

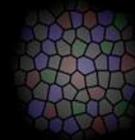
# Microengineered Physiological Bio-mimicry: Human Organs-on-Chips

D. Dan Huh

Wilf Family Term Assistant Professor  
Department of Bioengineering  
University of Pennsylvania  
<http://biolines.seas.upenn.edu>

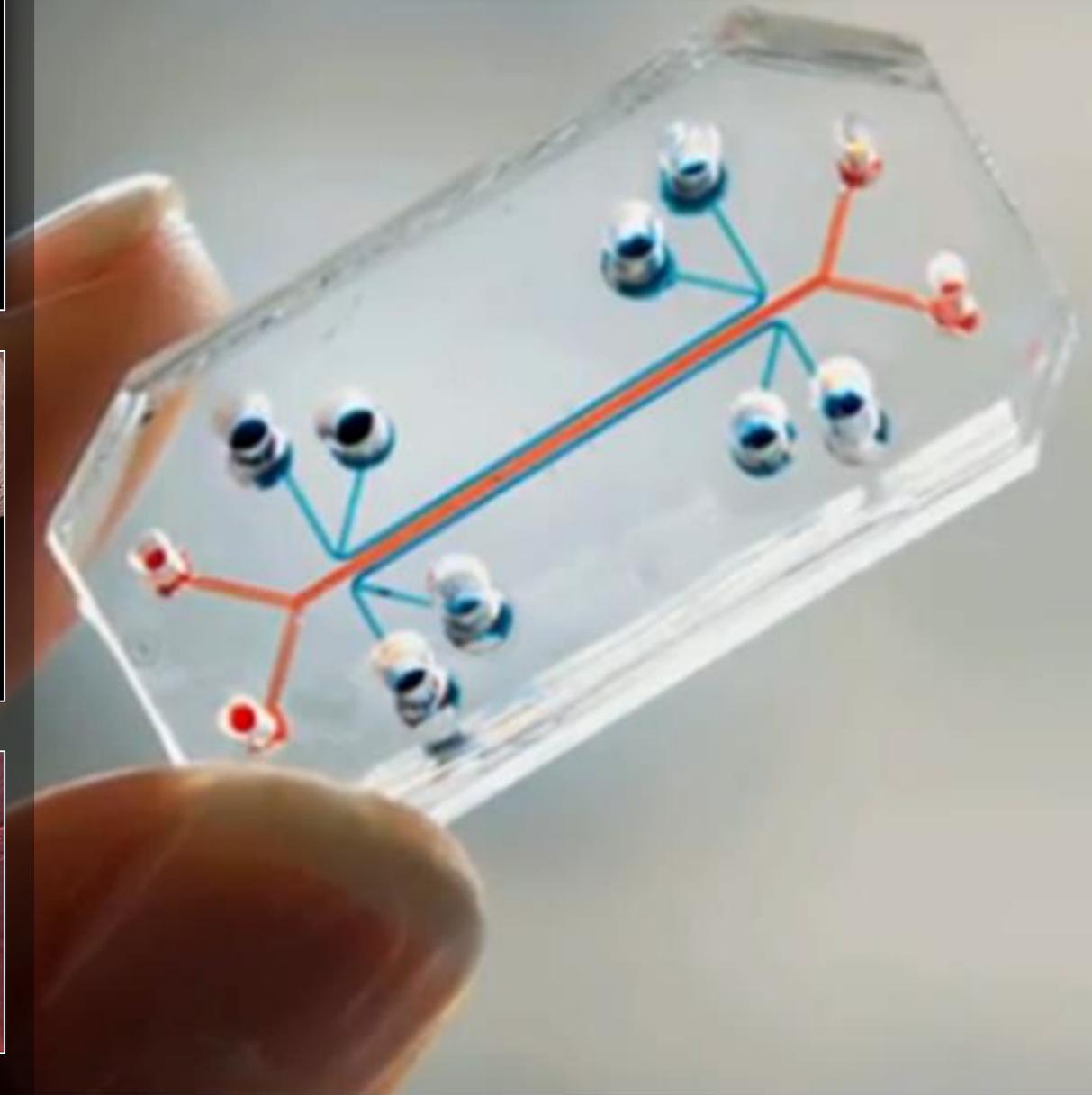
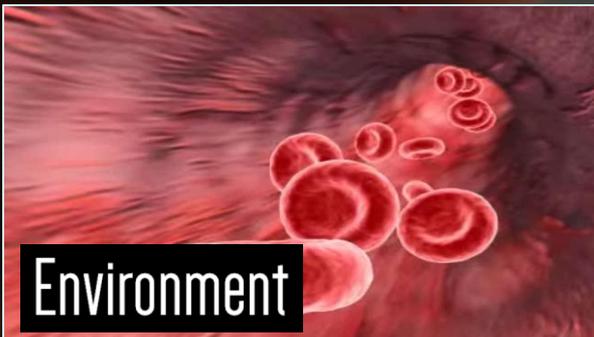
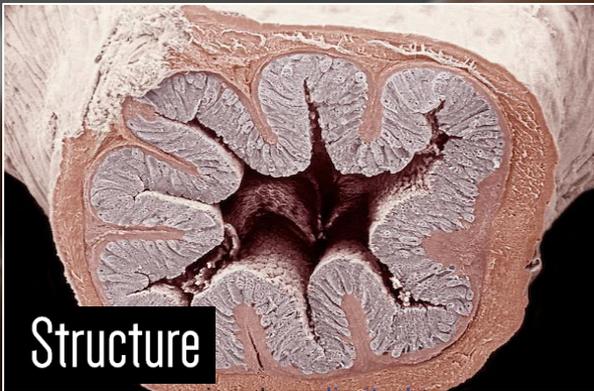
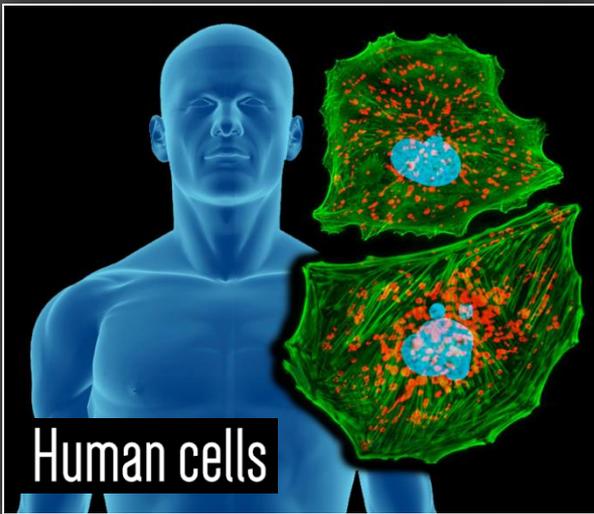


**BIOLOGICALLY INSPIRED**  
ENGINEERING SYSTEMS LABORATORY



**BIOLines**

# Human organs-on-a-chip

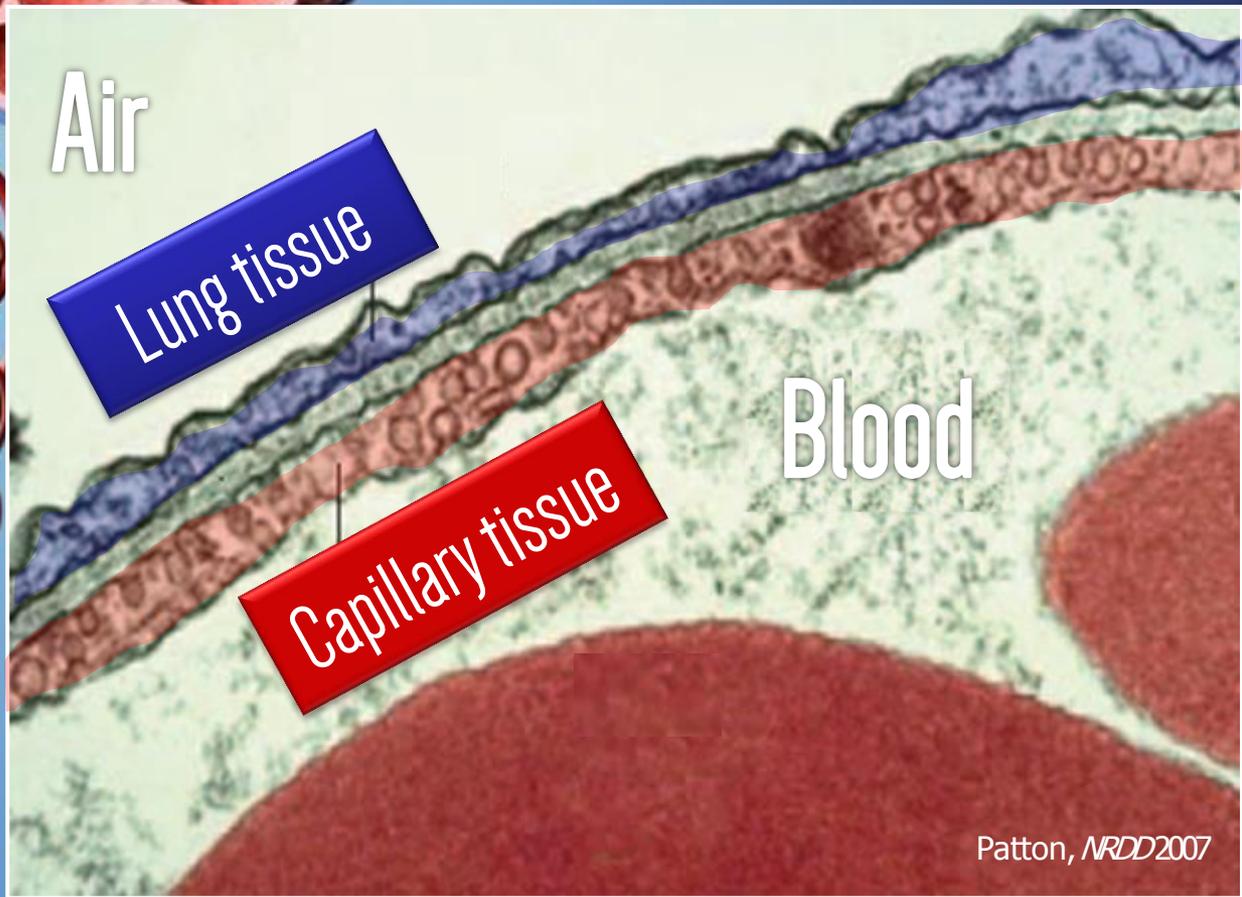
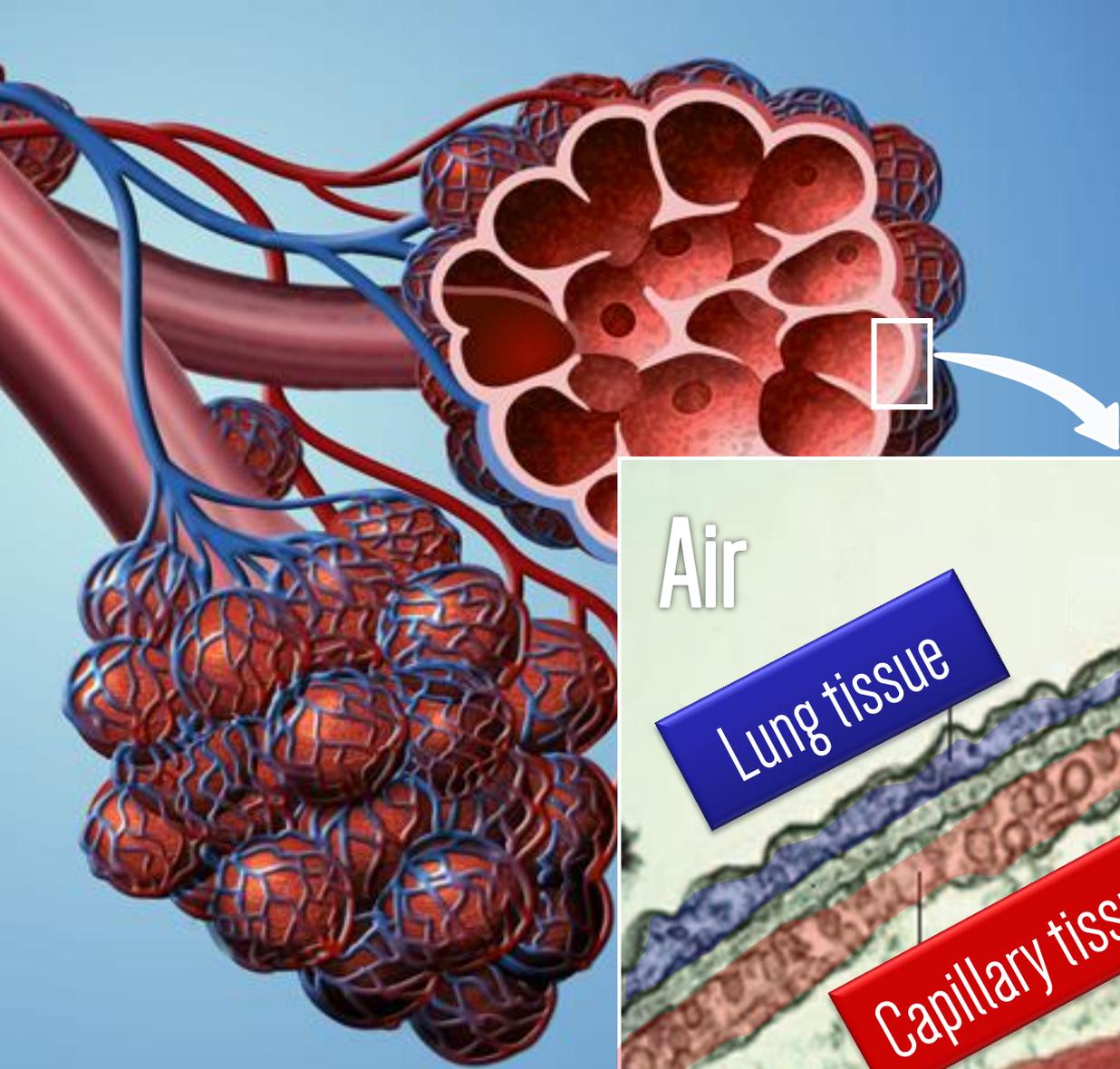




