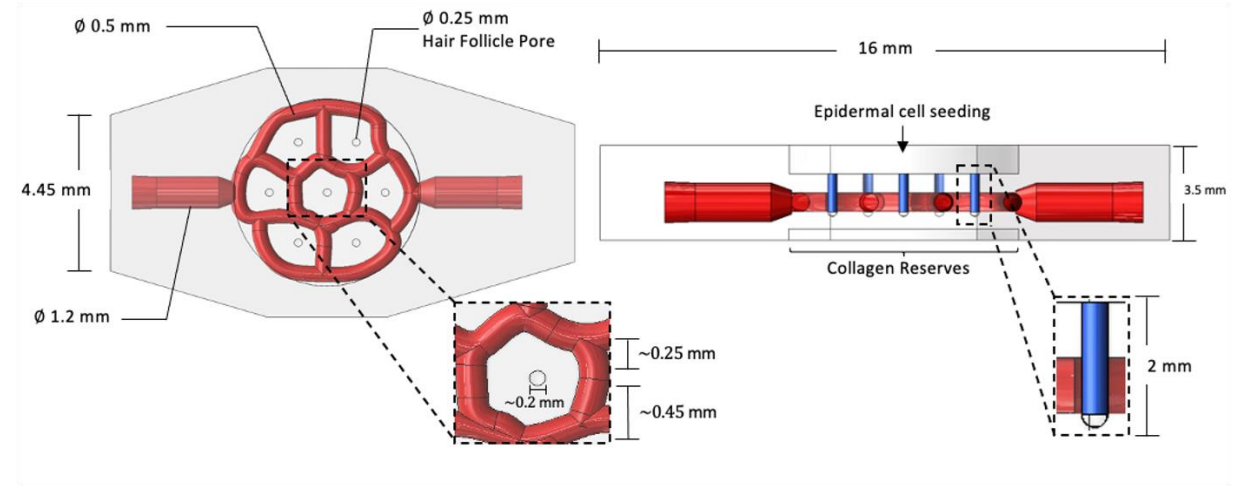
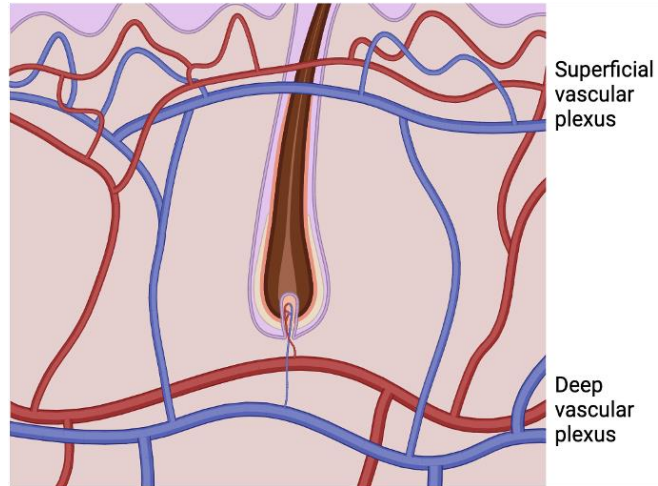
Guo et al.  
*Biotech. And Trans. Med*. 2021

## Appendages



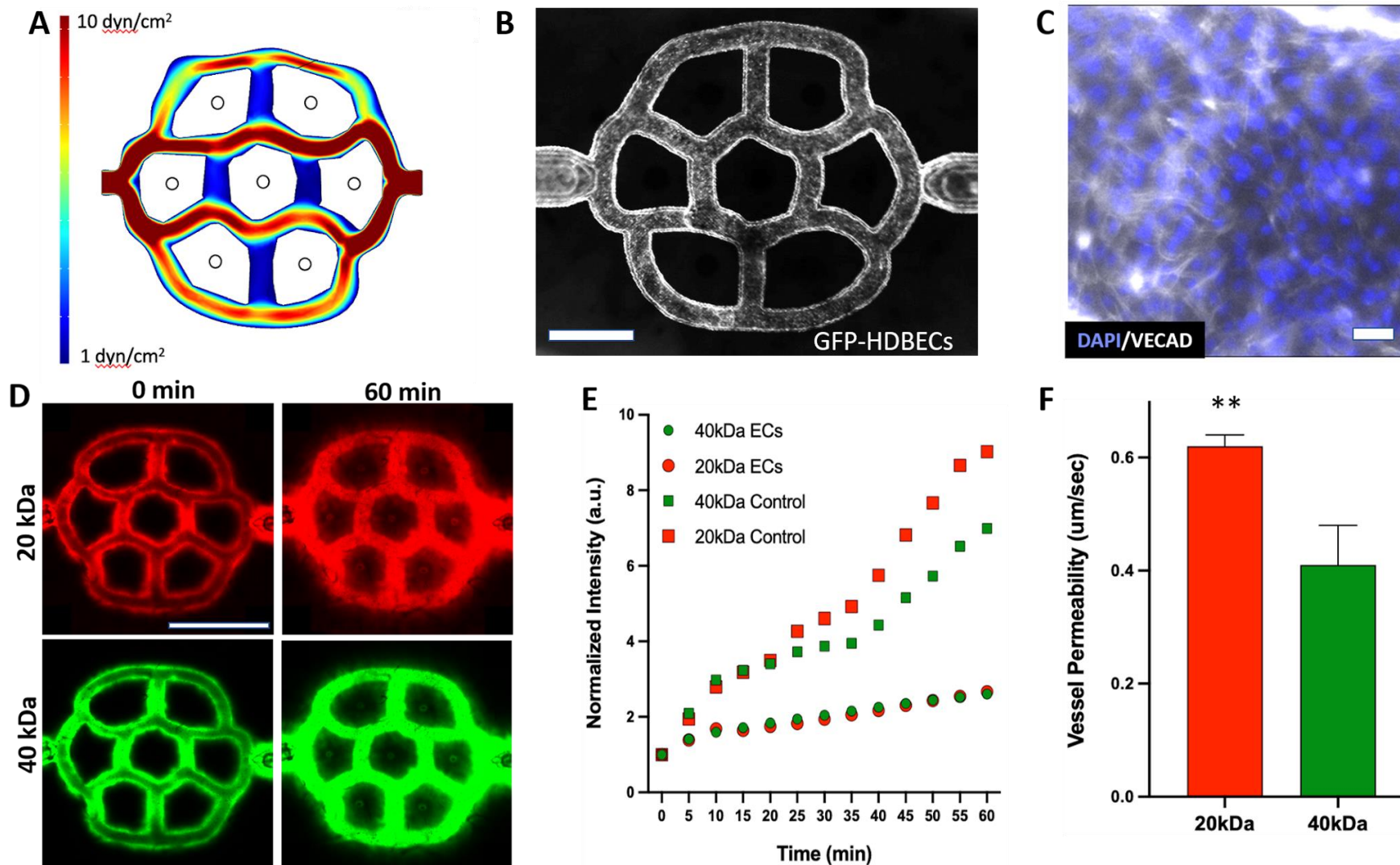
Abaci HE, et al.  
*Nat Commun*. 2018;9(1):5301

# Hydrogel Design and Fabrication

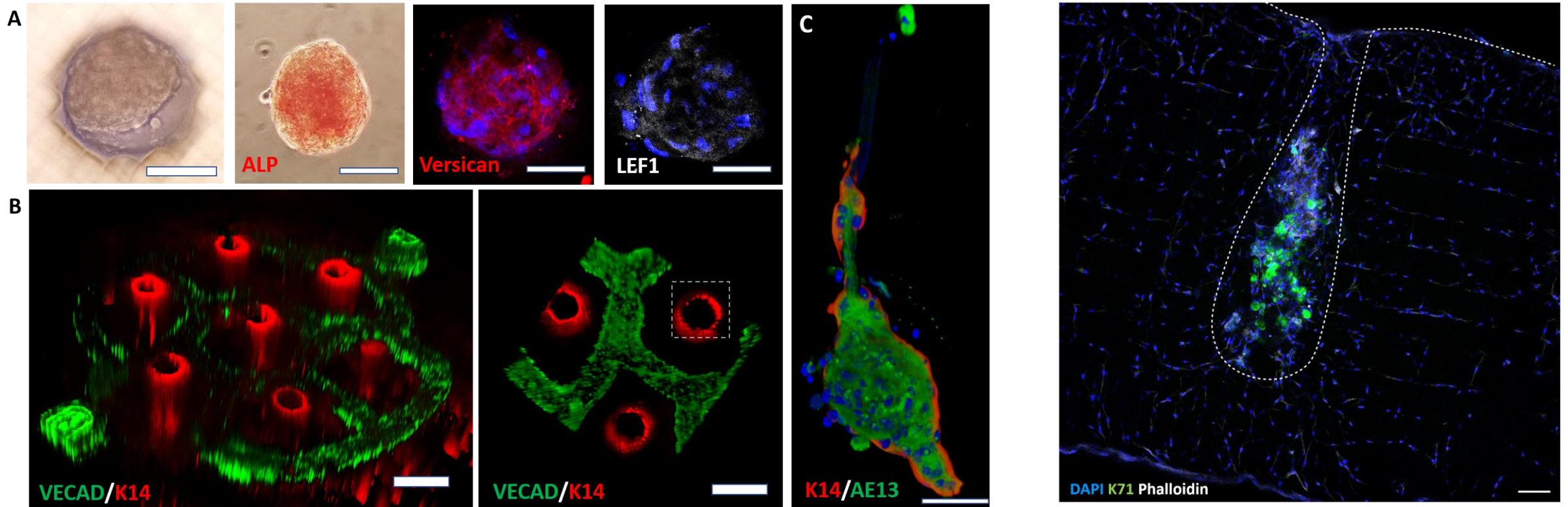




# Endothelial Cell Barrier Function

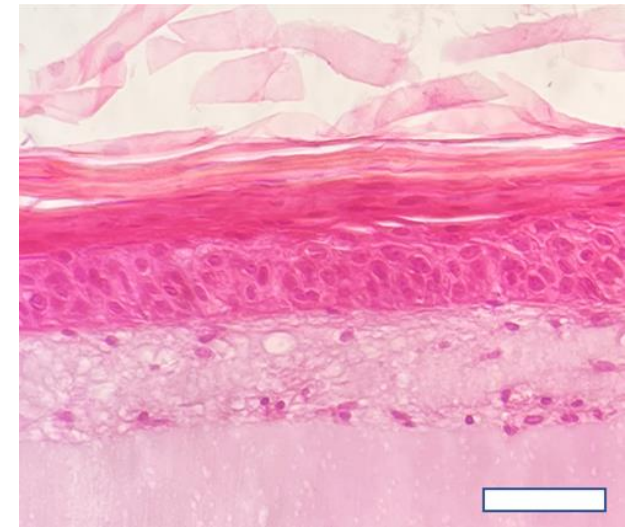
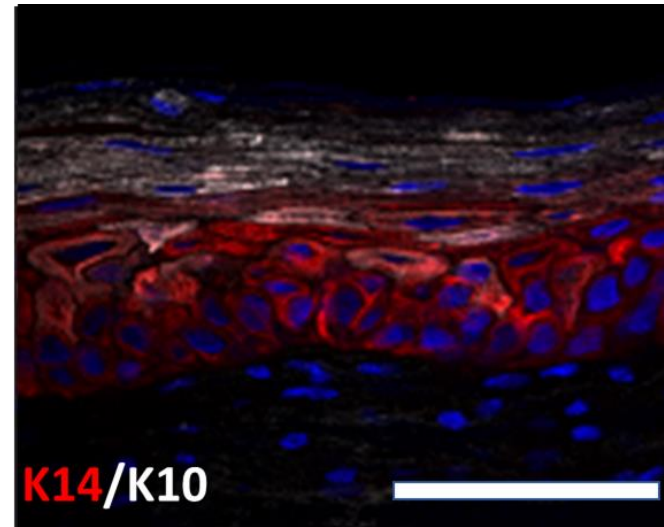
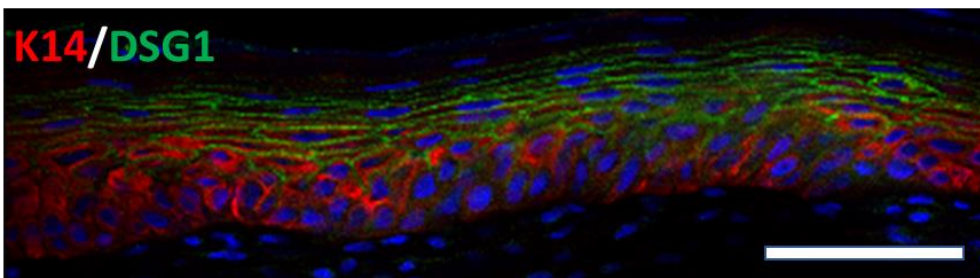
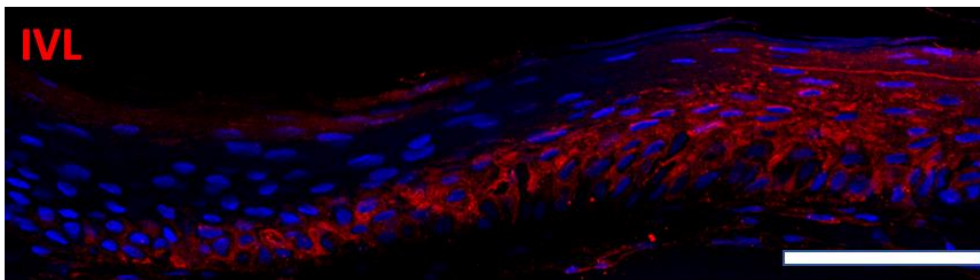
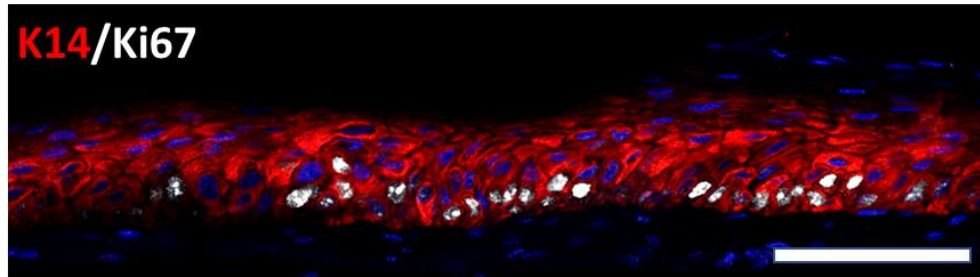
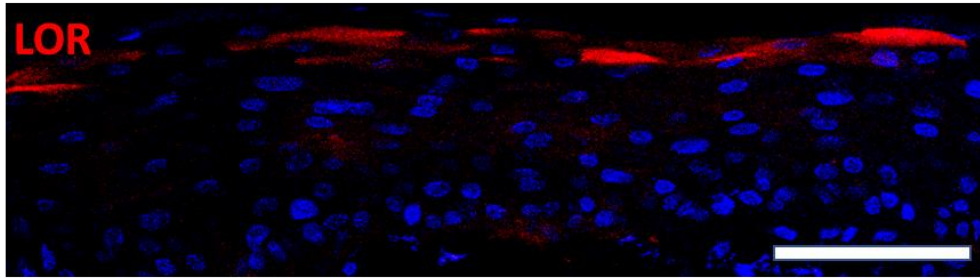


# Formation of Engineered Hair Follicles



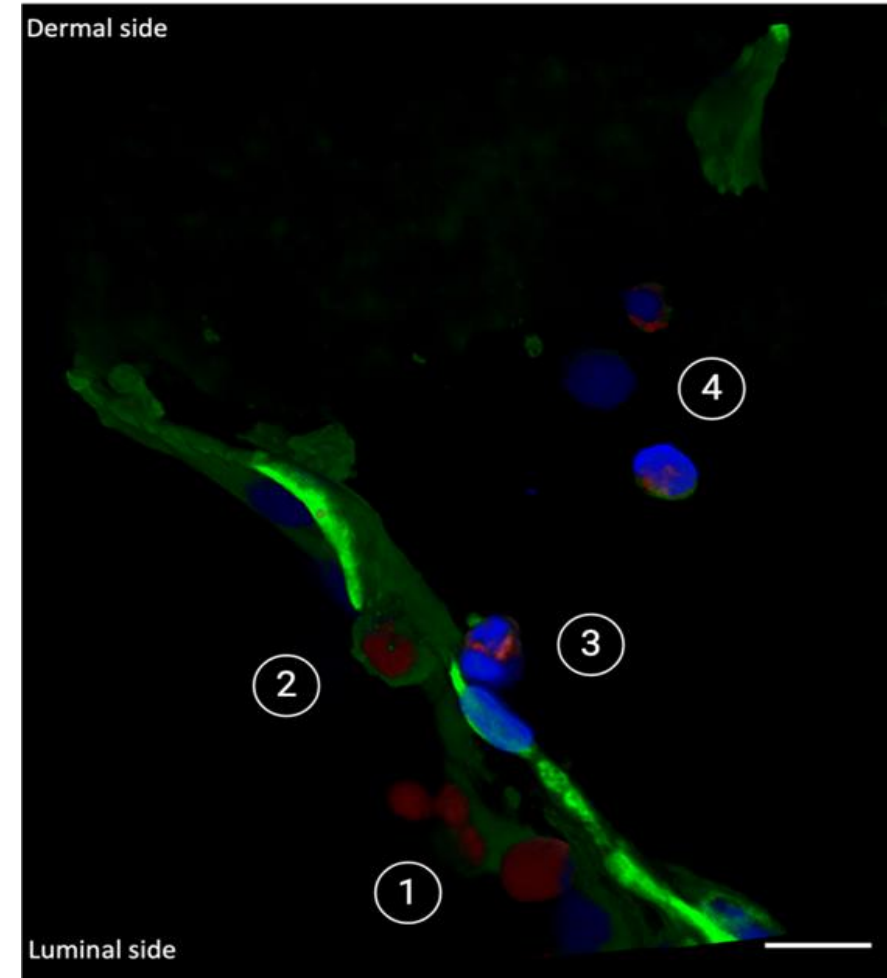
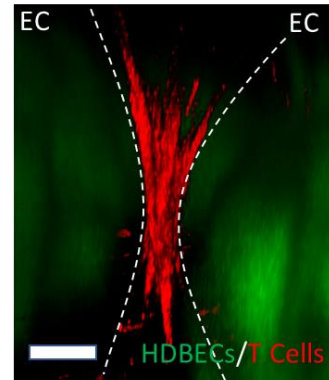
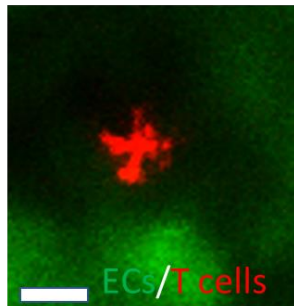
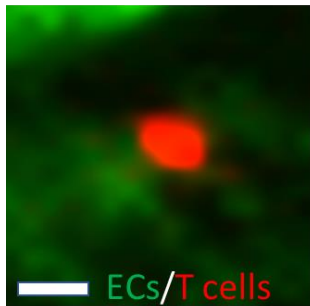
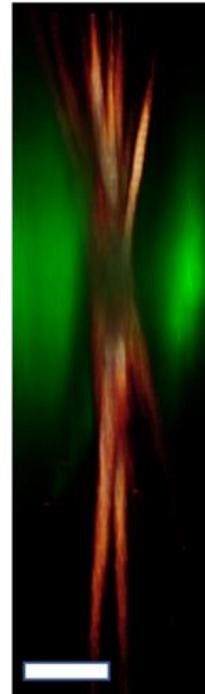
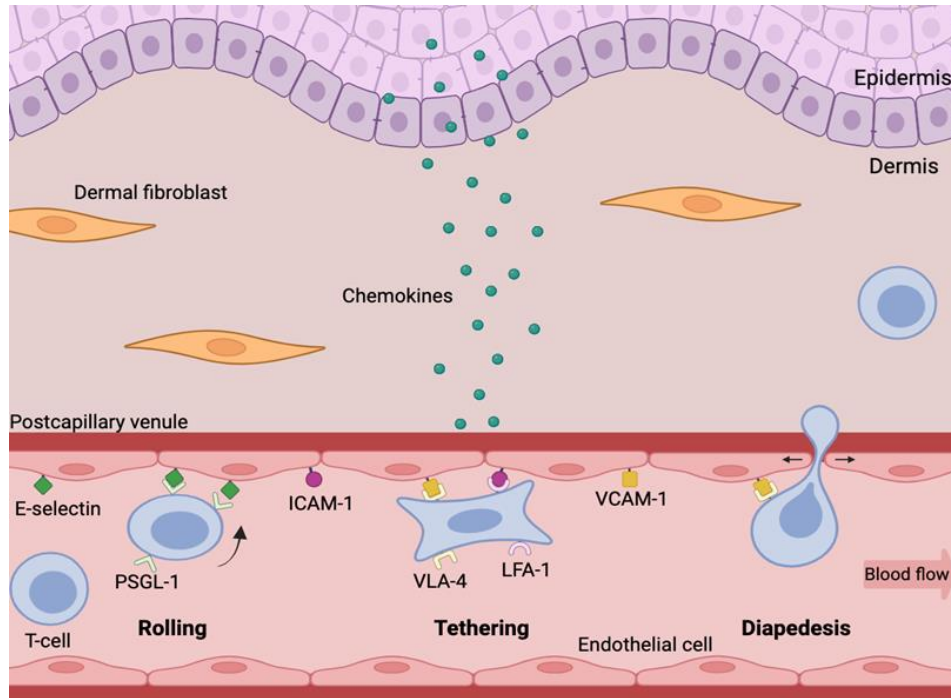


# Characterization of Epidermis

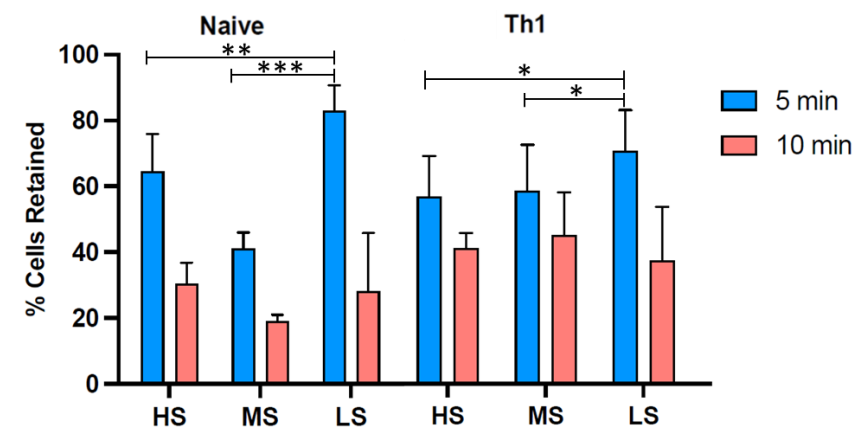
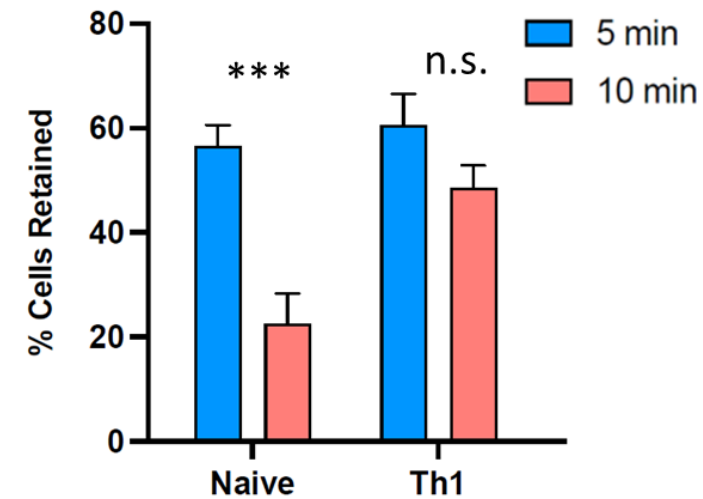
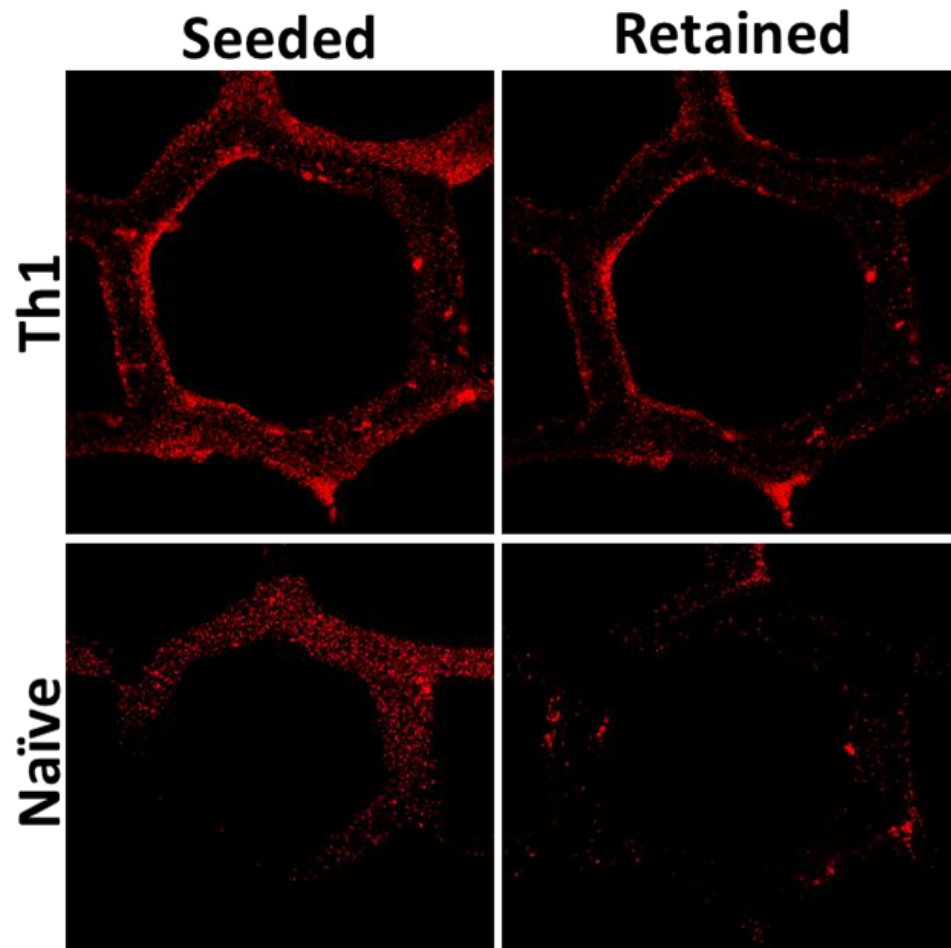
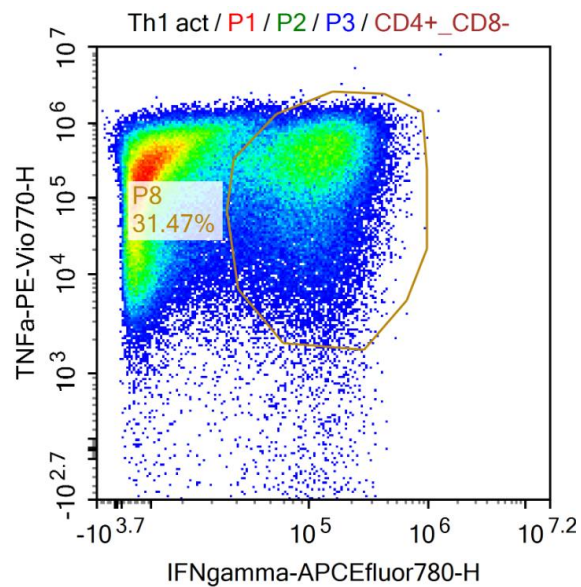