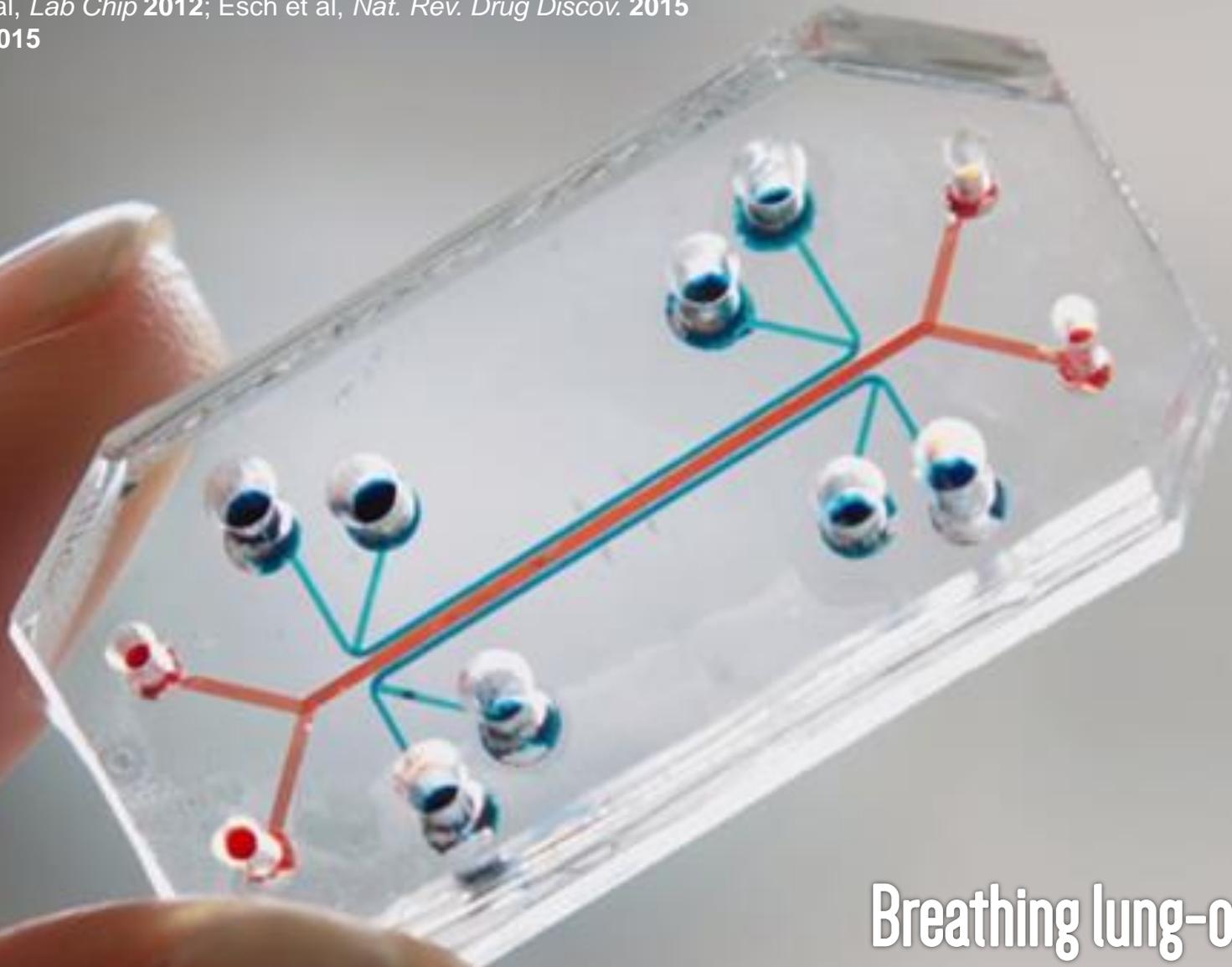
Human lung

# Alveoli



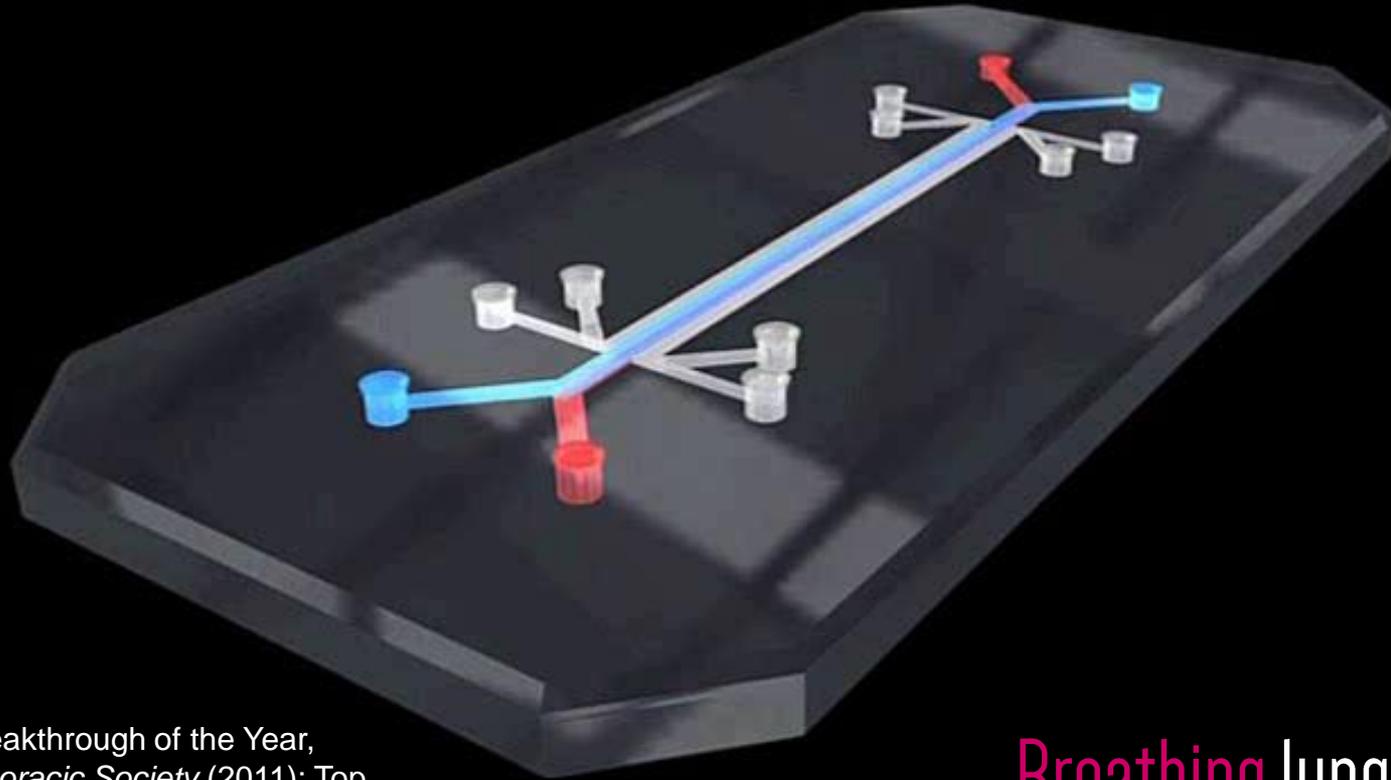


D. Huh et al, *Science* 2010; D. Huh et al, *Trends Cell Biol.* 2011; D. Huh et al, *Lab Chip* 2012; Esch et al, *Nat. Rev. Drug Discov.* 2015  
TEDx 2015



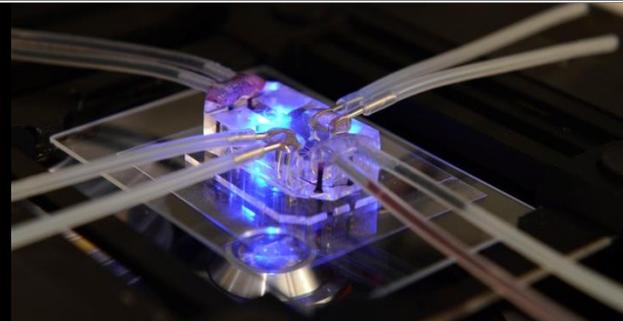
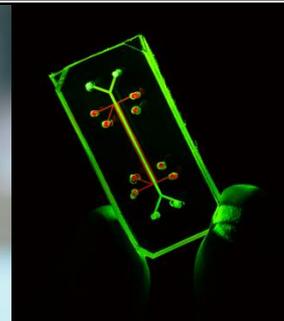
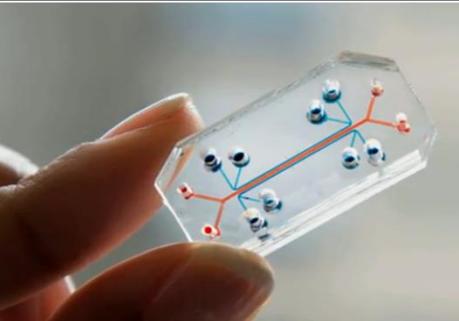
Breathing lung-on-a-chip

D. Huh et al, *Science* **2010**; D. Huh et al, *Trends Cell Biol.* **2011**; D. Huh et al, *Lab Chip* **2012**; Esch et al, *Nat. Rev. Drug Discov.* **2015**  
TEDx **2015**

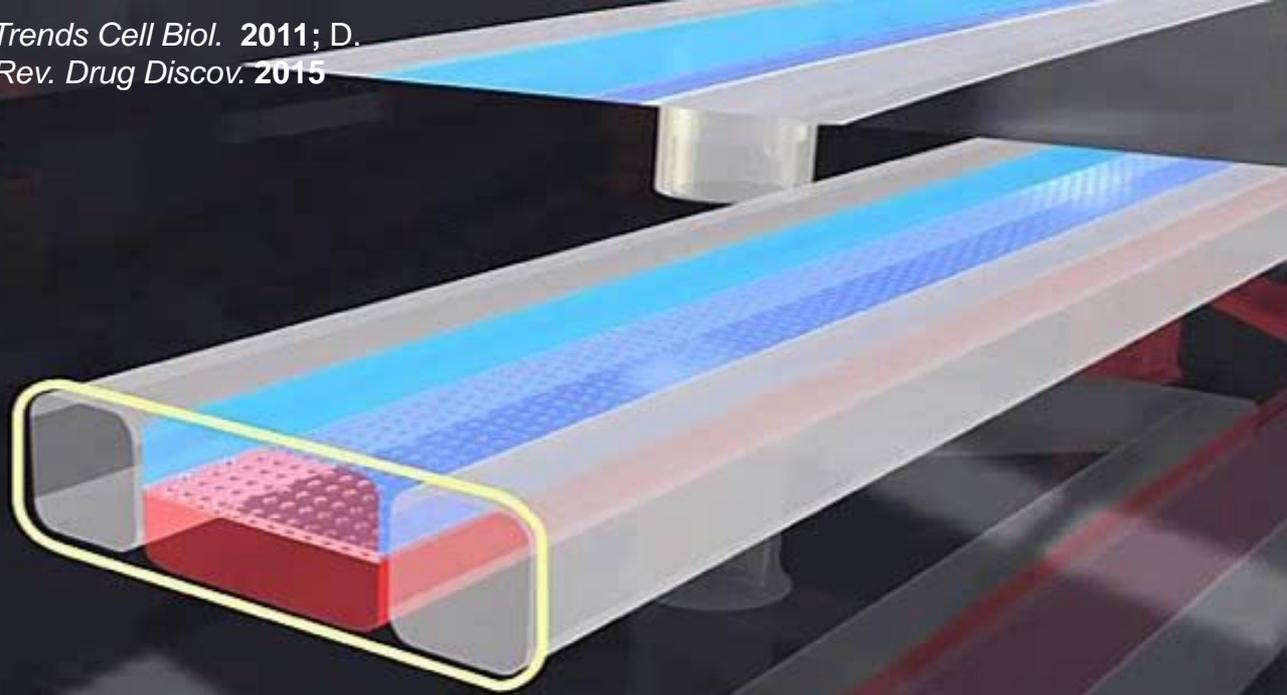


Scientific Breakthrough of the Year,  
*American Thoracic Society* (2011); Top  
100 stories of 2010, *Discover Magazine*