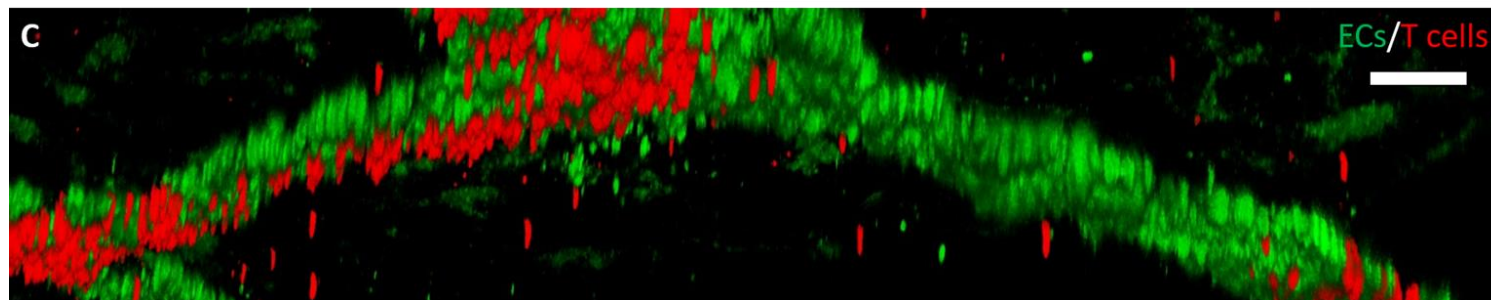
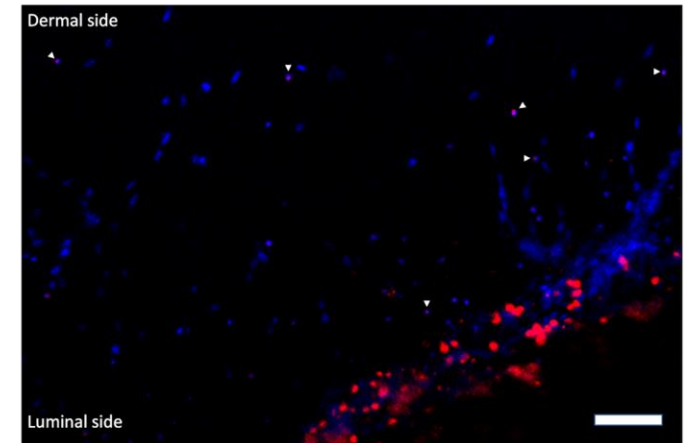
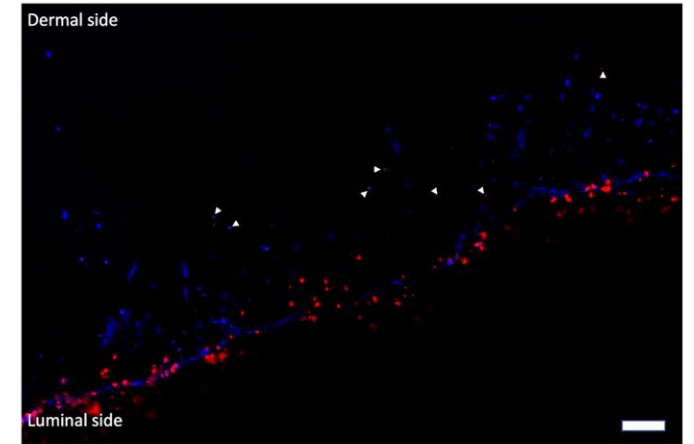
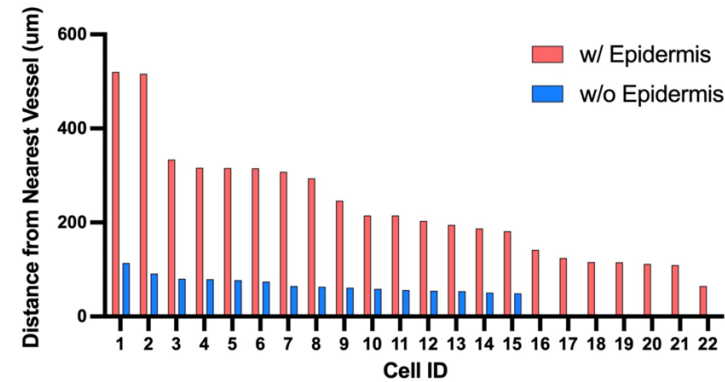
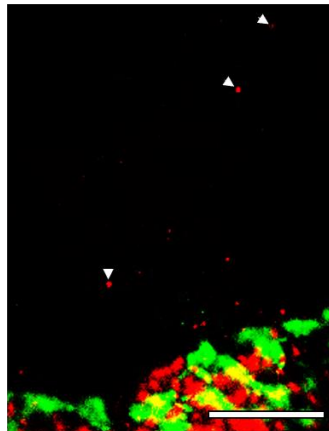
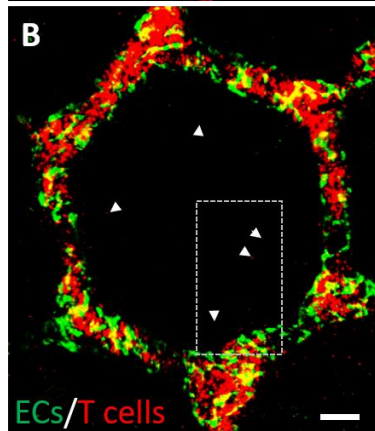
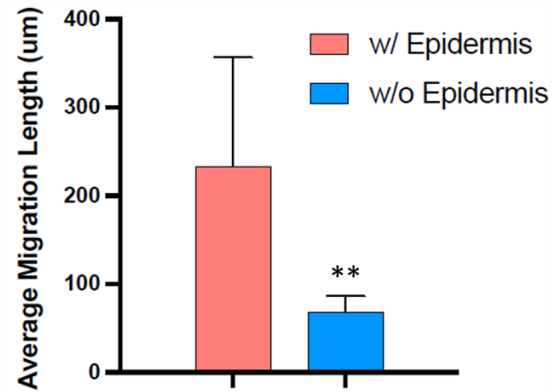
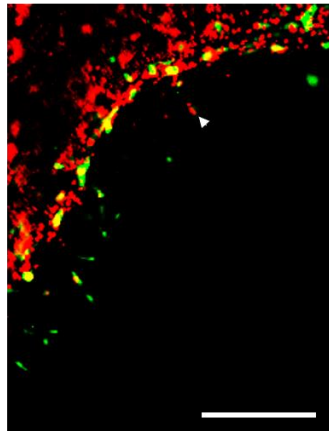
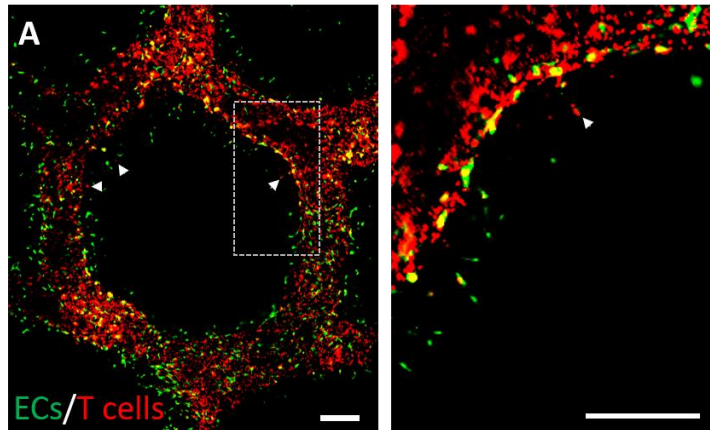
# T cell Trafficking



# T cell Attachment

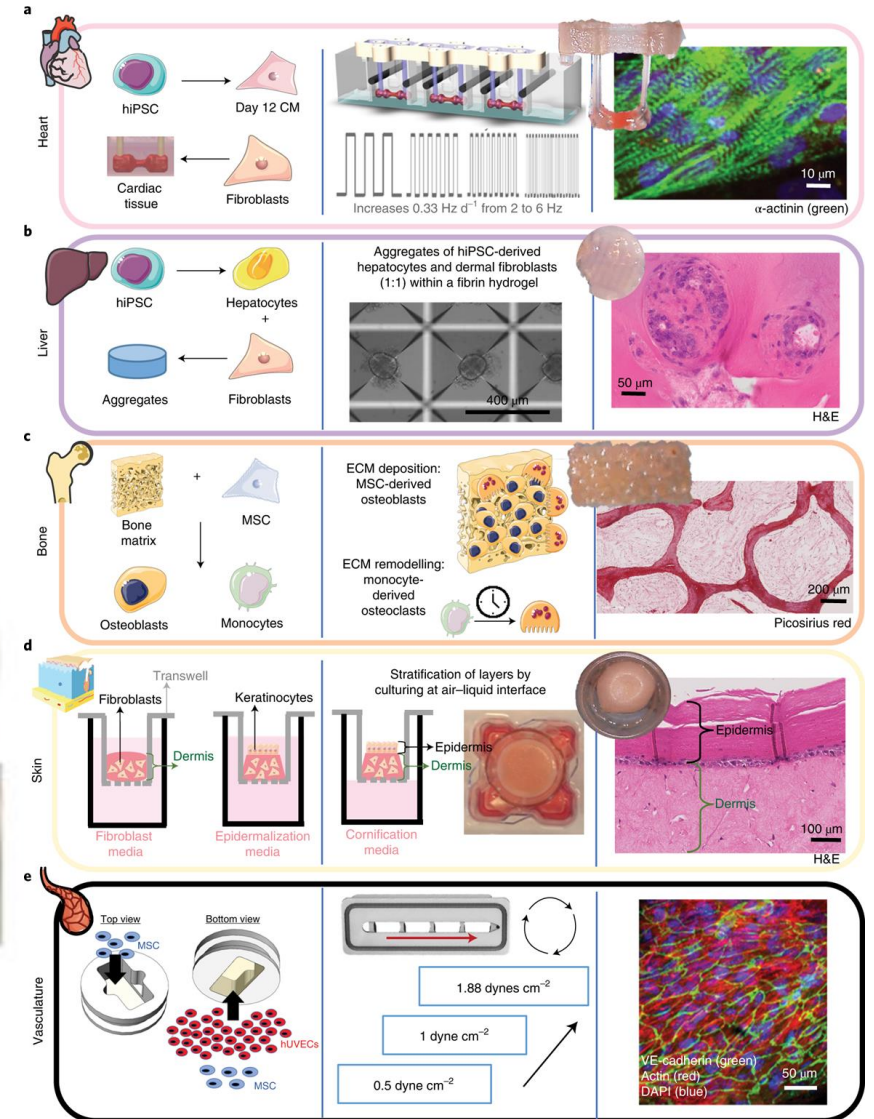
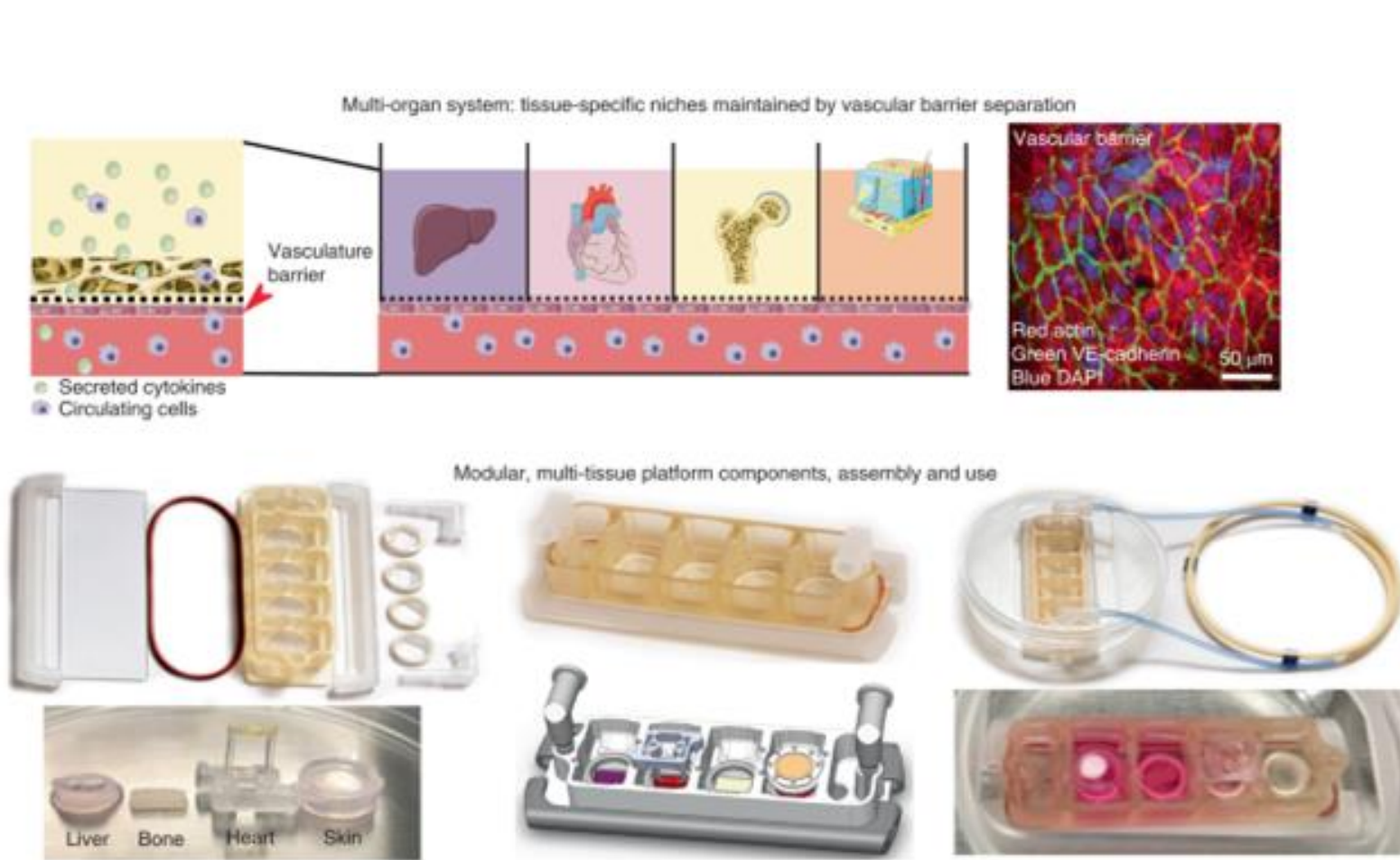