## Breathing lung-on-a-chip

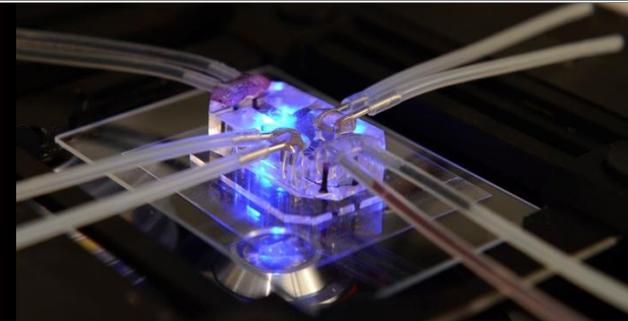
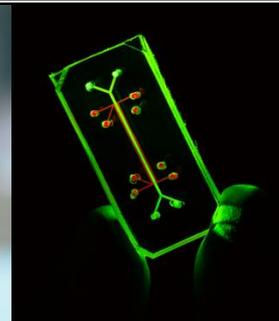
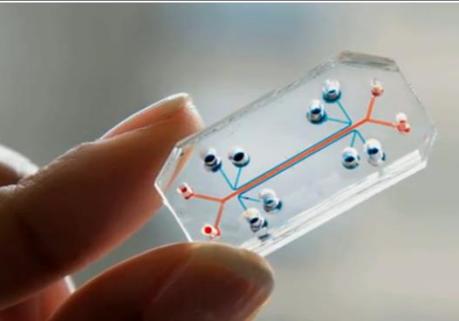


D. Huh et al, *Science* **2010**; D. Huh et al, *Trends Cell Biol.* **2011**; D. Huh et al, *Lab Chip* **2012**; Esch et al, *Nat. Rev. Drug Discov.* **2015**  
TEDx **2015**

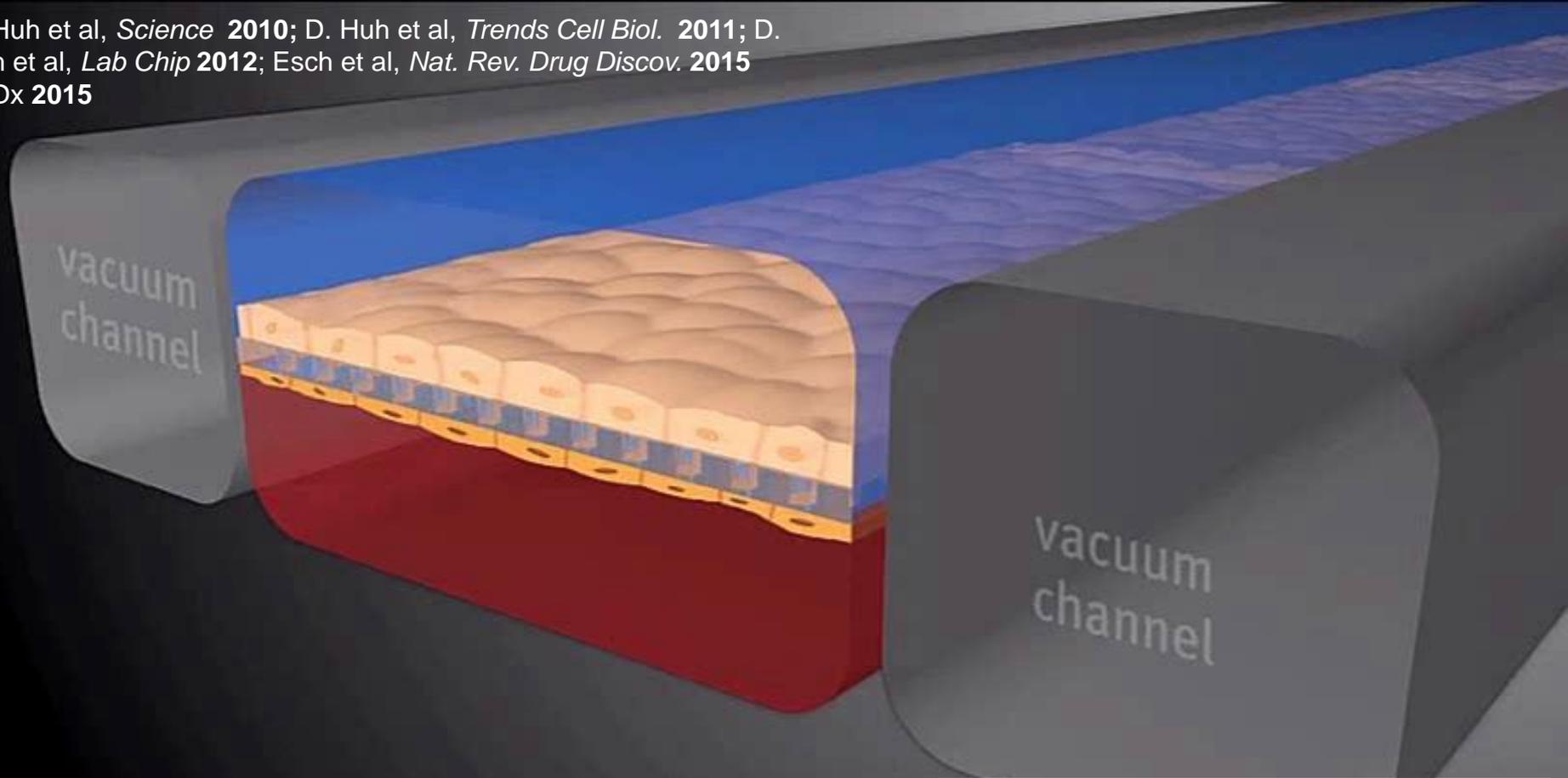


Scientific Breakthrough of the Year,  
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100 stories of 2010, *Discover Magazine*

Breathing lung-on-a-chip

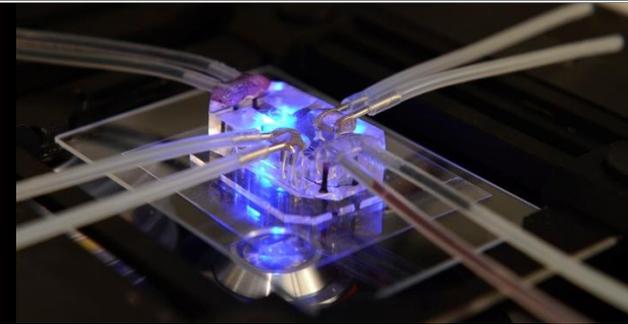
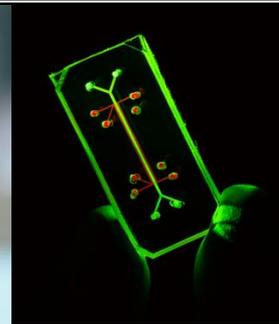


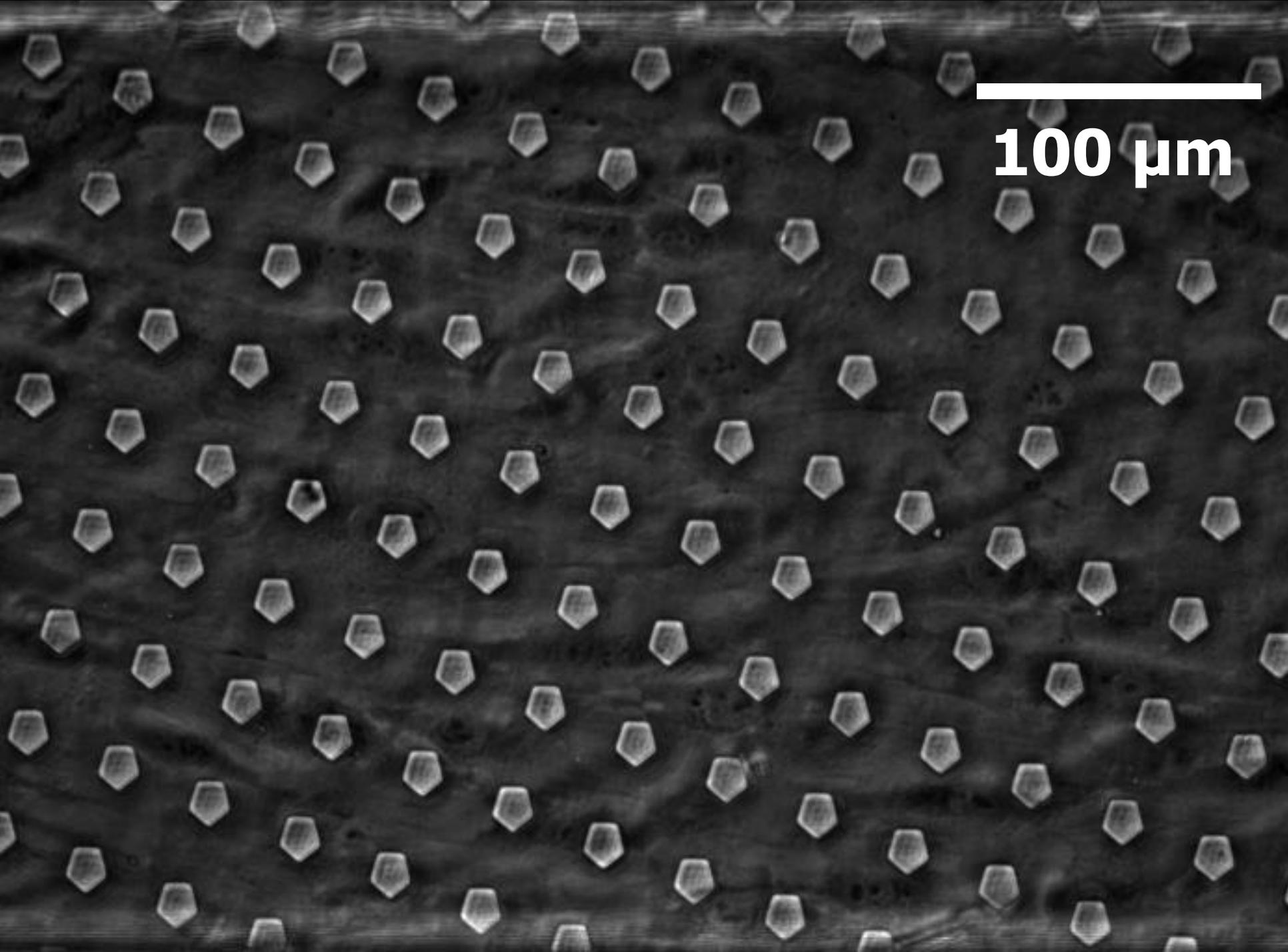
D. Huh et al, *Science* 2010; D. Huh et al, *Trends Cell Biol.* 2011; D. Huh et al, *Lab Chip* 2012; Esch et al, *Nat. Rev. Drug Discov.* 2015  
TEDx 2015



Scientific Breakthrough of the Year,  
*American Thoracic Society* (2011); Top  
100 stories of 2010, *Discover Magazine*

Breathing lung-on-a-chip





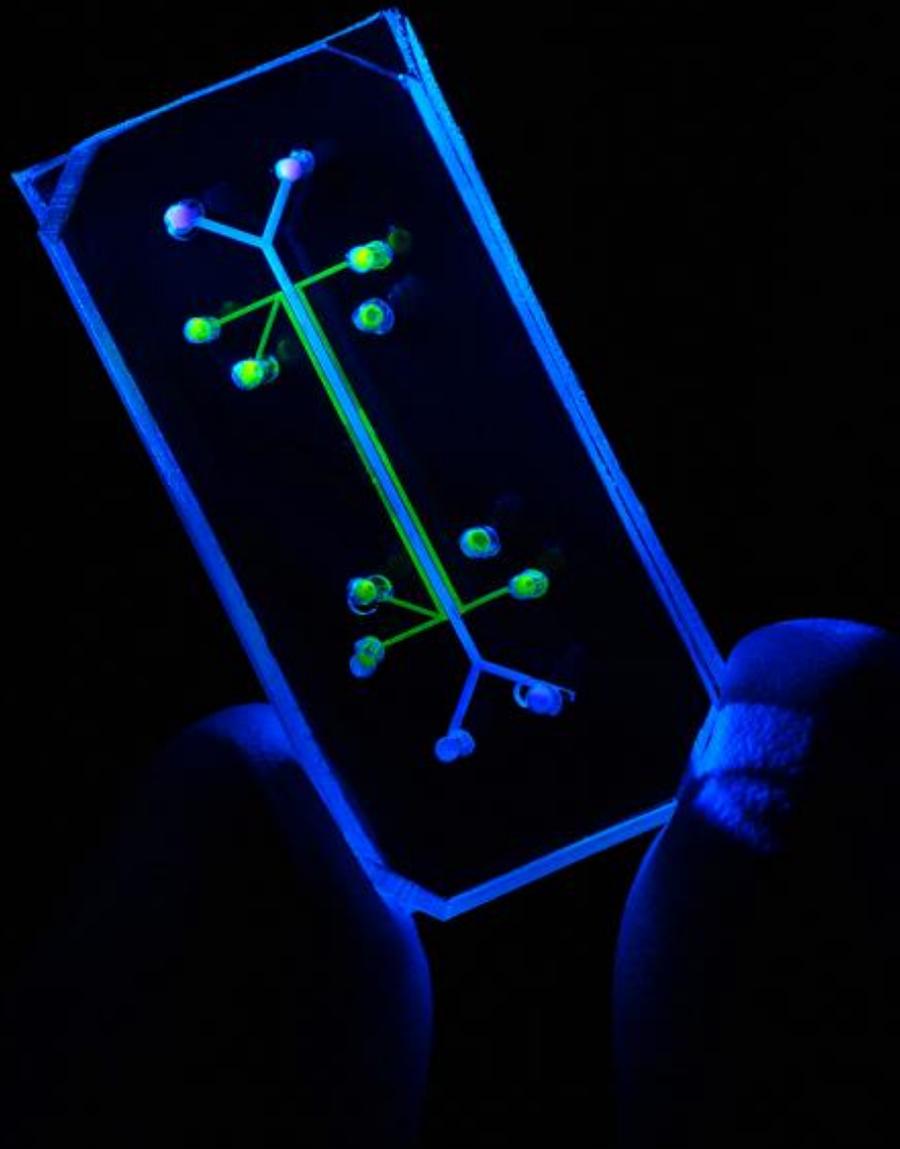
100  $\mu\text{m}$

**Air**

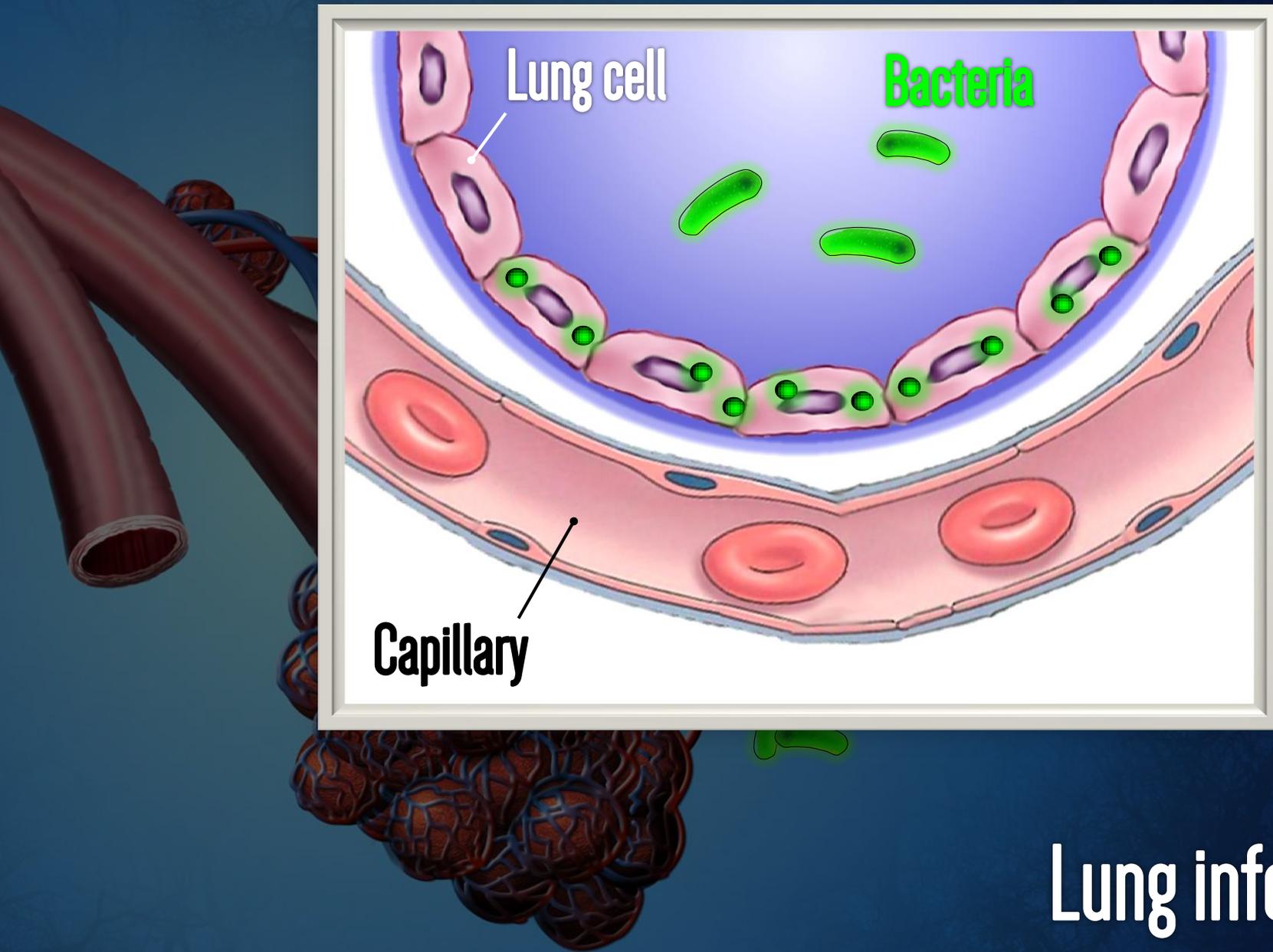
**Lung cells**

**Capillary cells**

**Liquid flow**



Mimicking complex organ-level functions



Lung cell

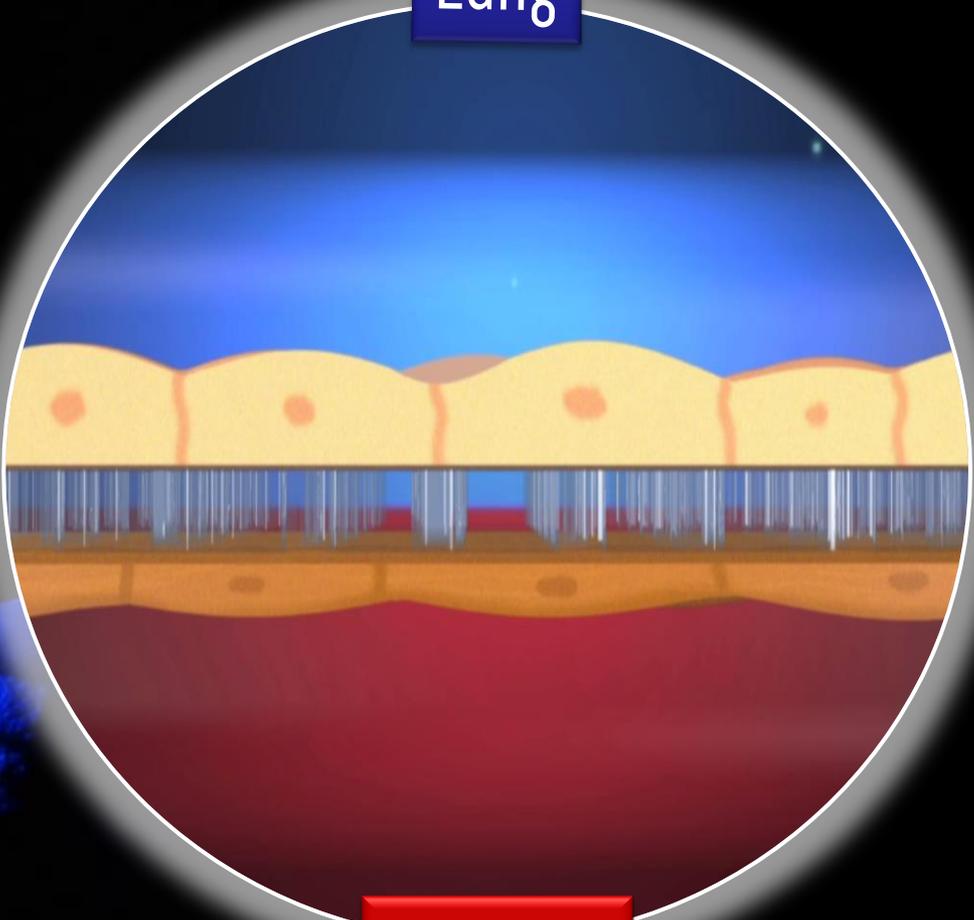
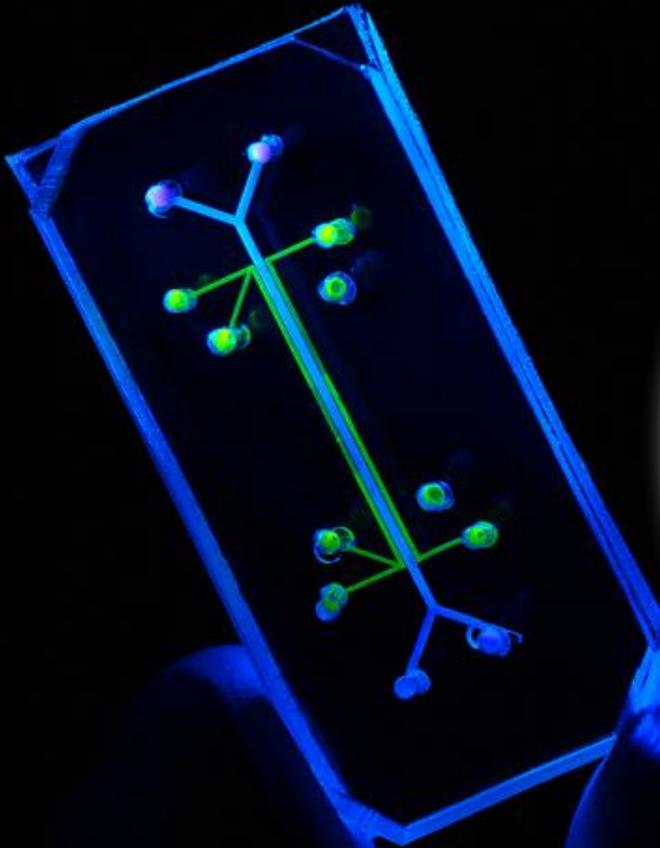
Bacteria

Capillary

Lung infection

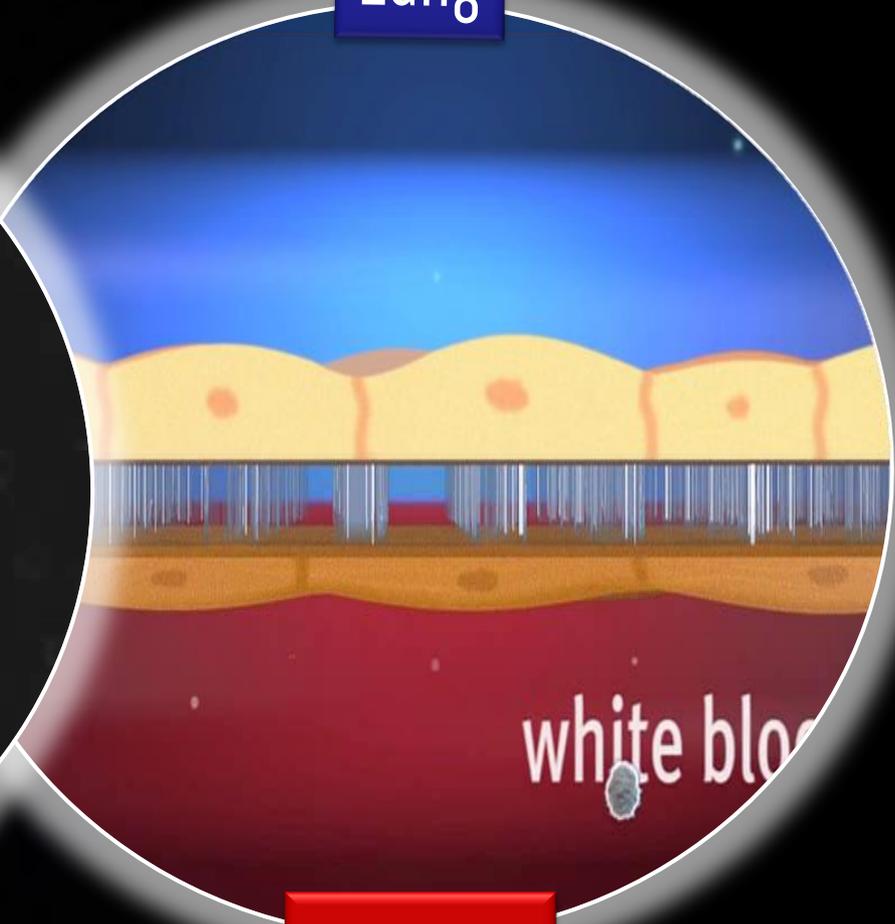
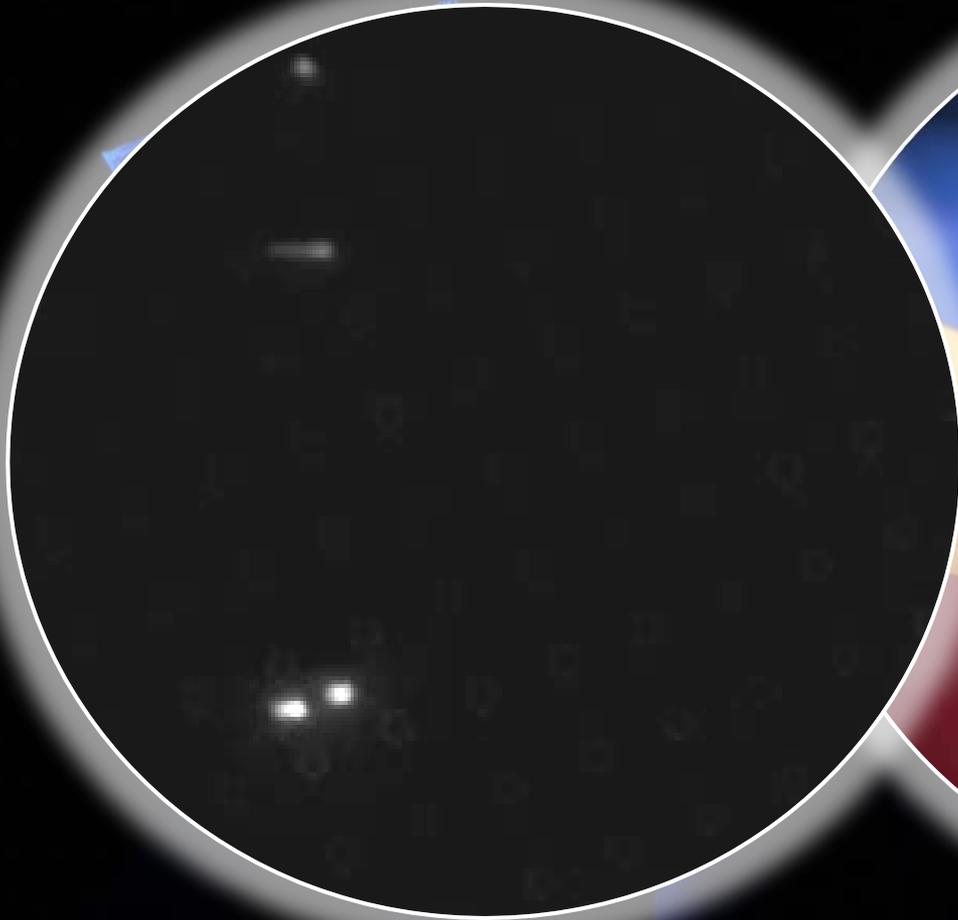