# Effect of Epidermis on Th1 Cell Infiltration into Dermis





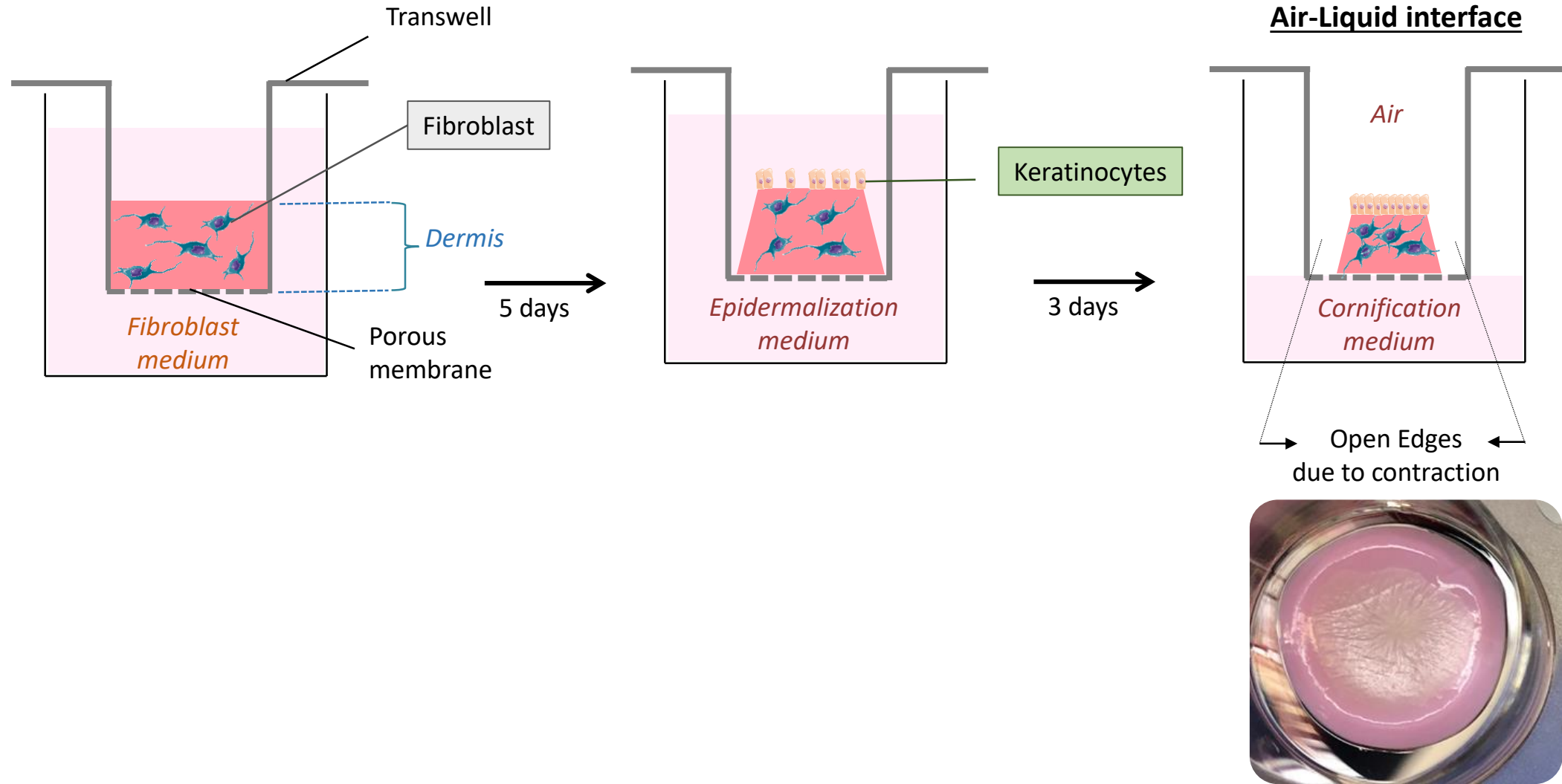
# A multi-organ chip with matured tissue niches **linked by vascular flow**



Ronaldson-Bouchard, *et al. Nat. Biomed. Eng* 6, 351–371 (2022).

Collaboration with Gordana Vunjak-Novakovic laboratory.

# An Overlooked Component: Geometry

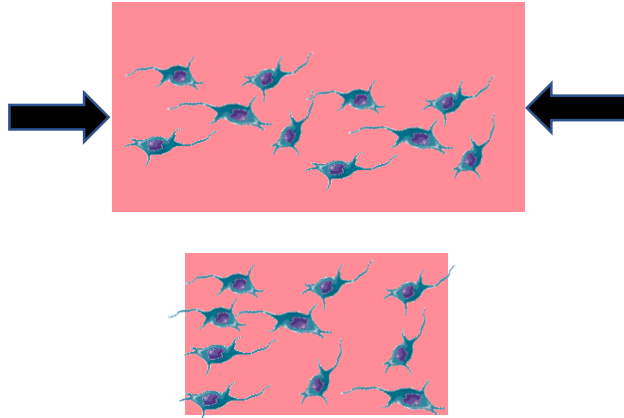




# Human Skin is Continuous and Fully Enclosed

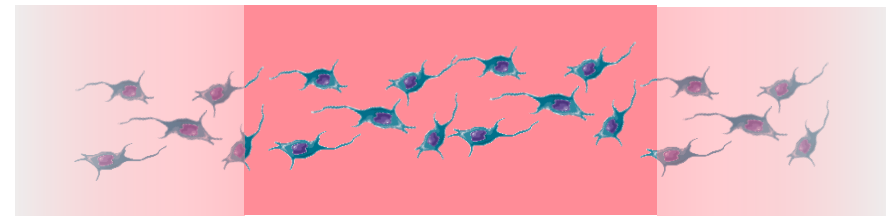


**Lateral Contraction**



Escher, 1956

**Mechanical Balance**

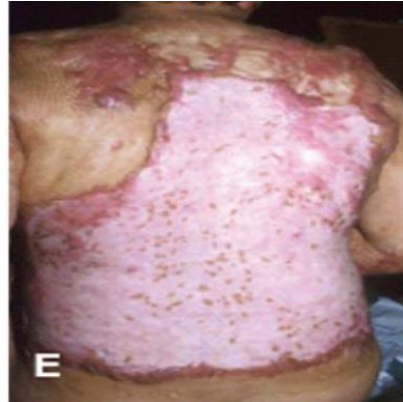
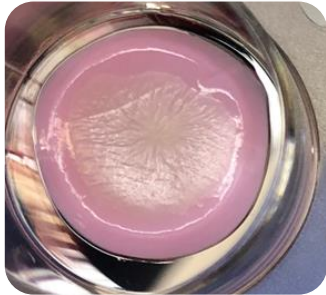




# Engineered Skin as an Edgeless (wearable) Tissue

- Difficult to cover body parts with irregular shapes, such as hands, feet, face, fingers, toes, ears, nose
- Takes many sutures to graft

**Grafting on Flat Body Parts**



Boyce ST, et al. *J Trauma*. 2006;60(4):821-9

**Grafting on Curved Body Parts**

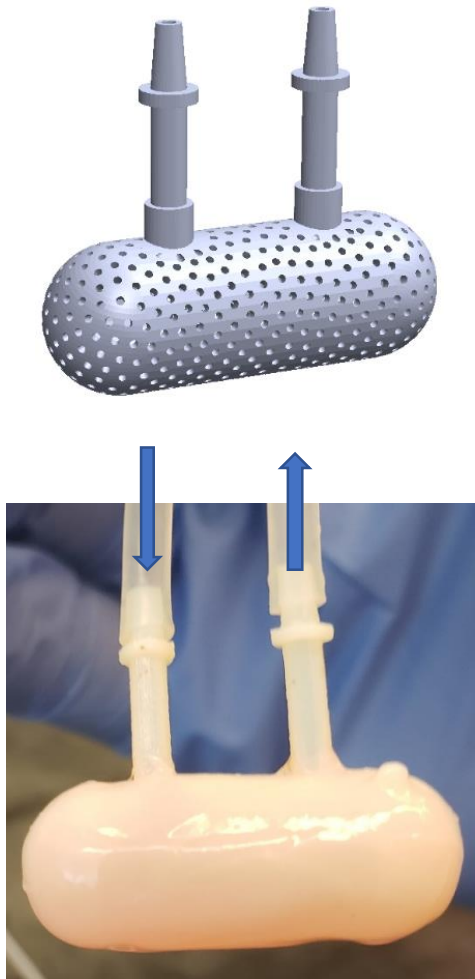


Jiang Y, et al. *Dermatol Ther*. 2020;33(6):e14466

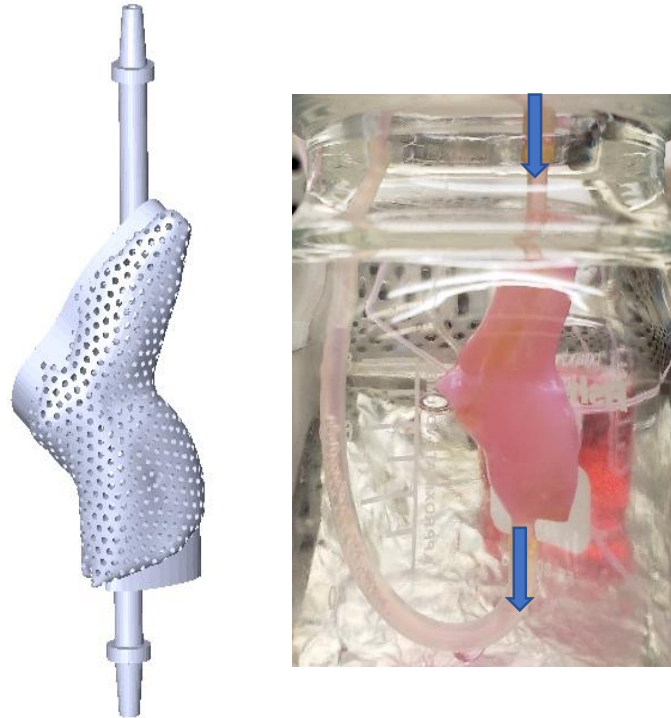


# Reshaping the Engineered Skin

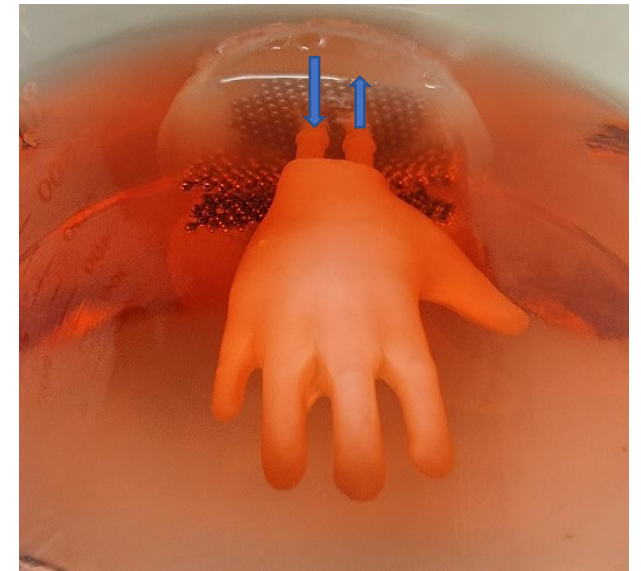
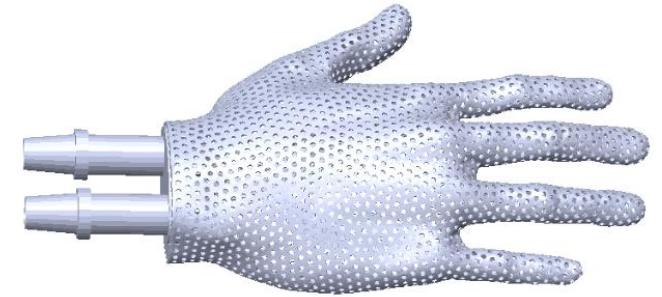
## The Cylinder



## The Hind Limb

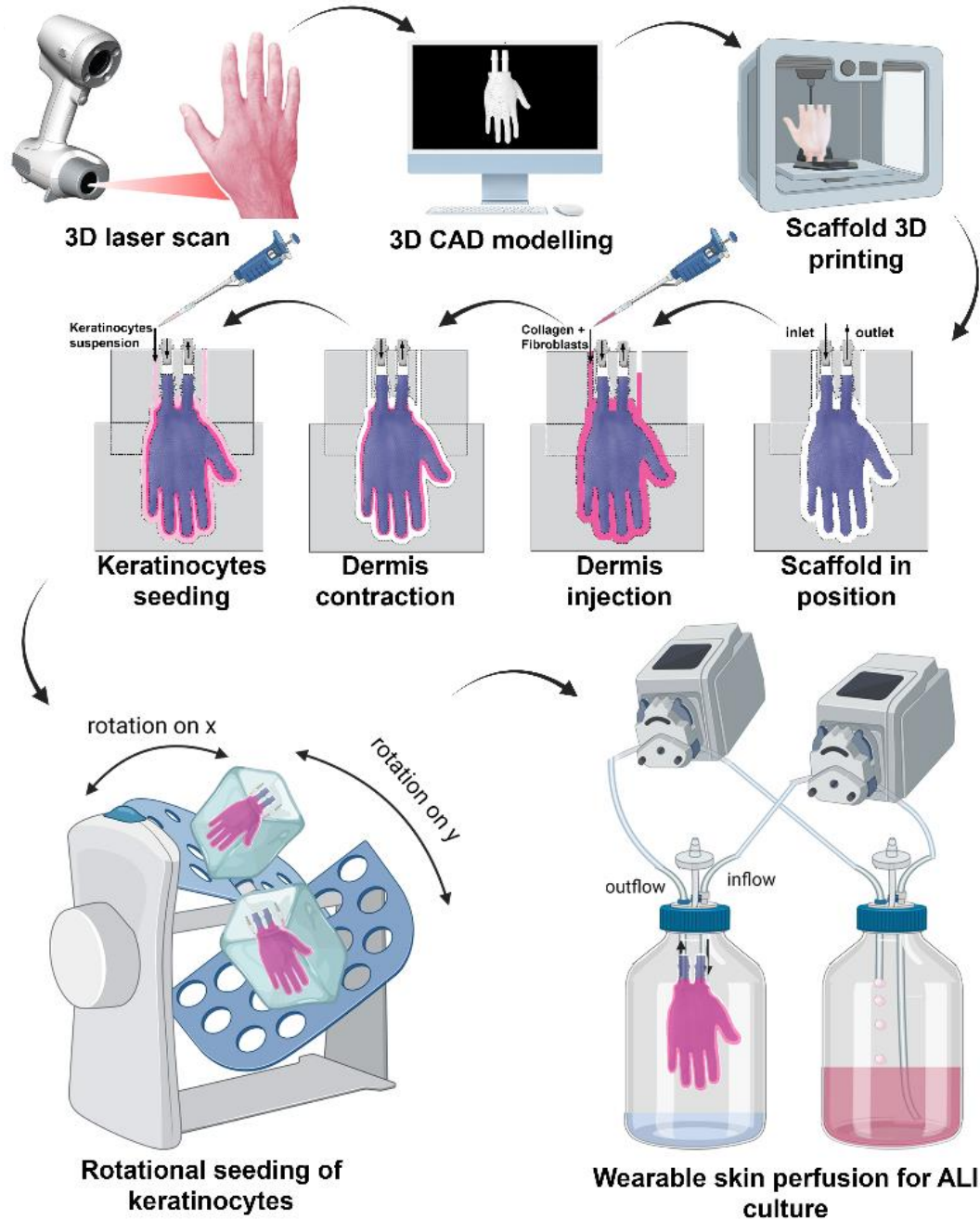


## The Hand



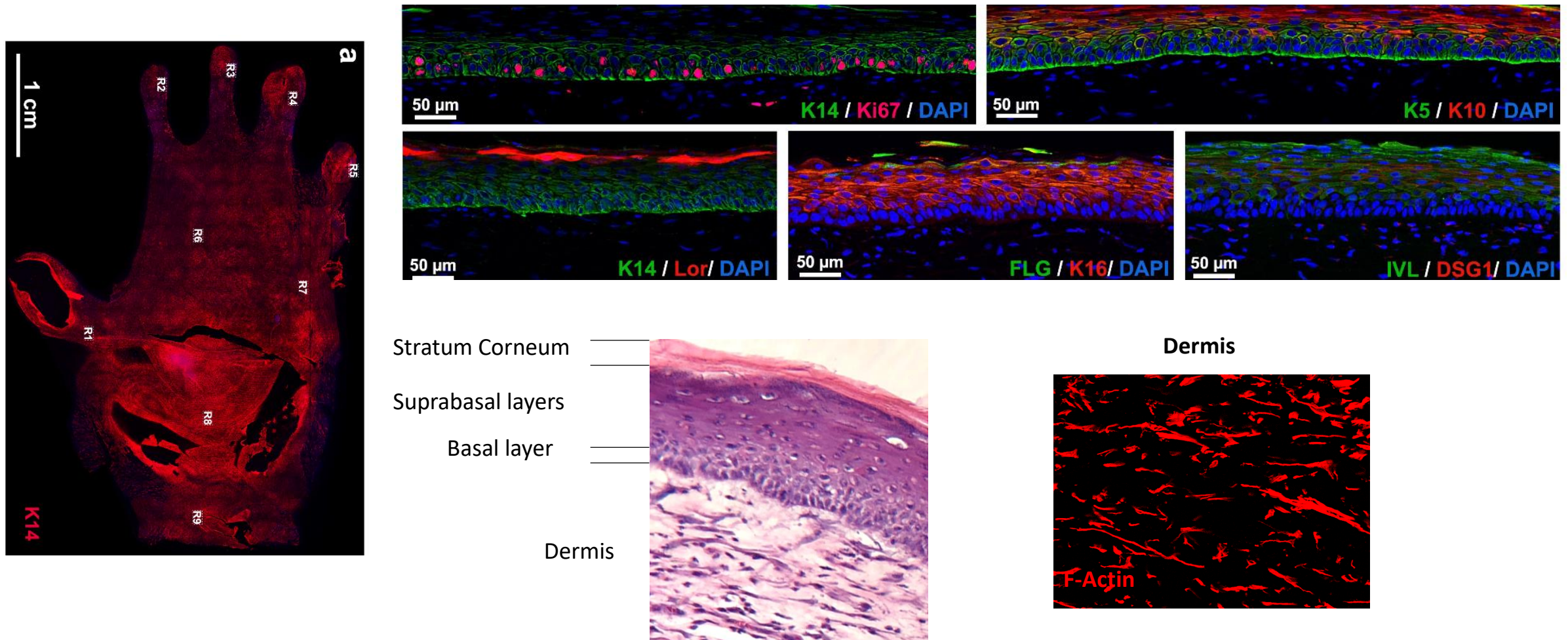
Pappalardo A, et al. *Sci Adv.* 2023;9(4):eade2514

# Overview of the Method

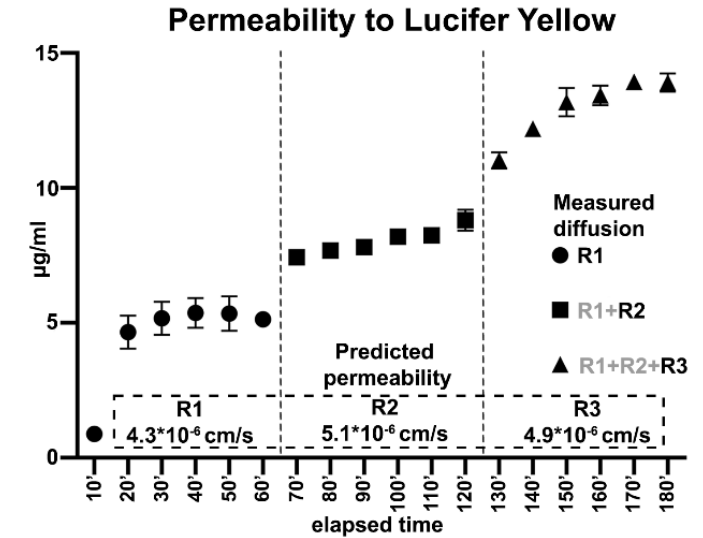
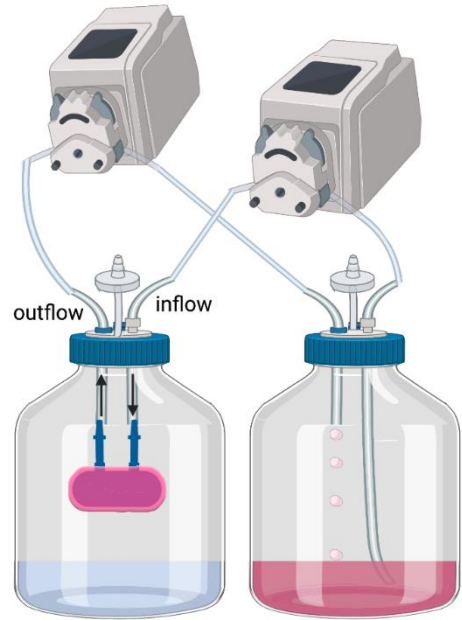




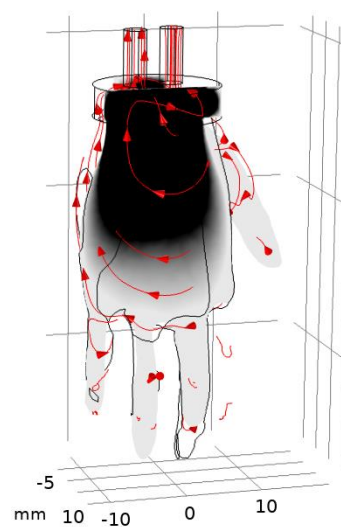
# Edgeless Skin Develops a Robust Epidermis



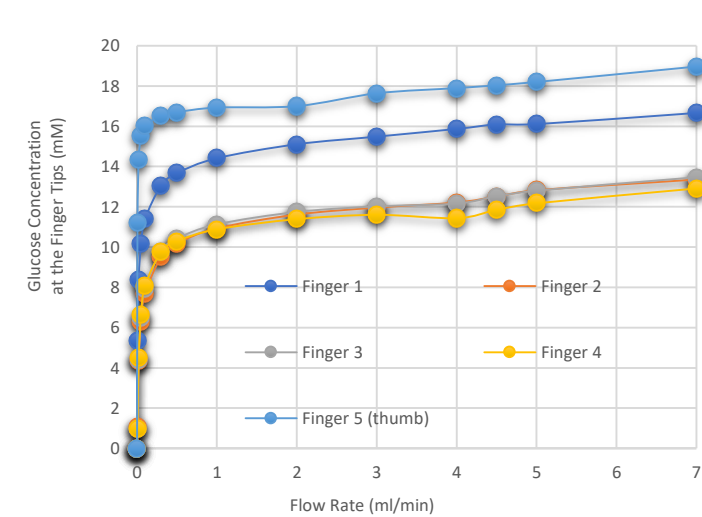
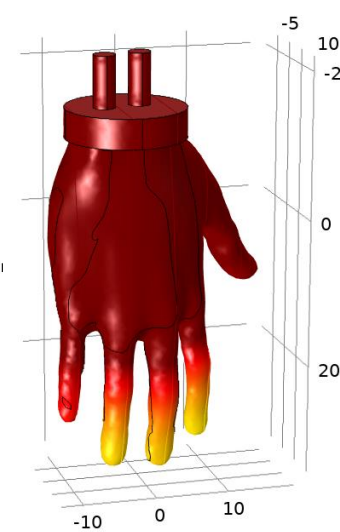
# Studying *In Vitro* Drug Transport in Human Skin



**Velocity Profile**



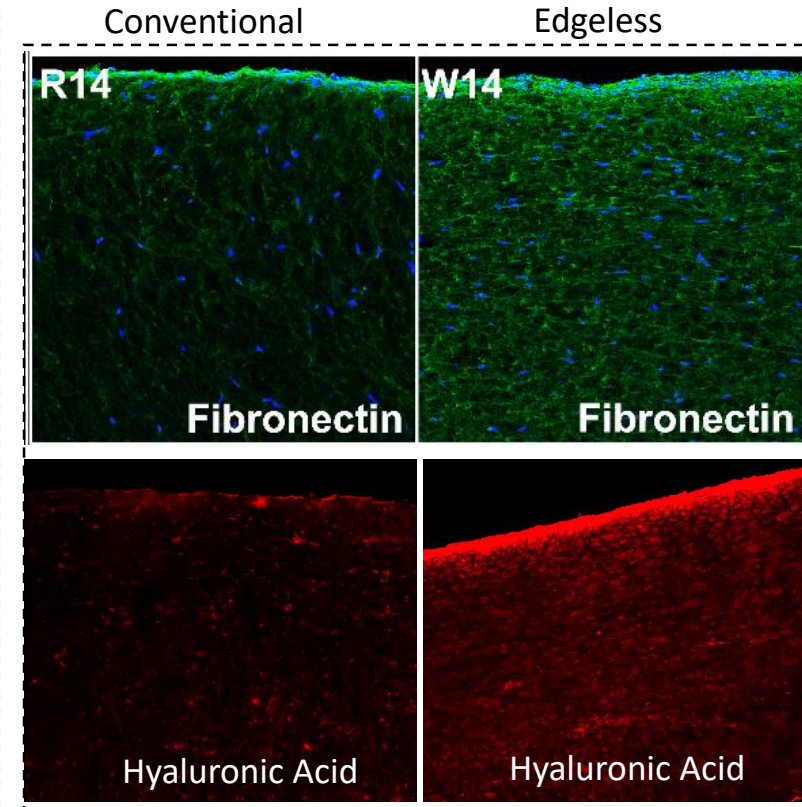
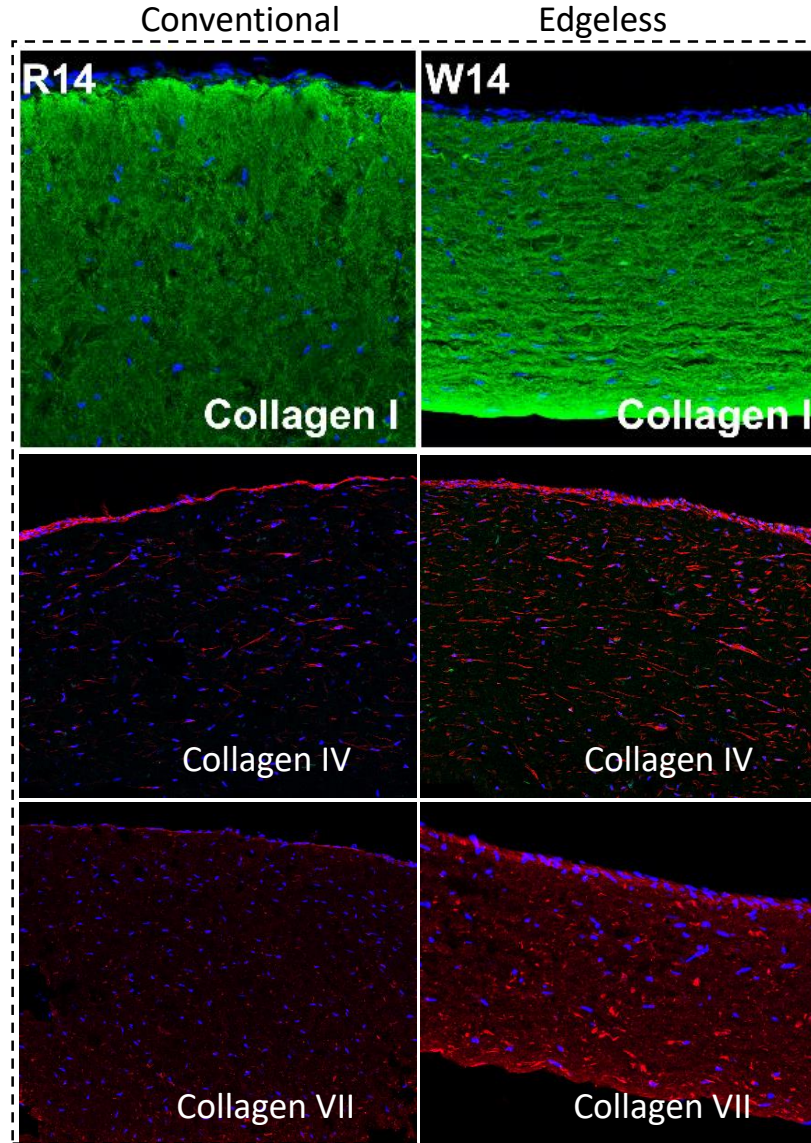
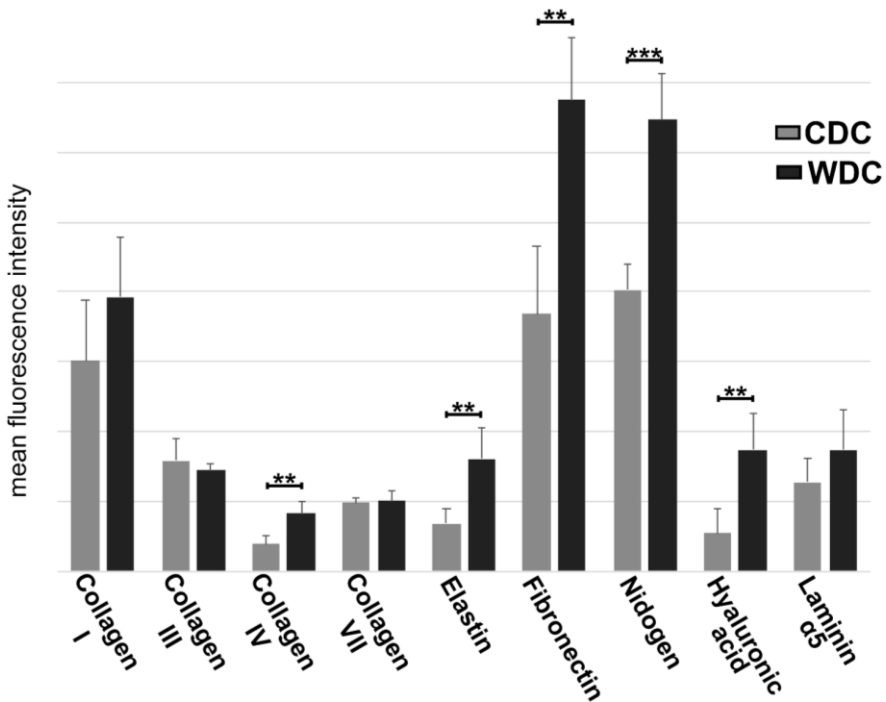
**Molecular Transport**