Lung



Capillary

Lung

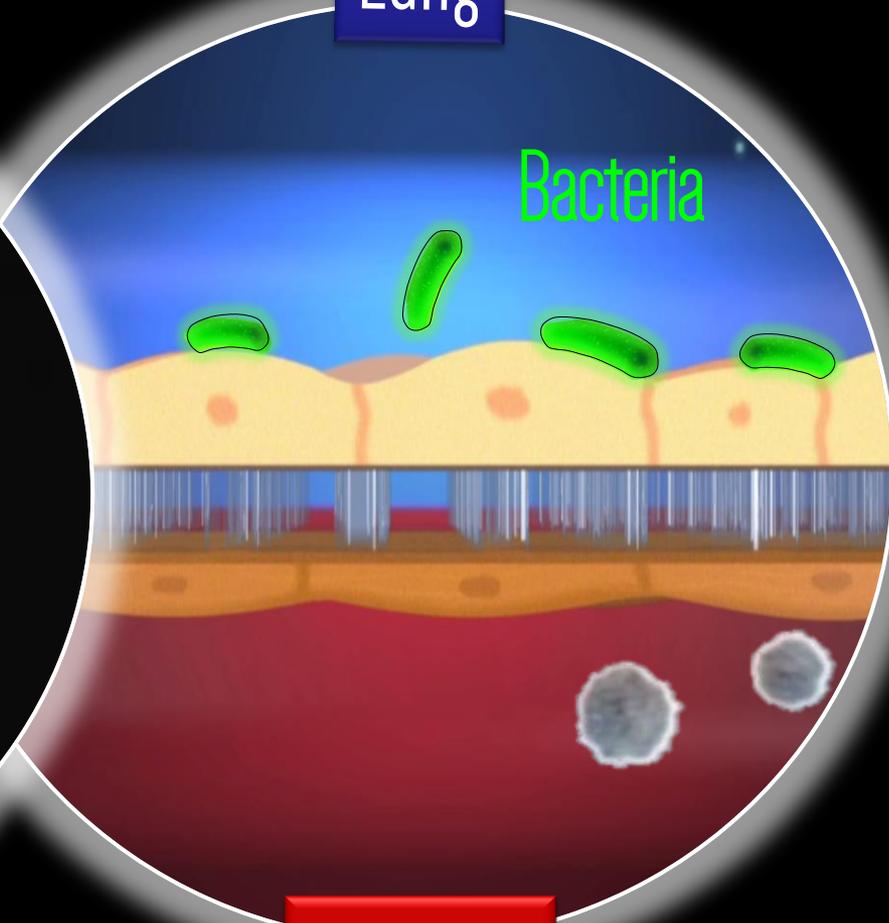
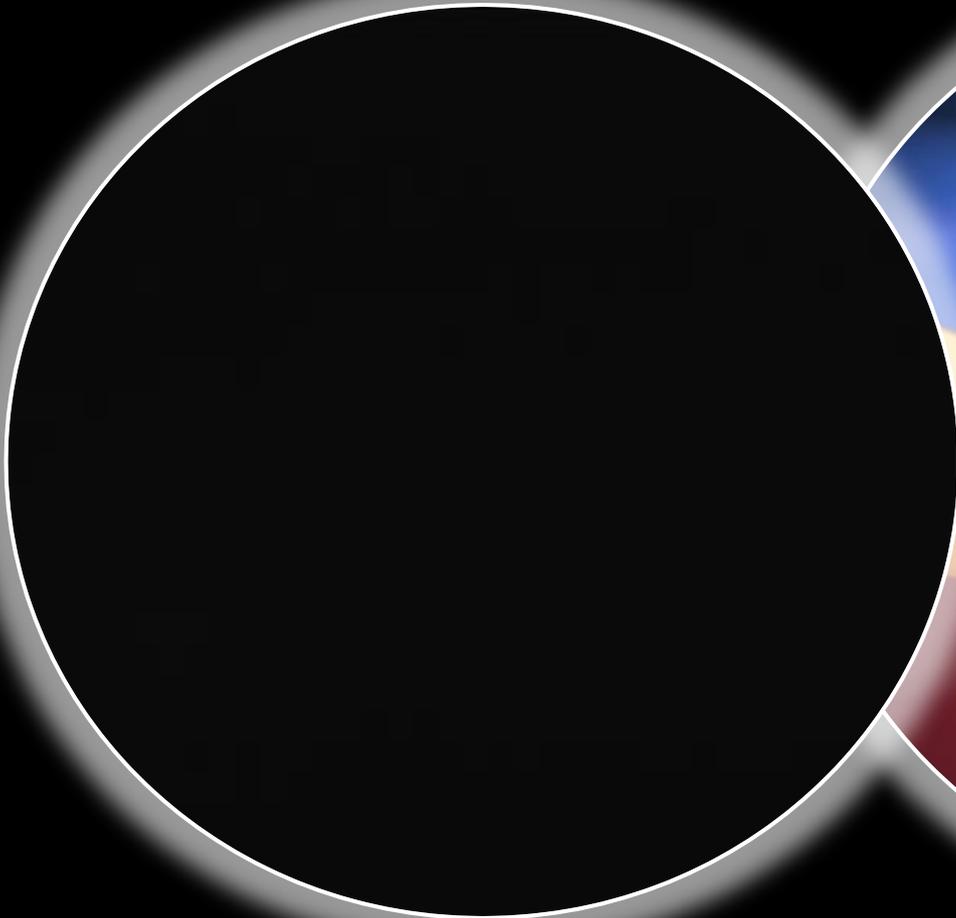


Capillary

Lung

Bacteria

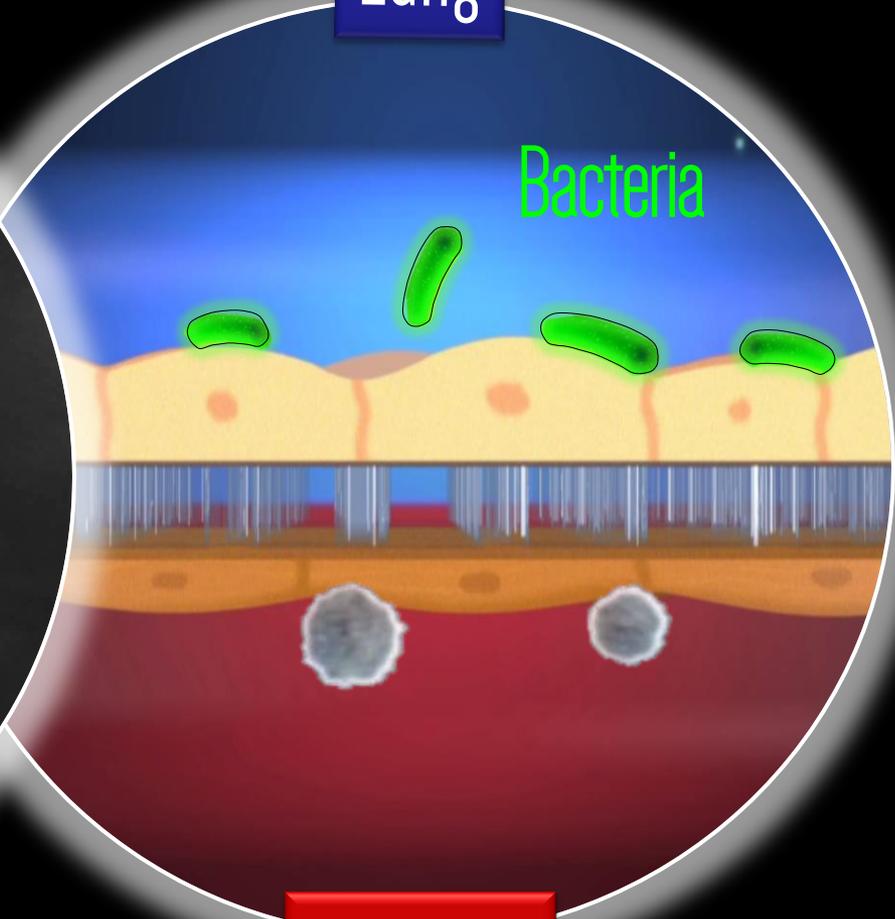
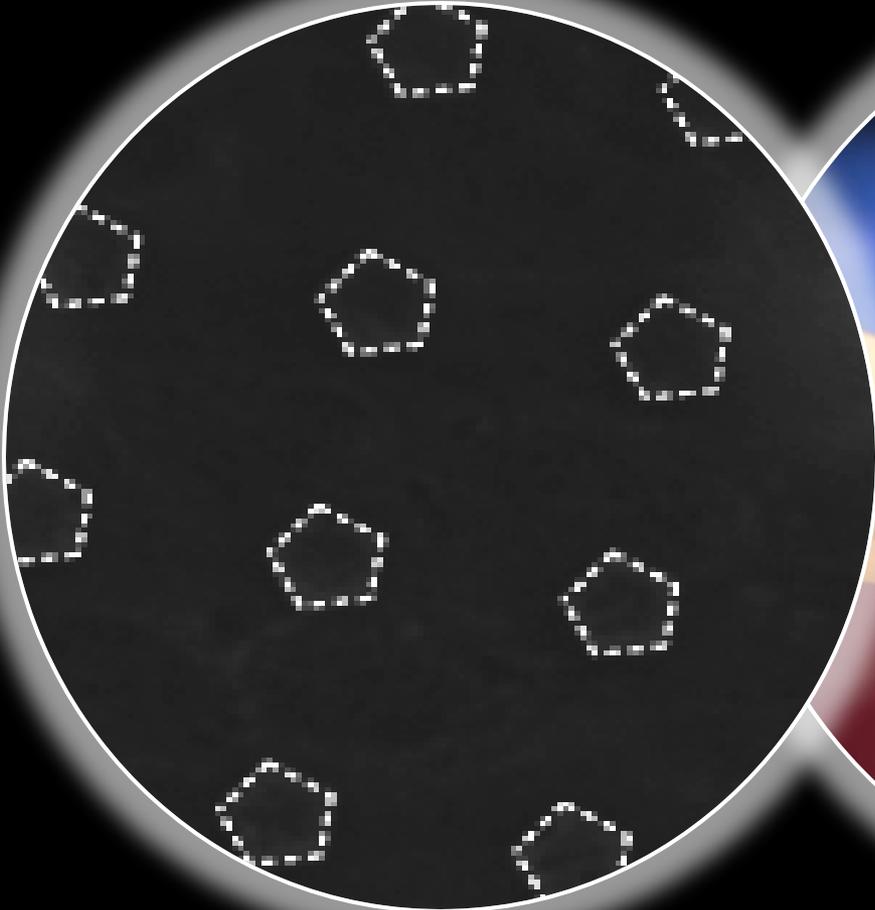
Capillary