# Enhanced Dermal Extracellular Matrix (ECM) and Remodeling

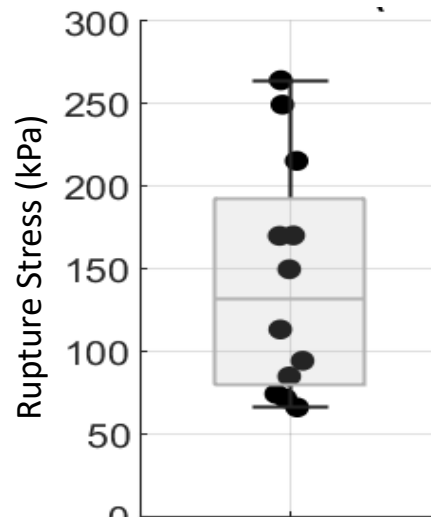
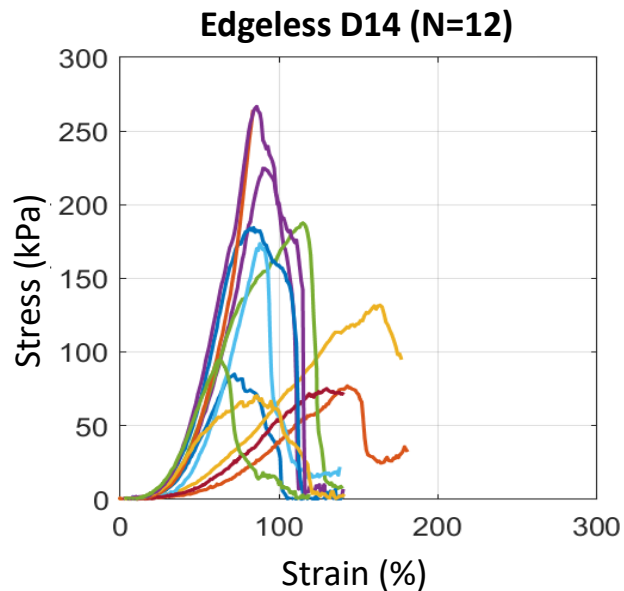
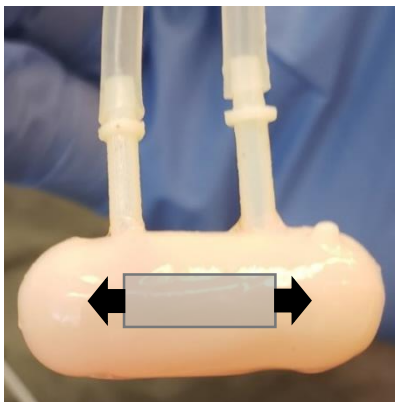
## The Cylinder



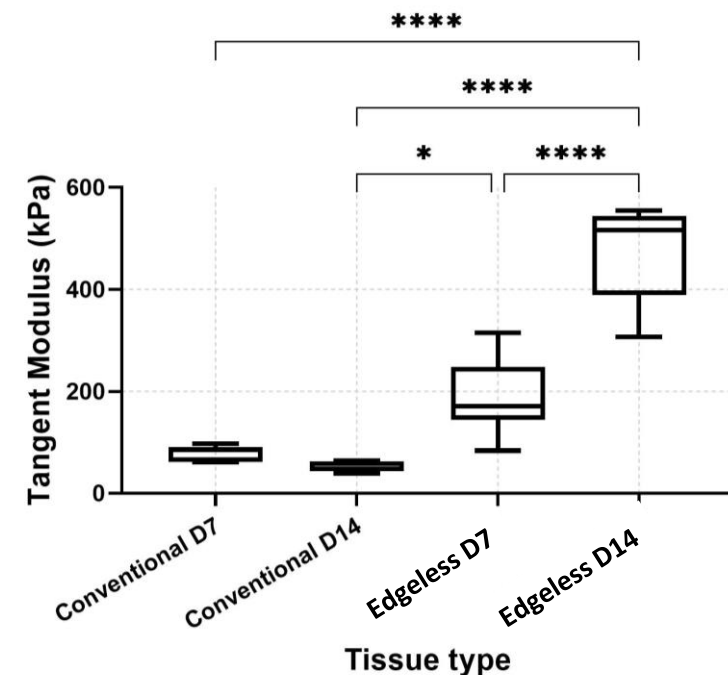
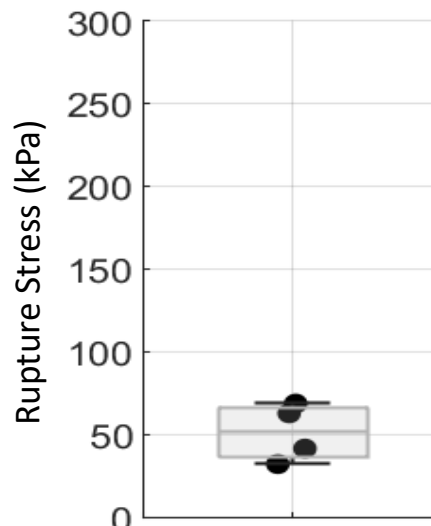
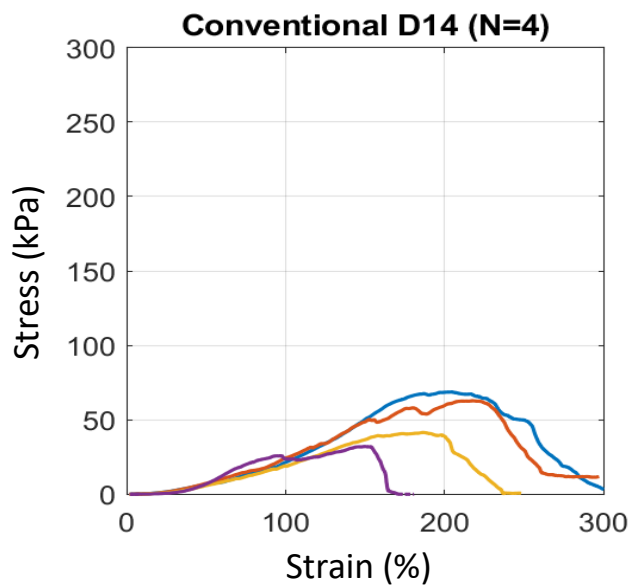
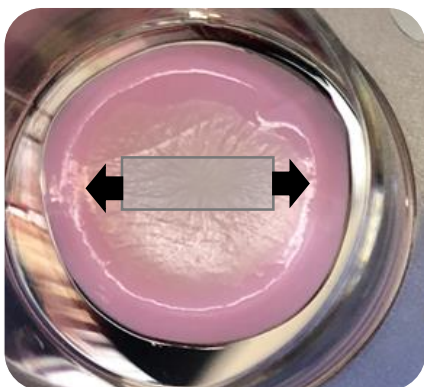


# Enhanced Mechanical Properties of Edgeless Skin

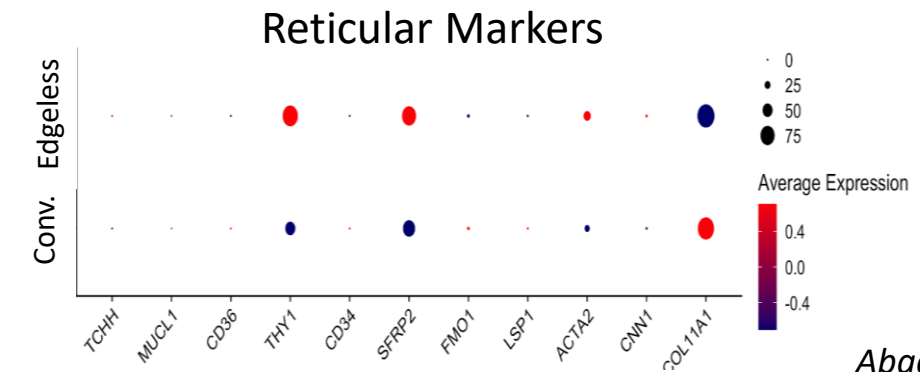
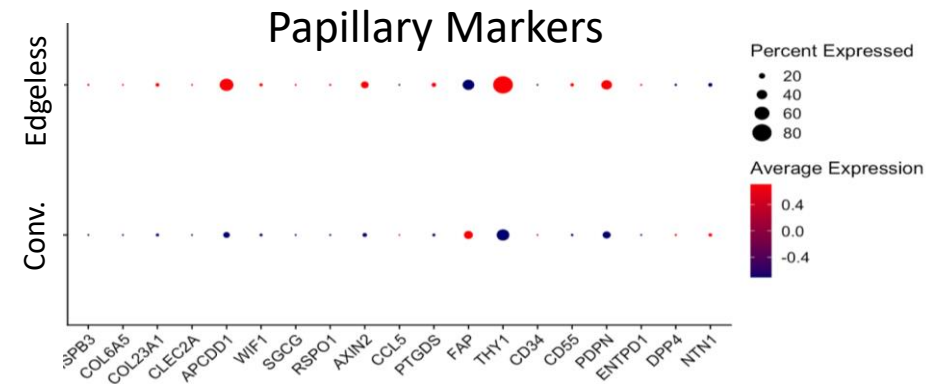
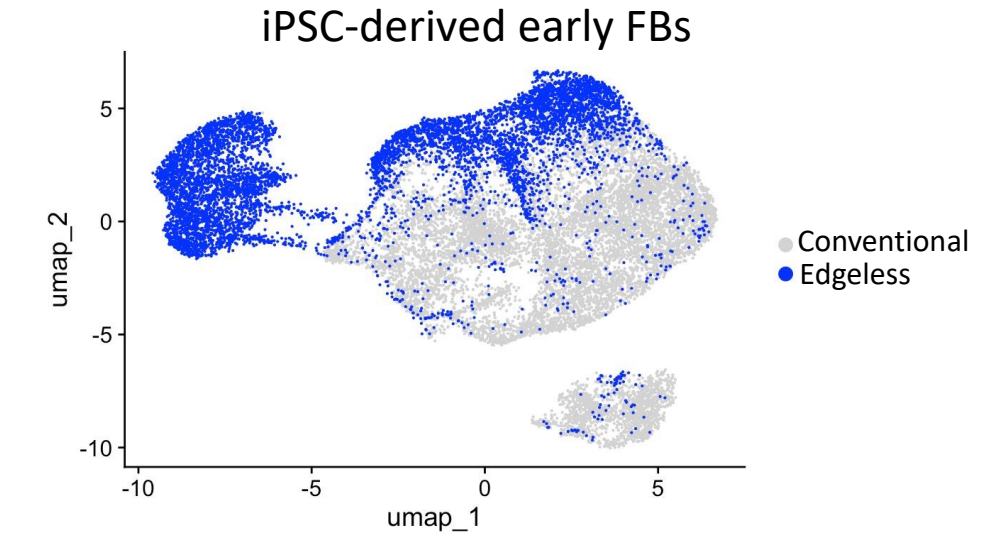
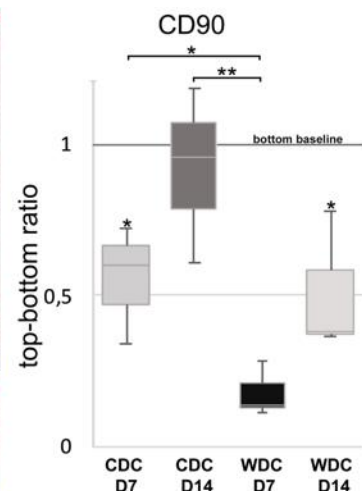
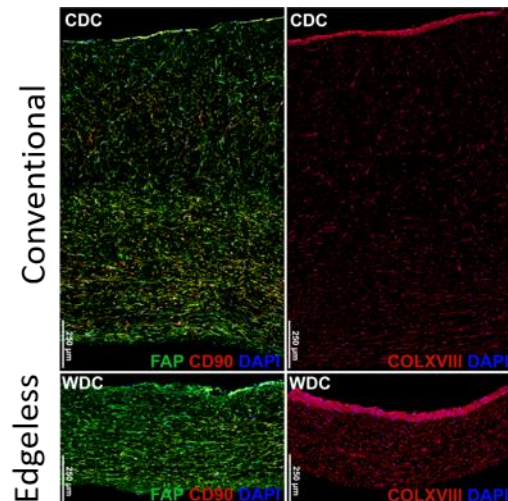
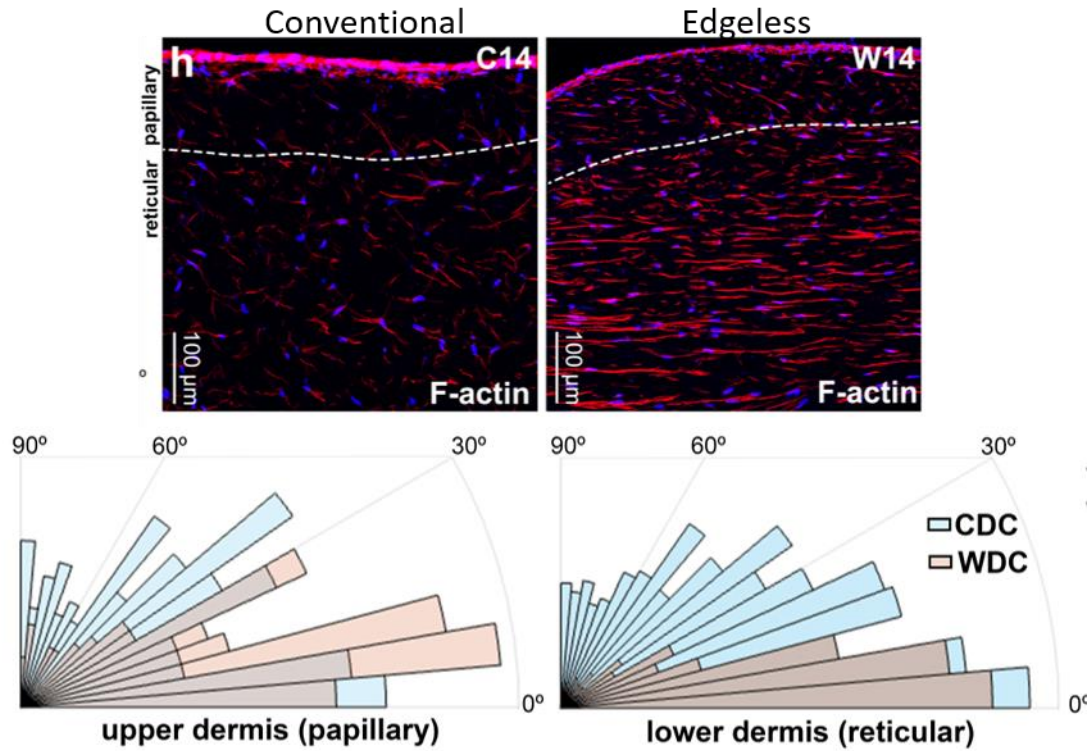
Edgeless



Conventional

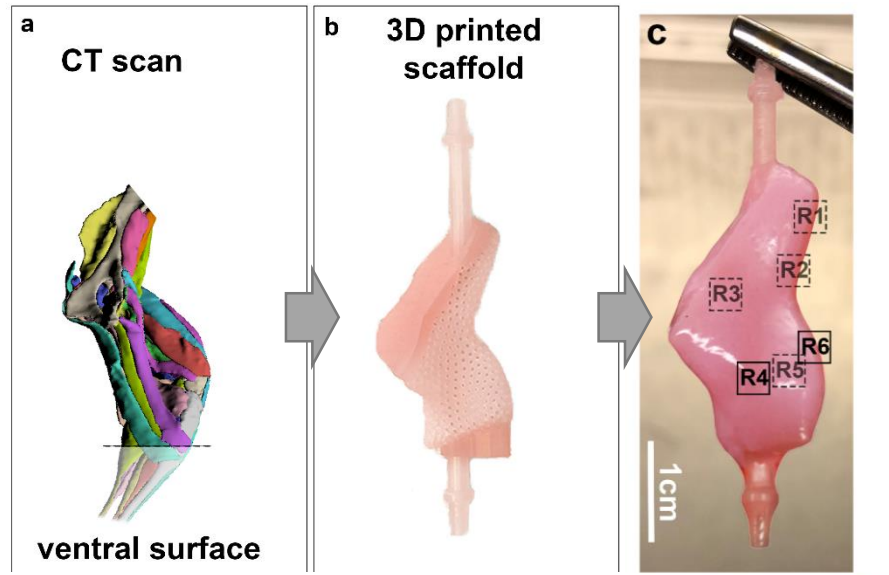


# Edgeless Skin Allows Papillary vs. Reticular Dermal Cell Distinction

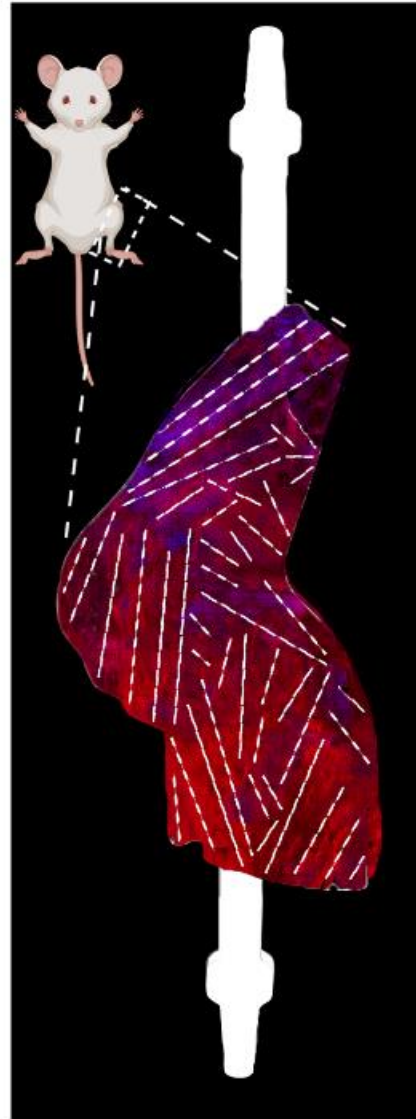




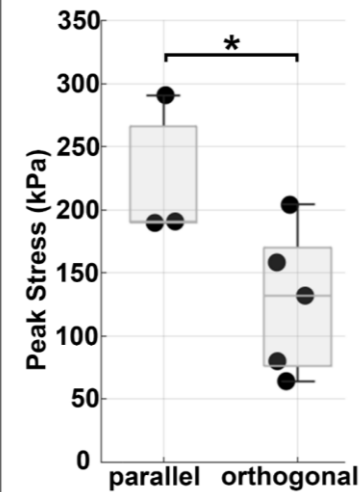
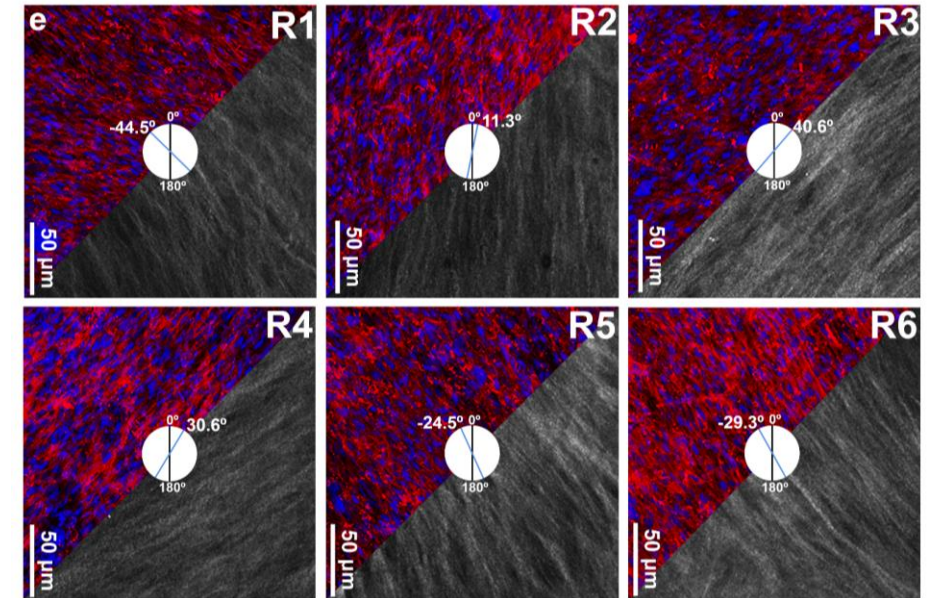
# Region-Specific Skin Properties



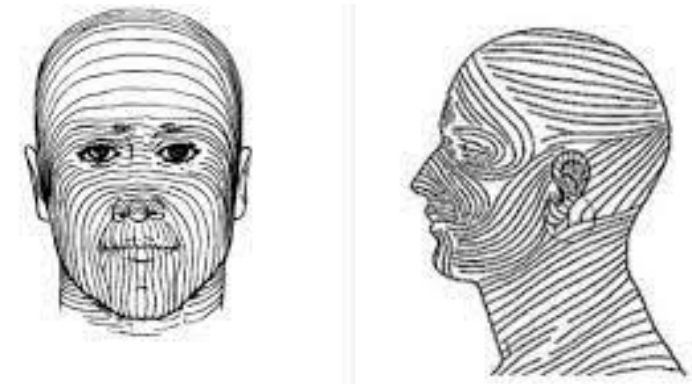
## F-actin map



Elastin/ $2^{\text{nd}}$  Harmonic

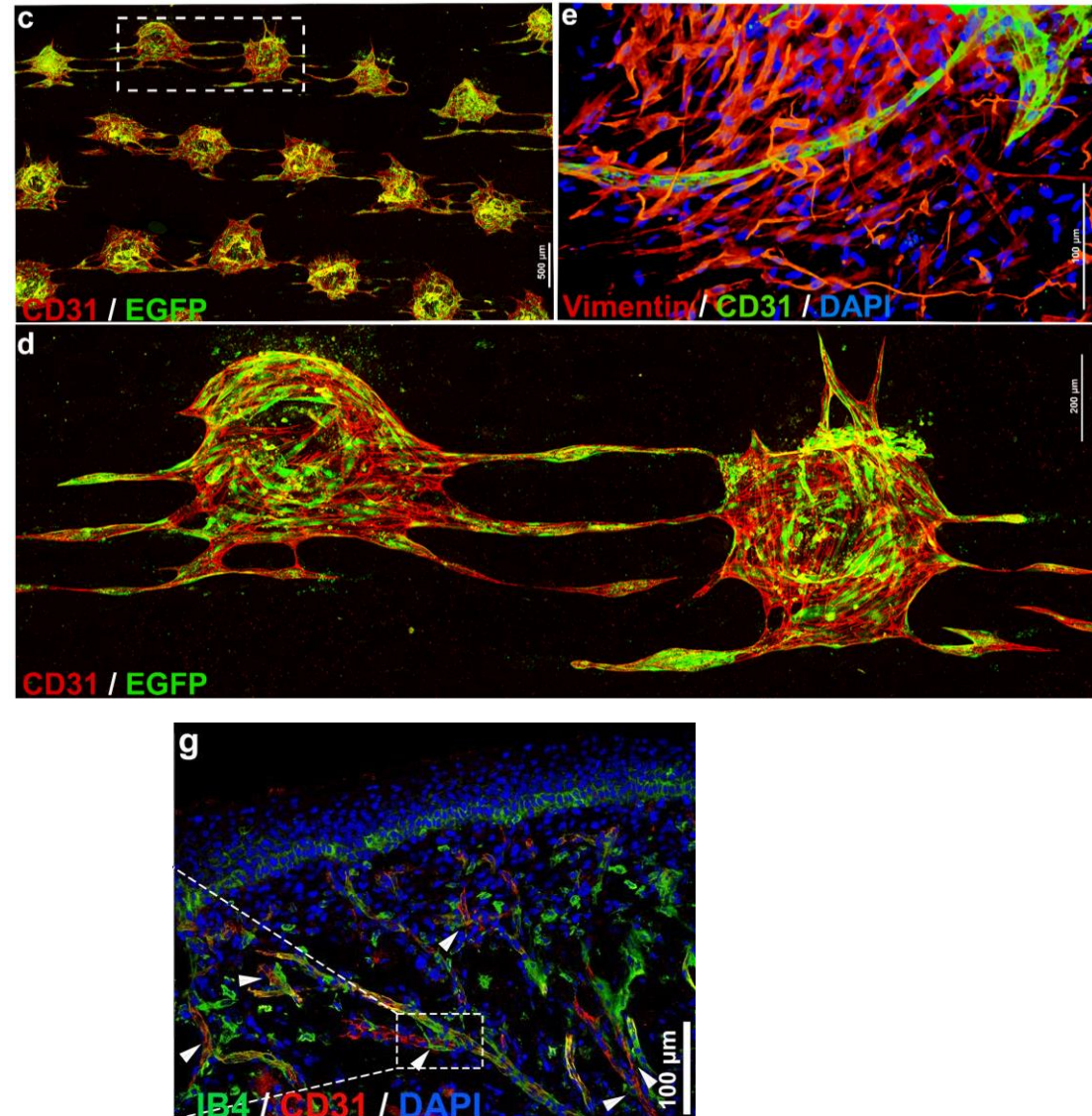
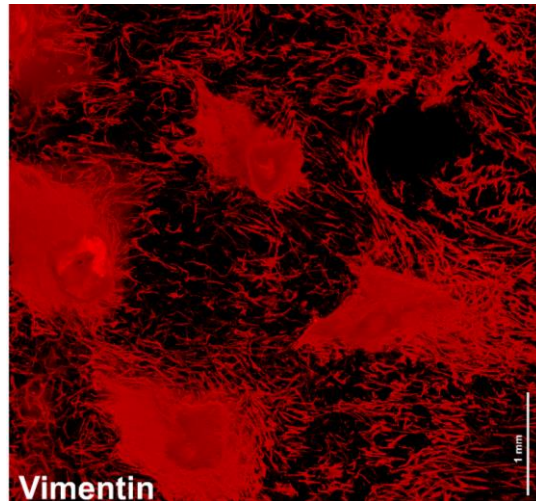
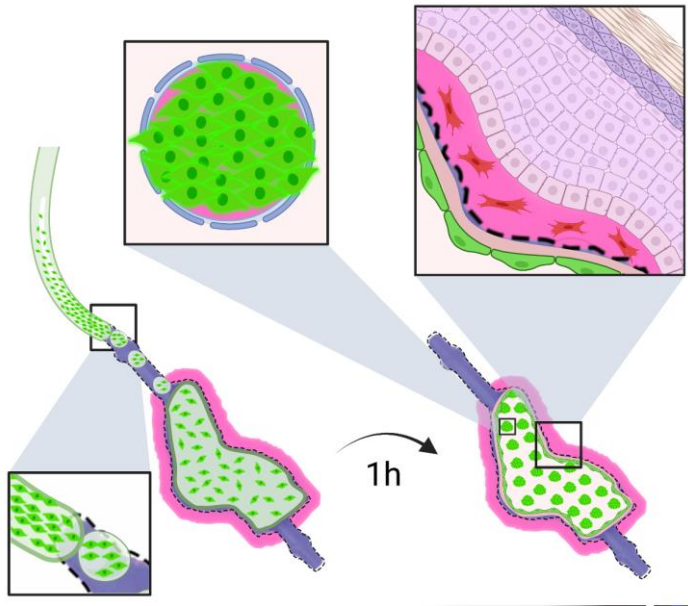


Langer Lines





# Vascularizing Wearable Skin



# Summary of Part I

- Dermal fibroblasts respond to a continuous geometry through ECM remodeling
- Edgeless skin develops anisotropic structural and mechanical properties
- The continuous geometry may determine FB heterogeneities and organization
- Enhances mechanical and ECM properties compared with conventional engineered skin
- It can be vascularized and made more complex

*Can 3D geometries of the skin determine tissue function? (e.g., function follows form)*