Lung

Bacteria

Capillary

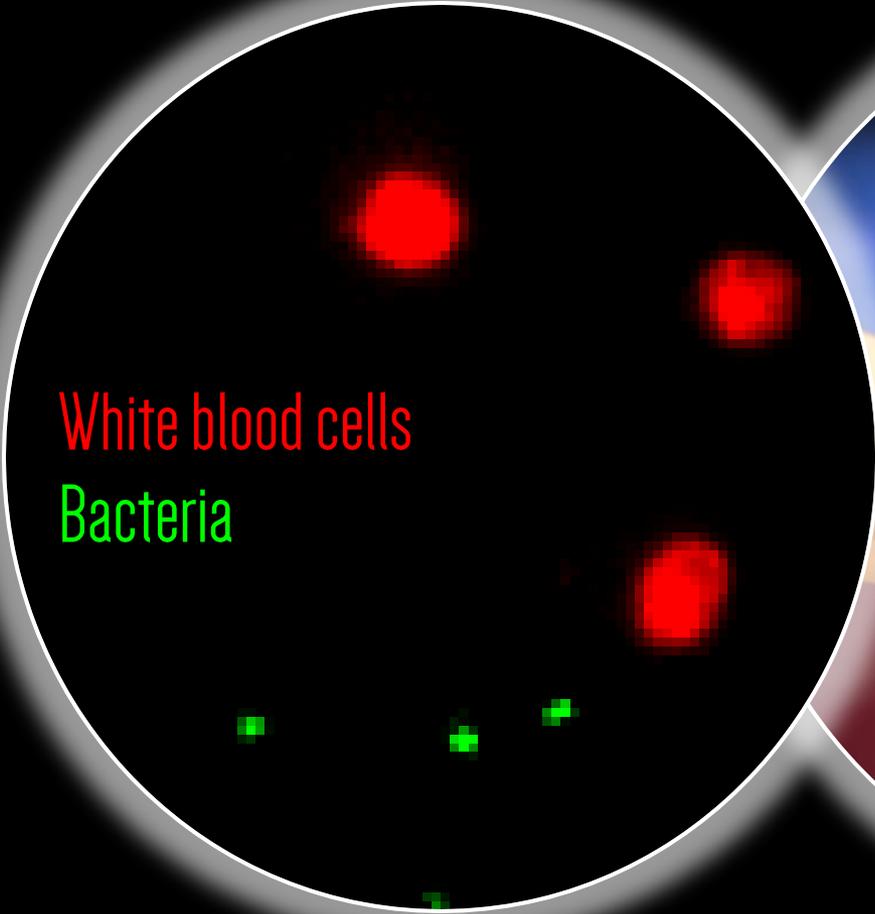


Lung

Bacteria



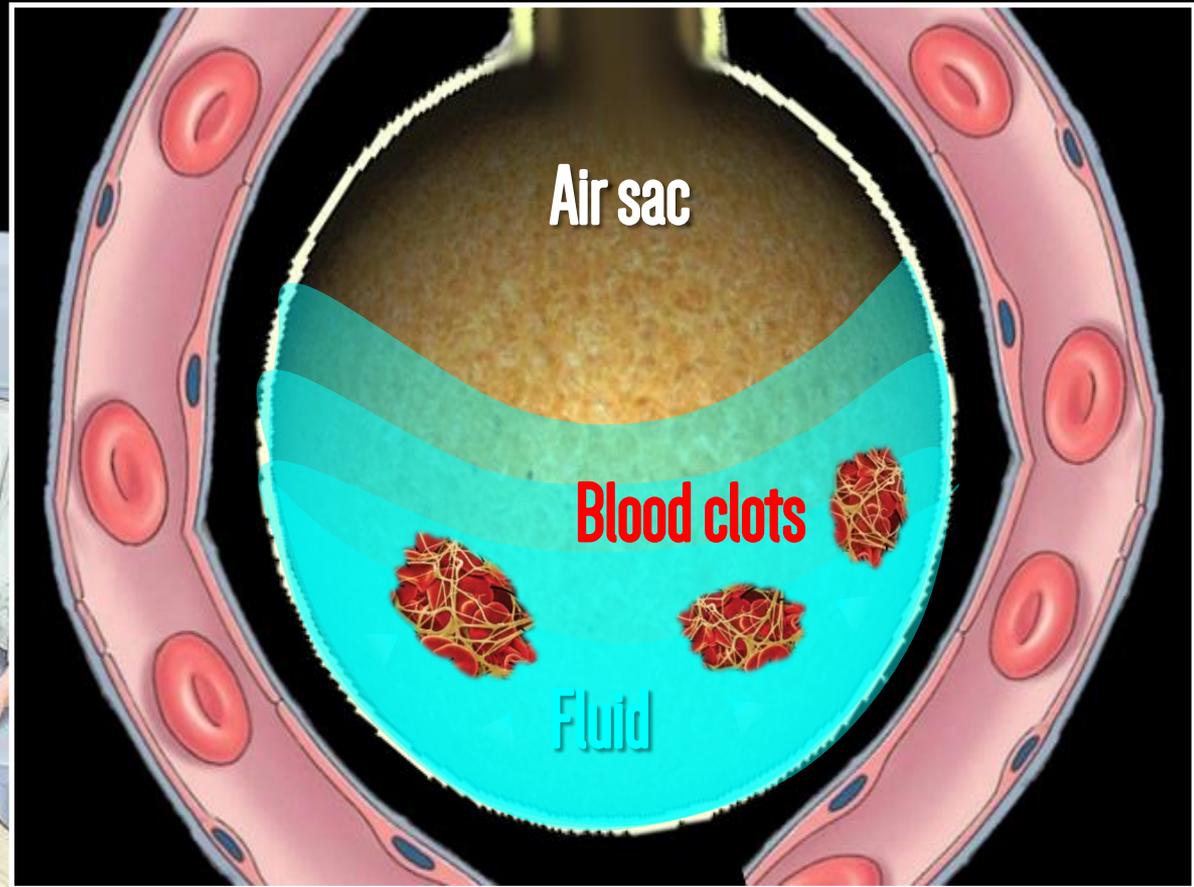
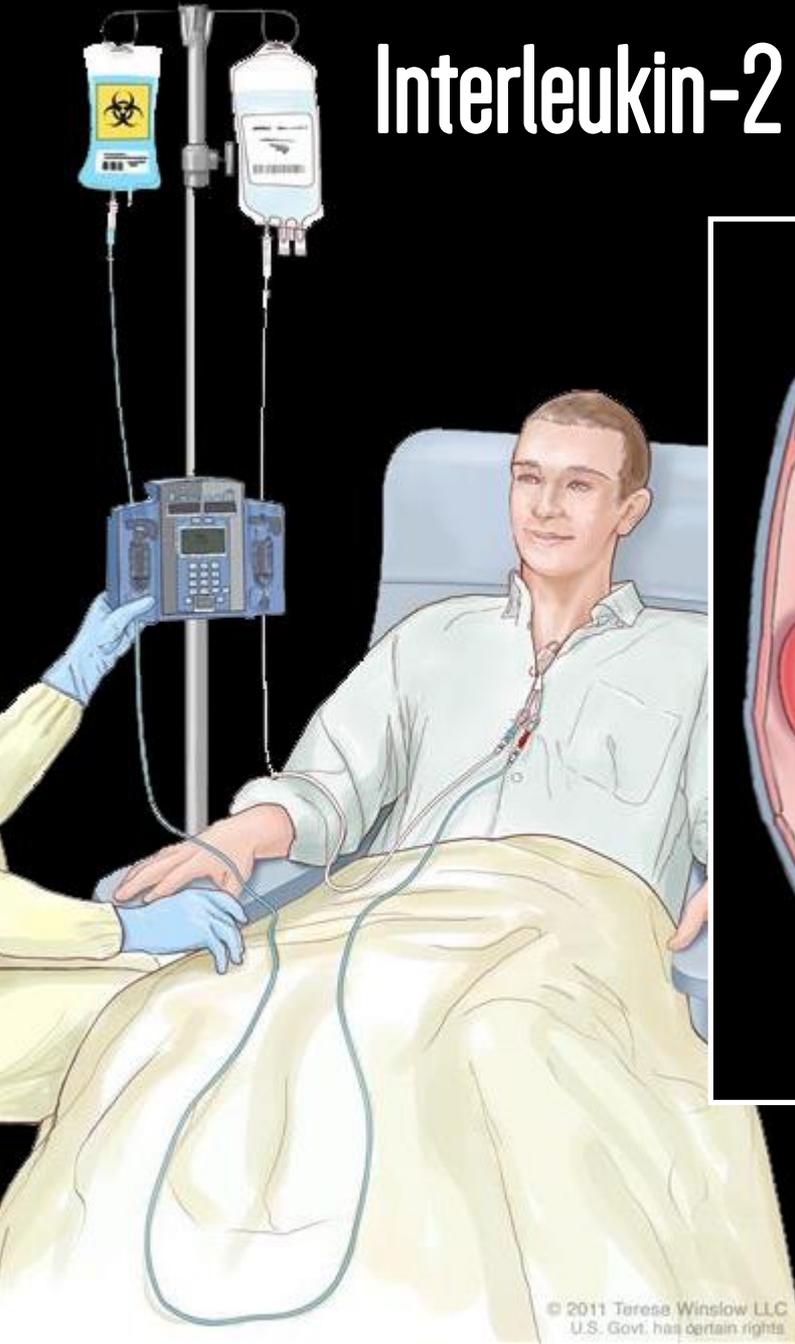
Capillary



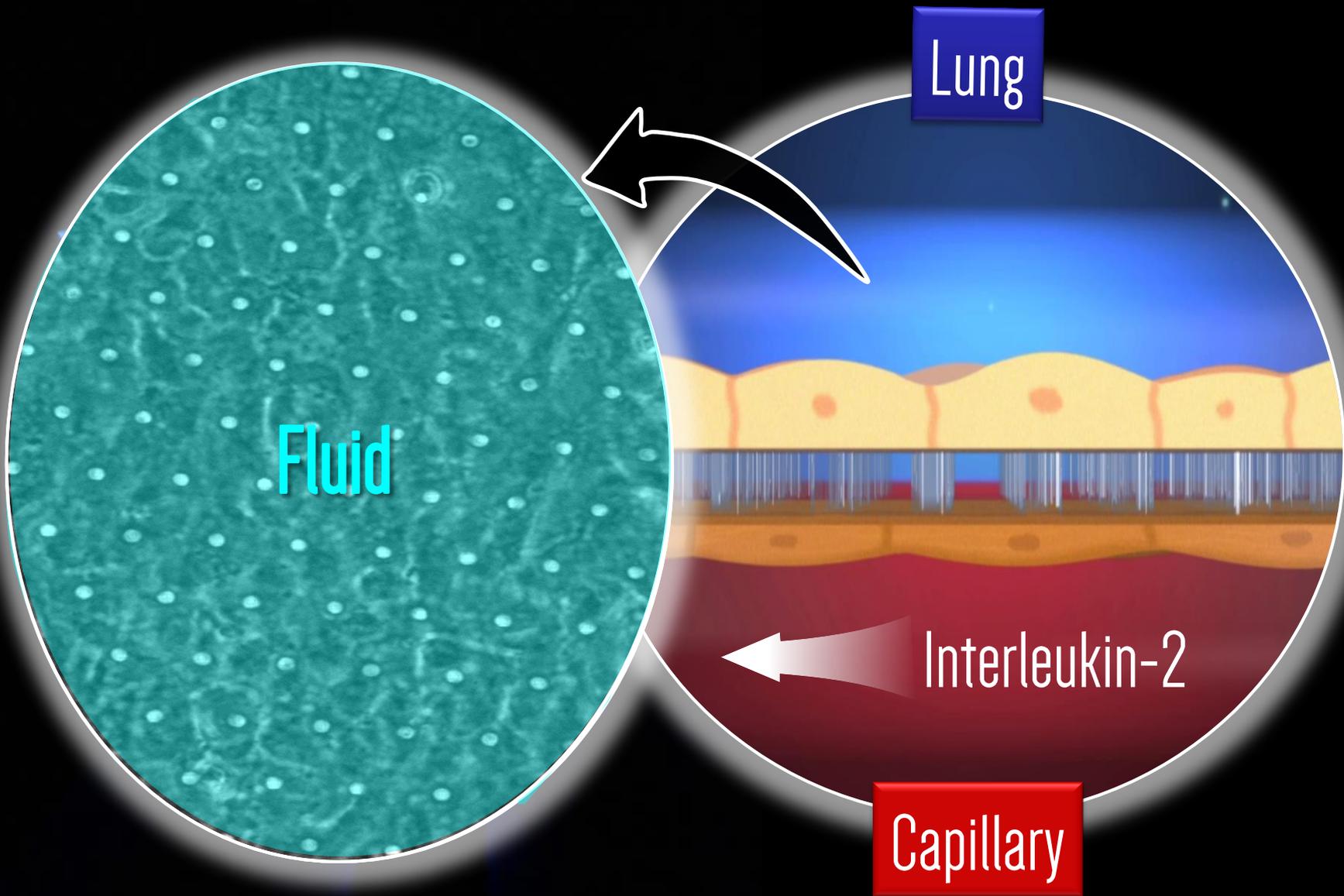
White blood cells  
Bacteria

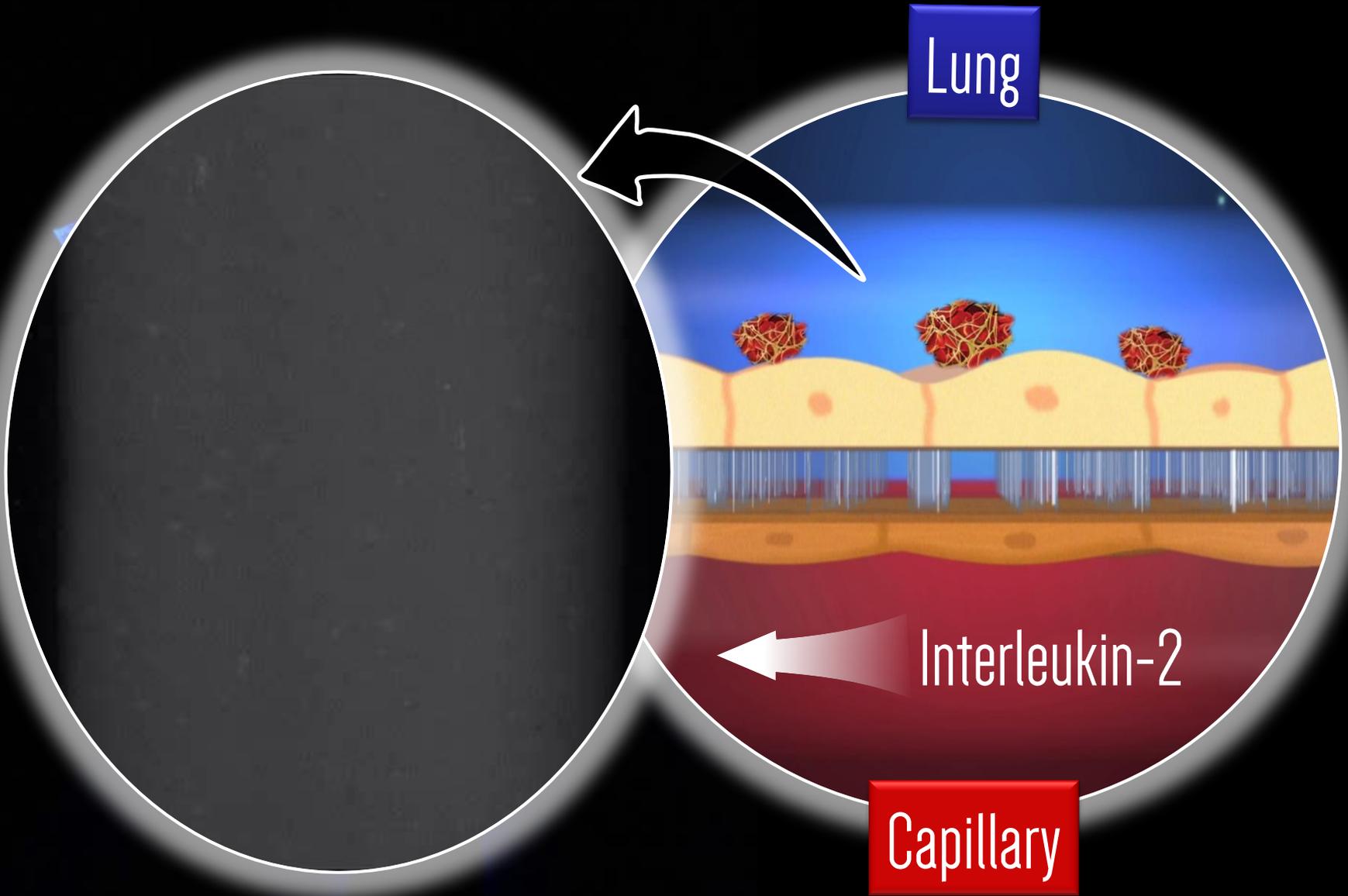
Disease-on-a-chip

# Interleukin-2



## Pulmonary edema

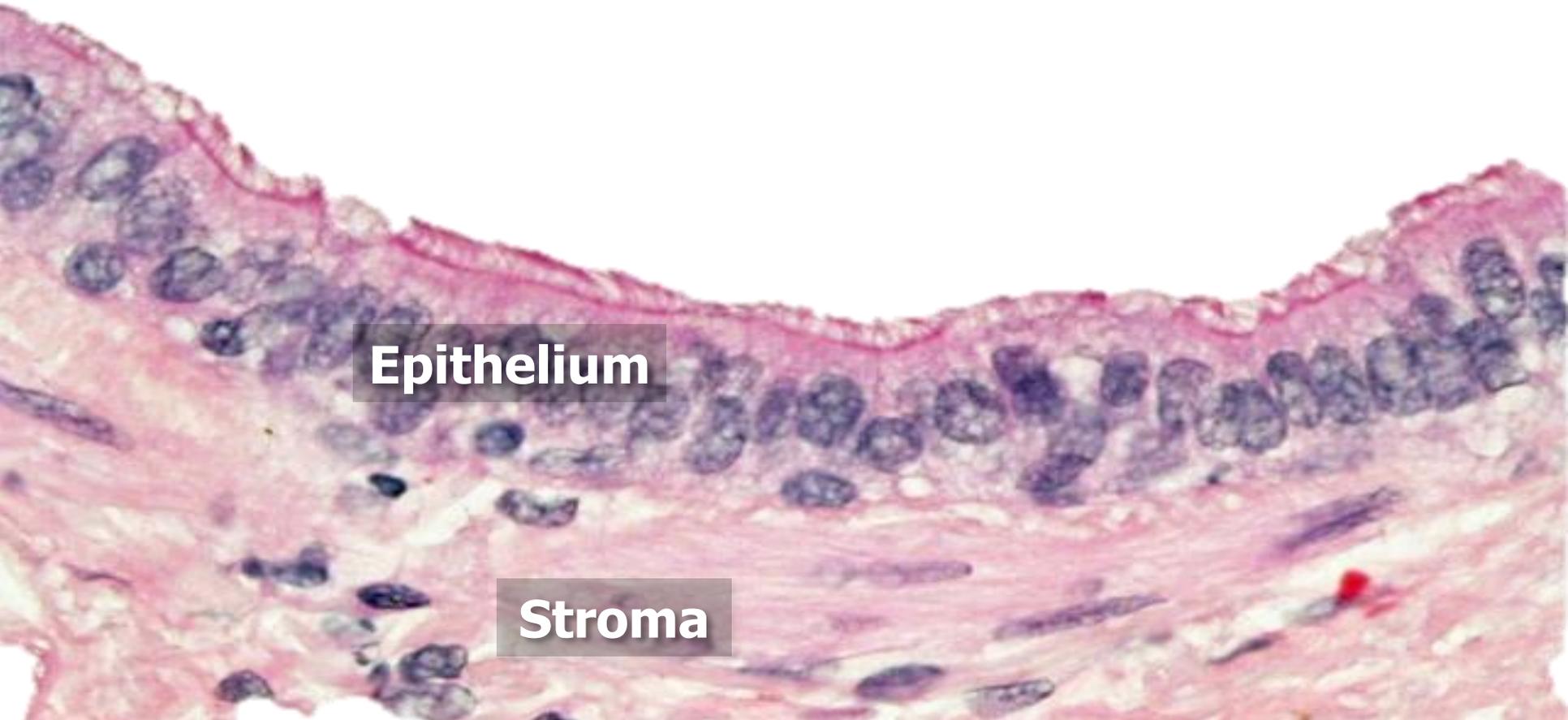




Smoking lung-on-a-chip

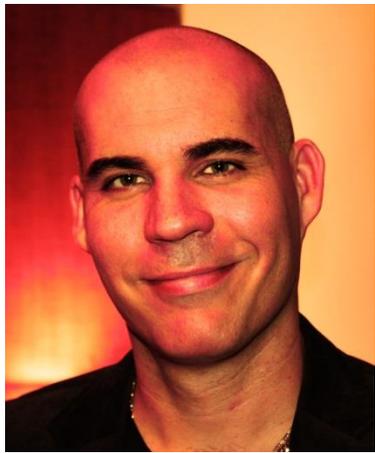


# Small airway

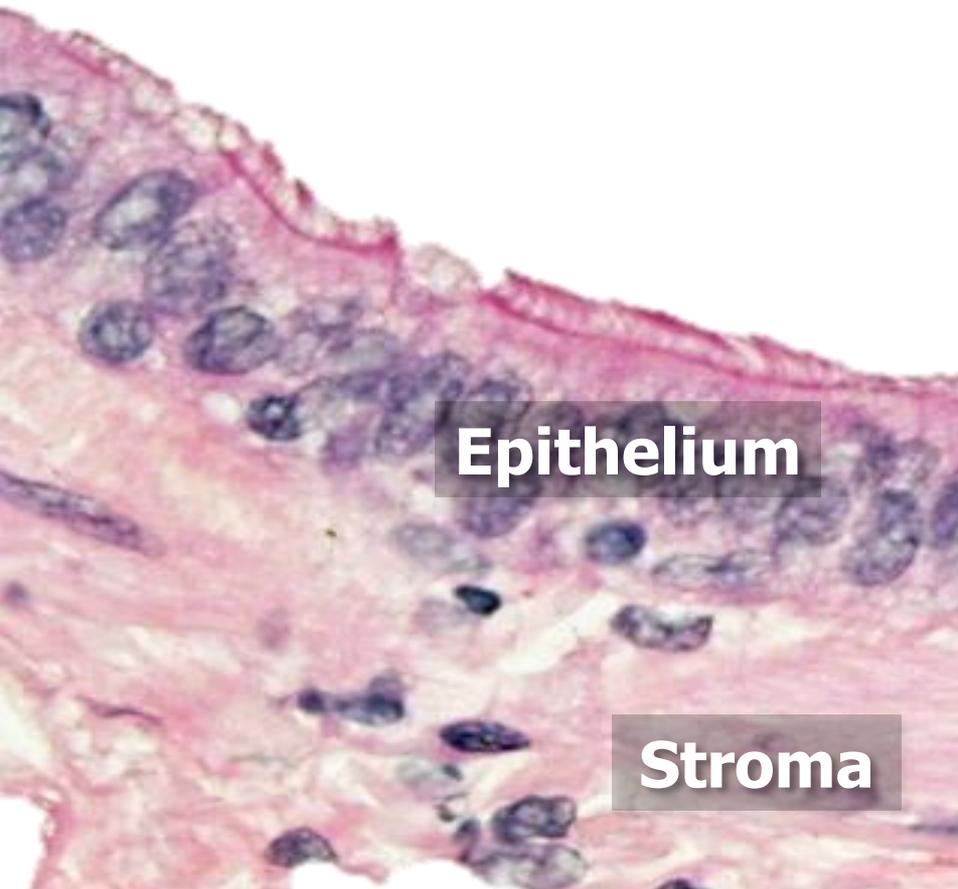


Epithelium

Stroma

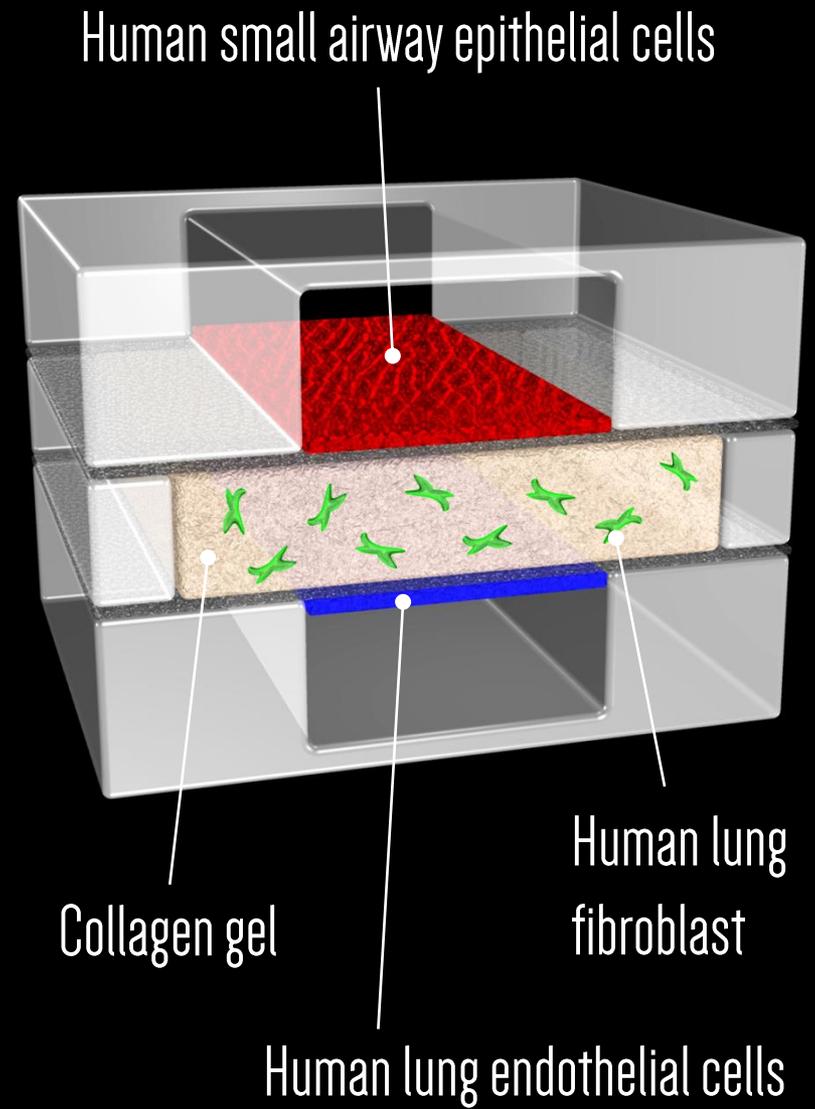


**Mark Mondrinos**



**Epithelium**

**Stroma**

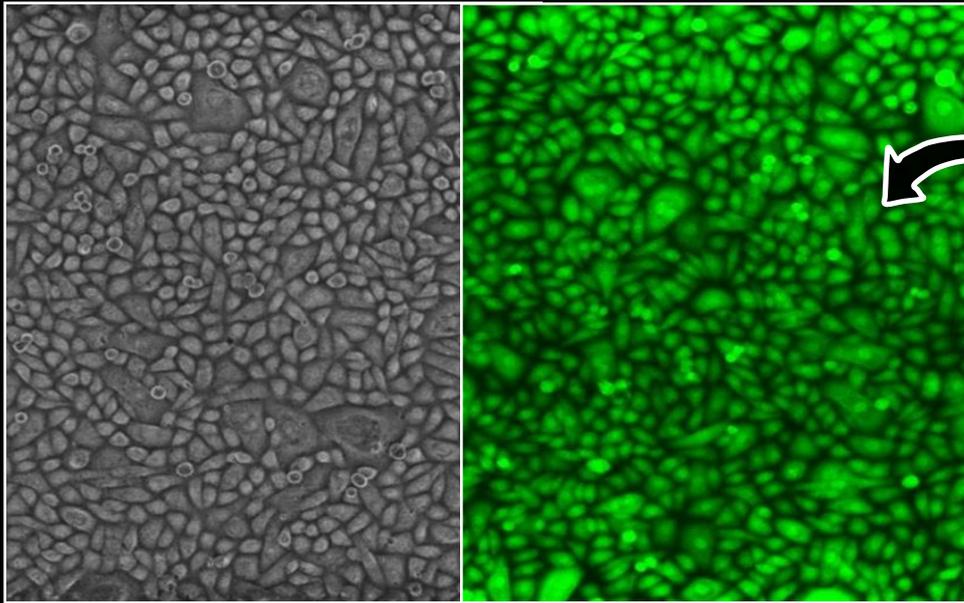


Human small airway epithelial cells

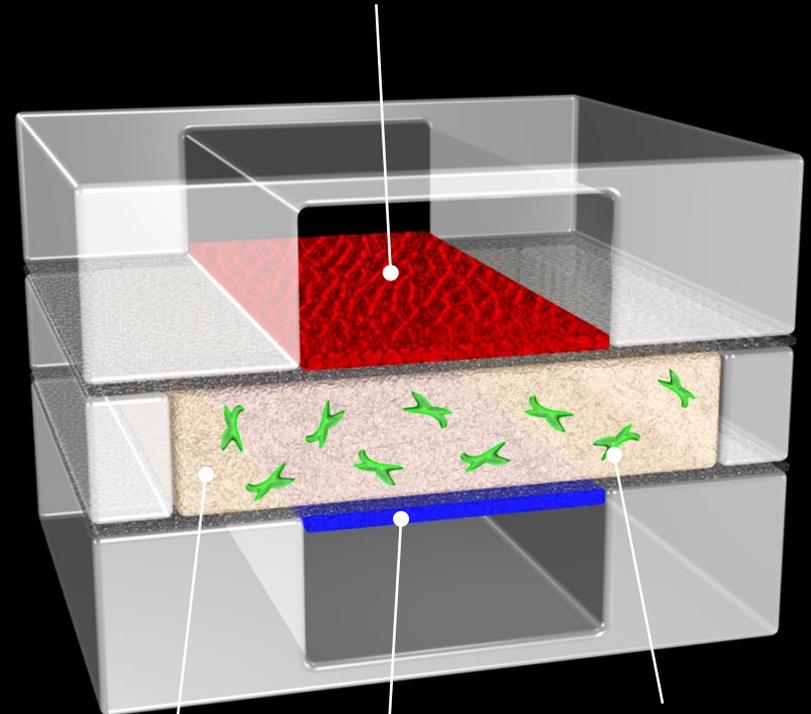