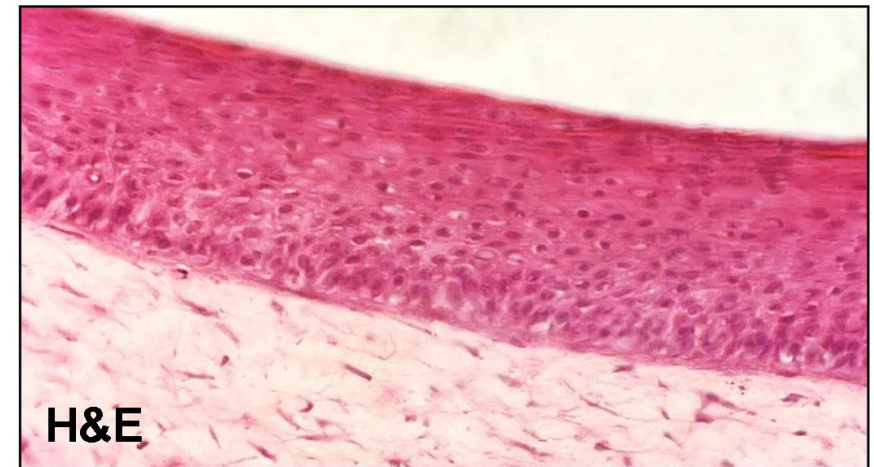
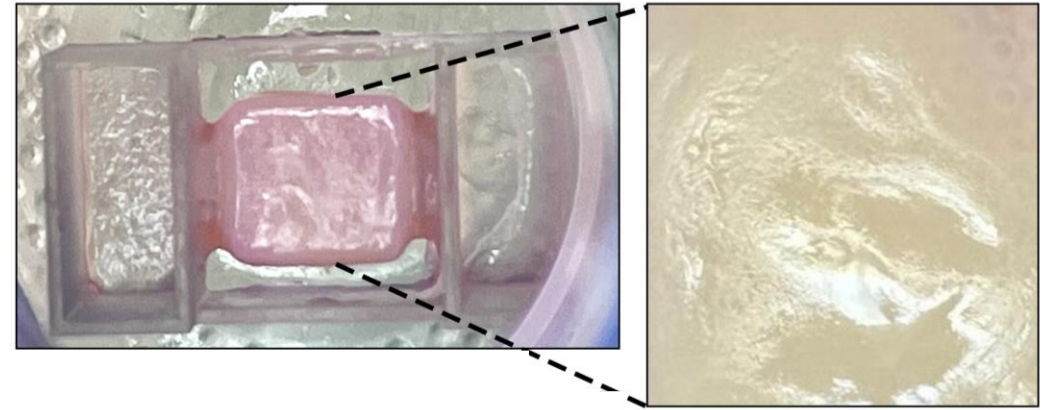
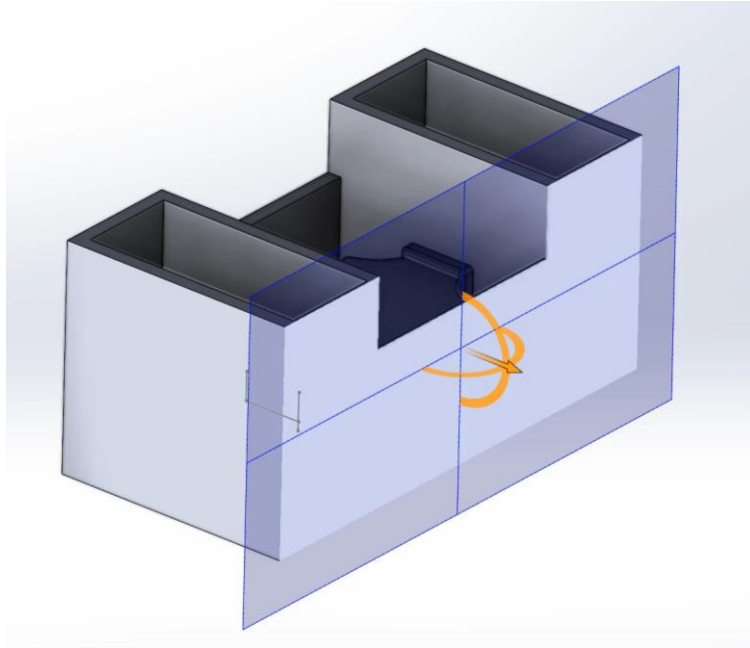
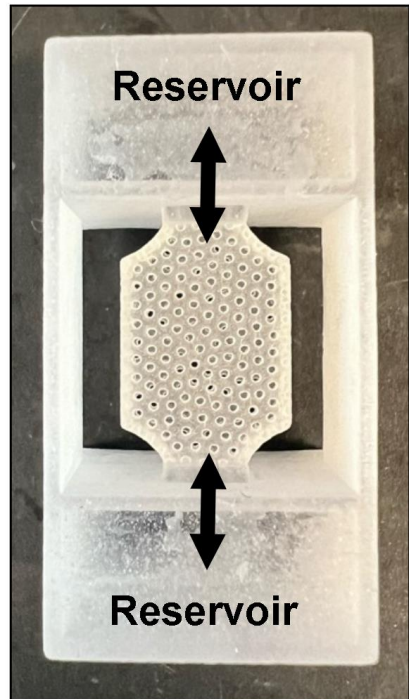


# Miniaturizing and Simplifying Wearable Skin



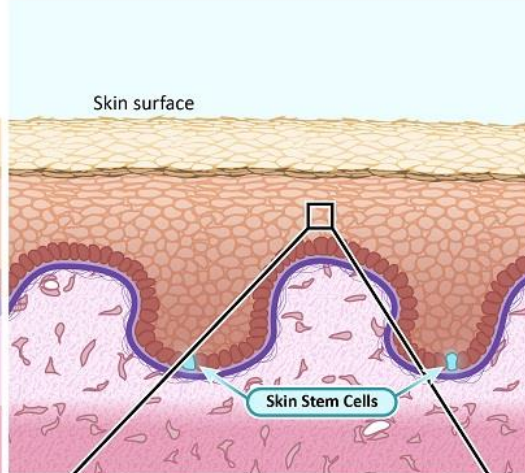
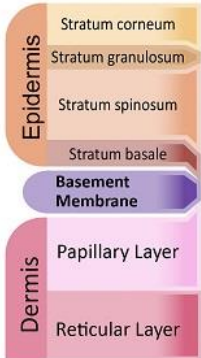


# Miniaturizing and Simplifying Wearable Skin

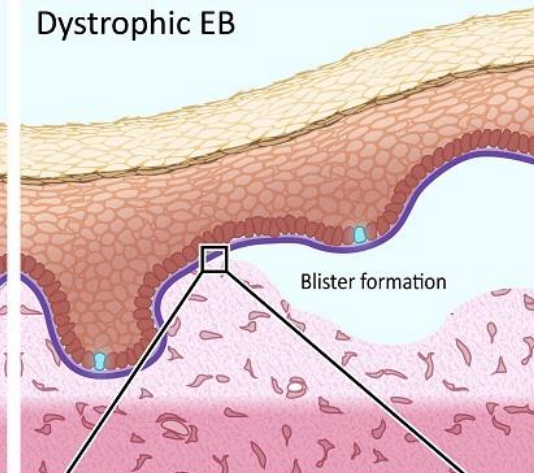


# Recessive Dystrophic Epidermolysis Bullosa

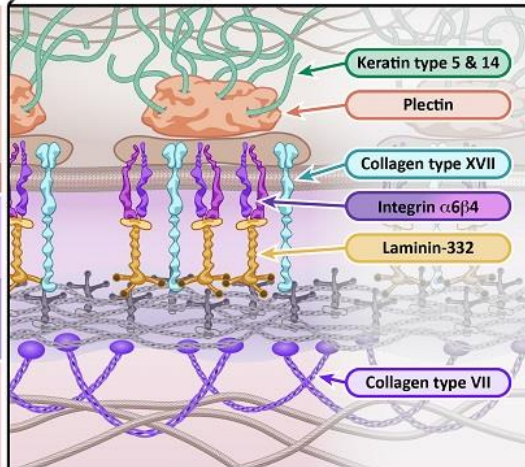
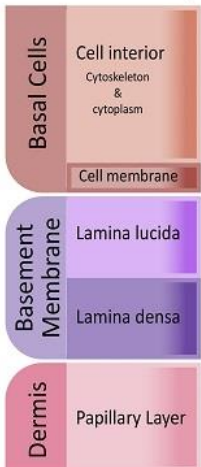
Healthy Skin



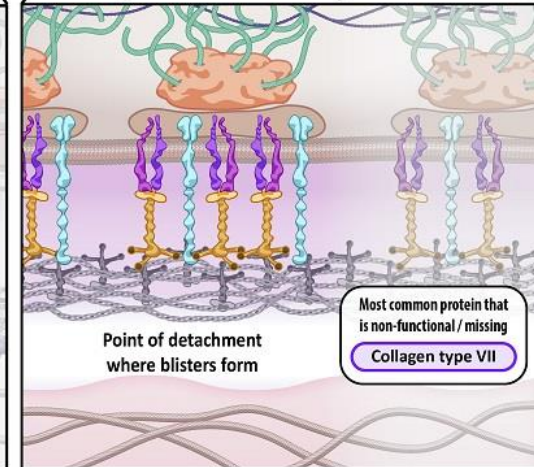
Dystrophic EB



Proteins of epidermis-dermis junction



Epidermis-dermis junction in DEB



A



C

Mitten-like deformity



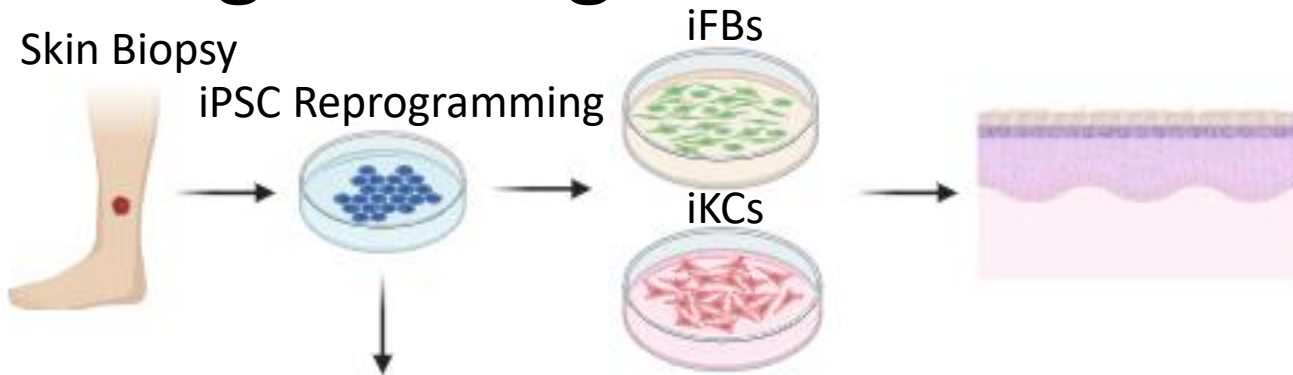
a

Lembo. BMC. 2021

Bellon et al, JAAD, 2024



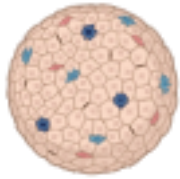
# Engineering RDEB Skin from iPSC-derived cells



## Limitations

- Promising in mice but poor 3D skin in vitro
- Not reproducible
- EMT in culture or in 3D Skin

Embryoid Bodies

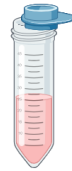


Complex Skin Organoids

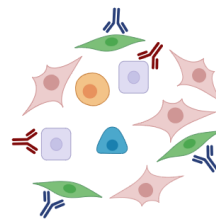


Koehler's Lab, Nature, 2020

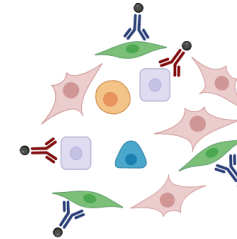
Dissociate  
Strain



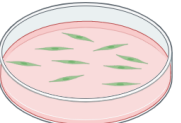
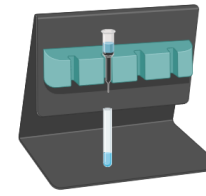
Primary  
antibody



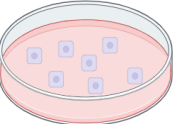
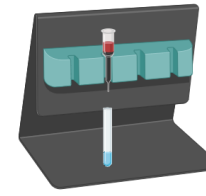
Magnetic  
beads



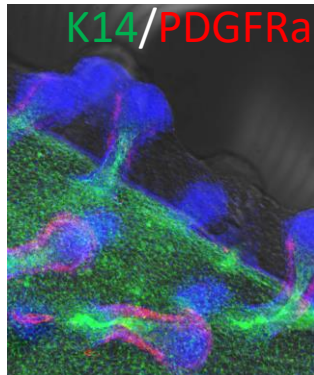
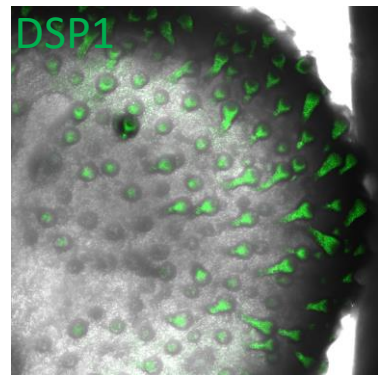
Magnetic  
sorting



iPSC-derived  
Fibroblasts



iPSC-derived  
Keratinocytes



Abaci Lab, Unpublished

Day 75

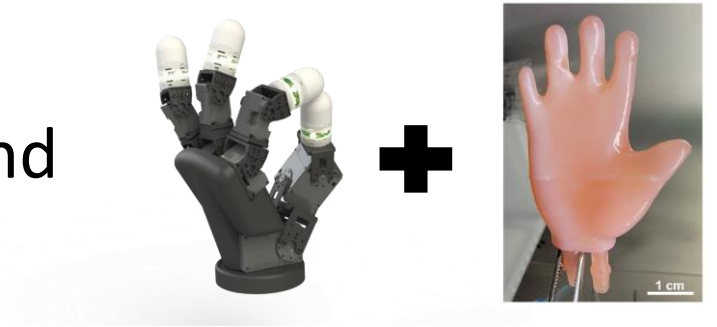


# Summary

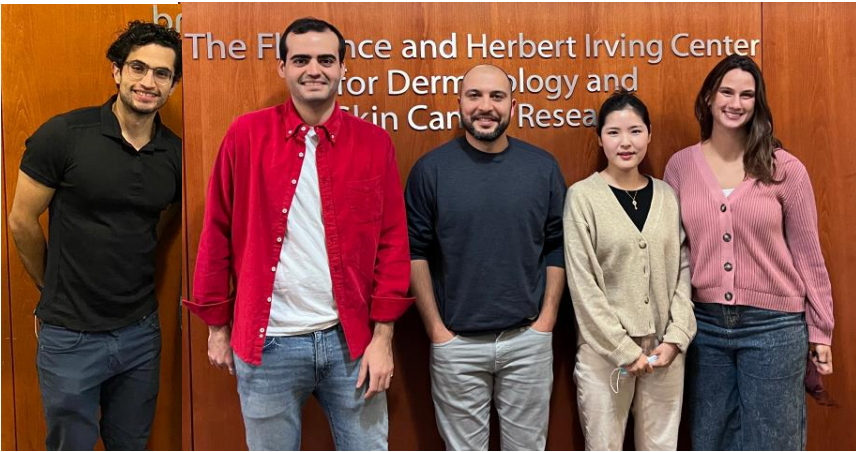
- Miniaturized 3-dimensional (3D) wearable skin model allows for disease modelling
- Pluripotent cell derived skin organoids can be used as a source of iKCs and iFBs for RDEB modelling
- Early organoid morphology can be monitored to optimize each cell line.
- Our method allows for engineering 3D skin in vitro using RDEB cells

# Ongoing/Future Work

- Mechanotransduction in skin development, fibrosis and aging (in the context of geometry).
- Integration with robotic systems to study mechanical stimulation in development and aging (in collaboration with Dr. Matei Ciocarlie at Columbia)
- Skin transplantation on challenging body sites and integration with VCAs (in collaboration with Dr. Gerald Brandacher and Dr. BC Oh and at JHU Surgery)



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## Abaci Lab

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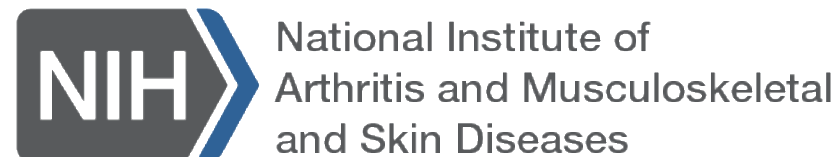


## Myers Lab

Shuynag Fang, Ph.D.

## Kysar Lab

Abigail Herschman





# Thank You!



Escher, 1956