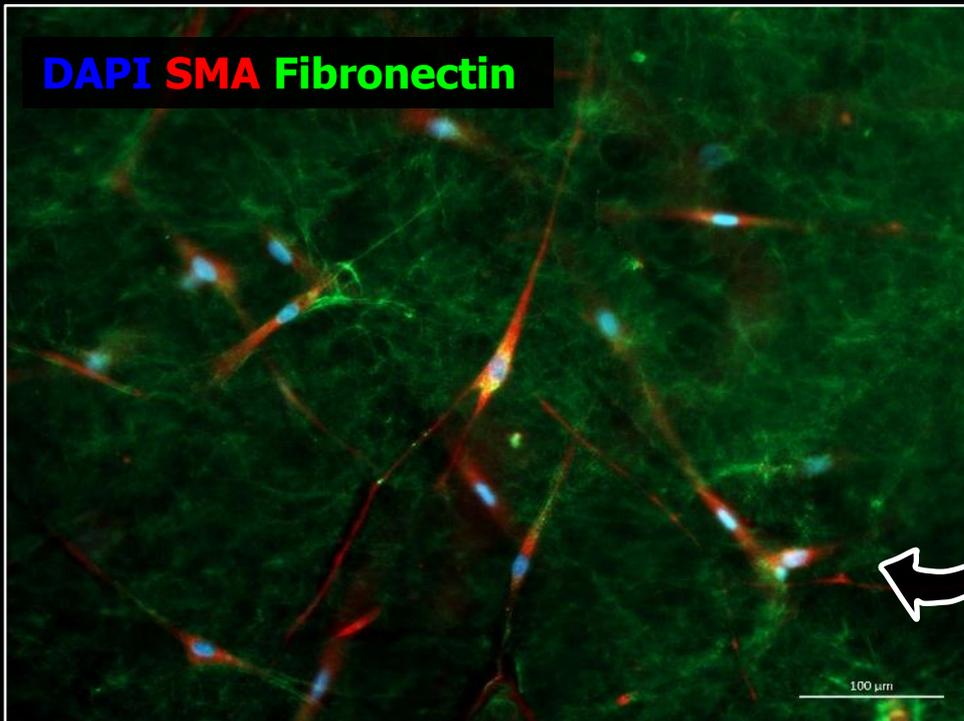
Collagen gel

Human lung fibroblast

Human lung endothelial cells



Human small airway epithelial cells



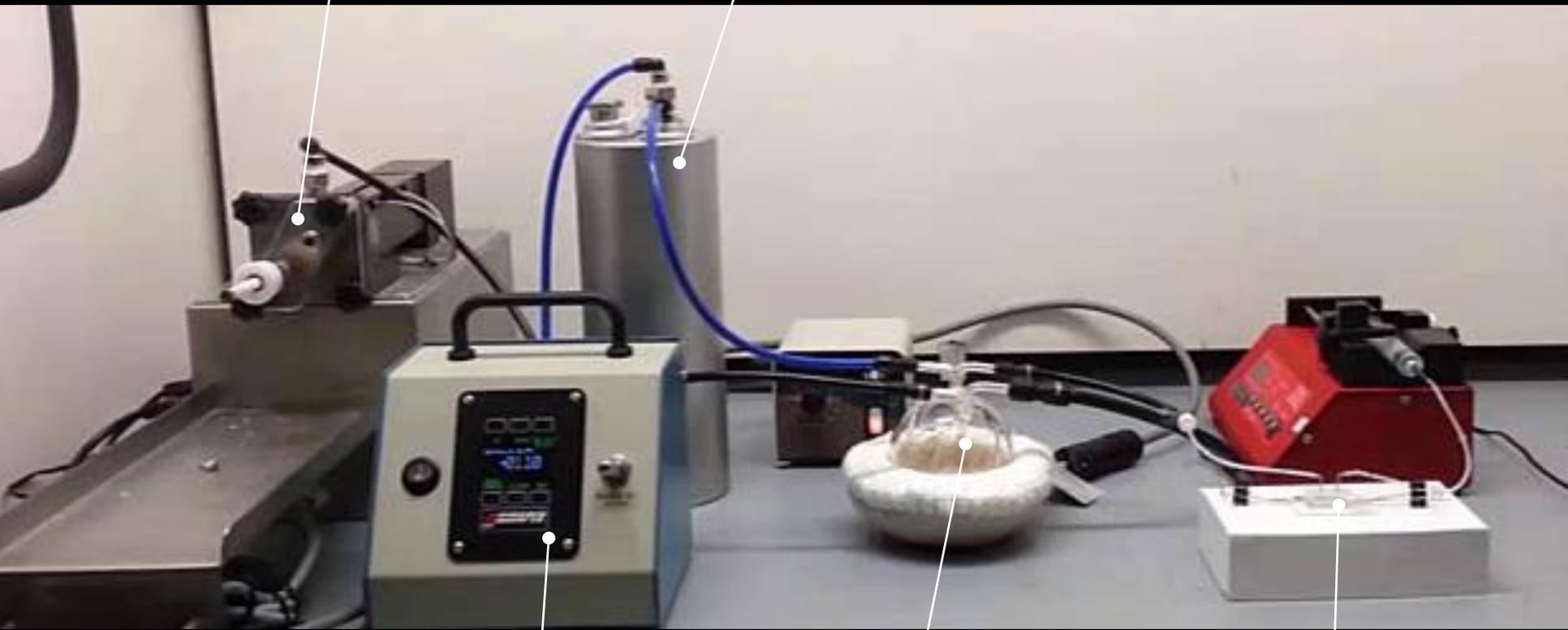
Collagen gel

Human lung fibroblast

Human lung endothelial cells

Cigarette smoking machine

Humidifier



Smoking lung-on-a-chip

Airway tissue injury

Endoplasmic reticulum stress

Unfolded protein response

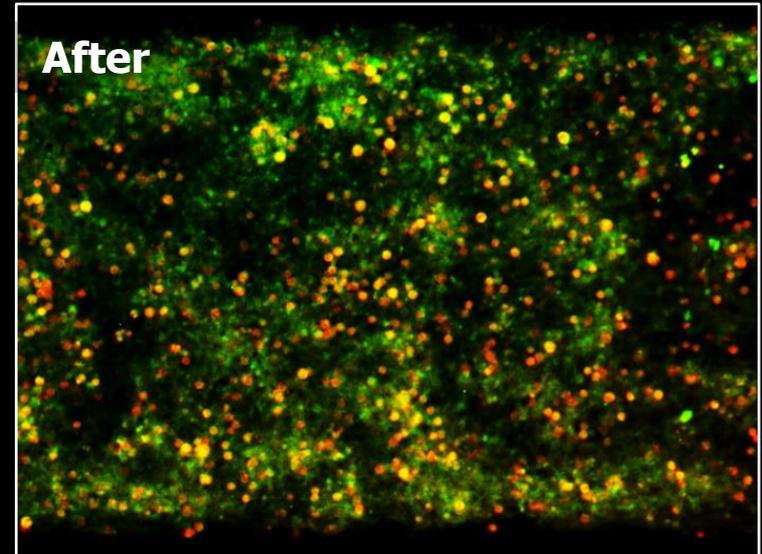
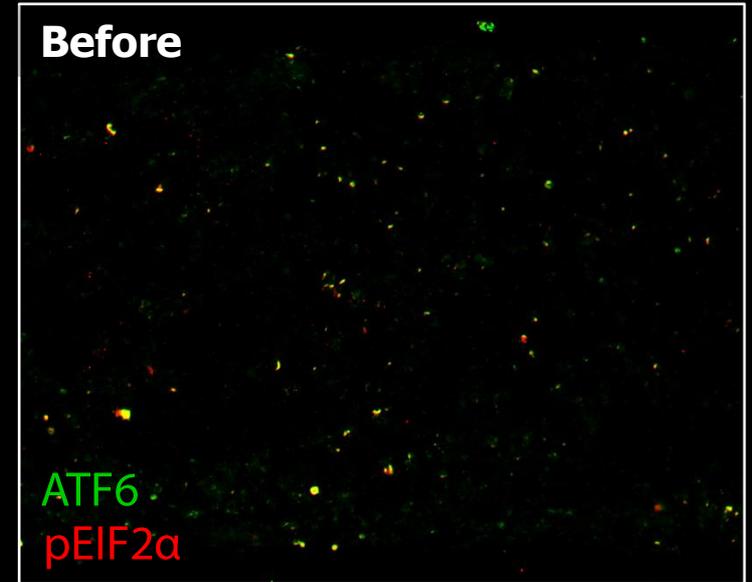
Airway remodeling

Airway tissue injury

Endoplasmic reticulum stress

Unfolded protein response

Airway remodeling

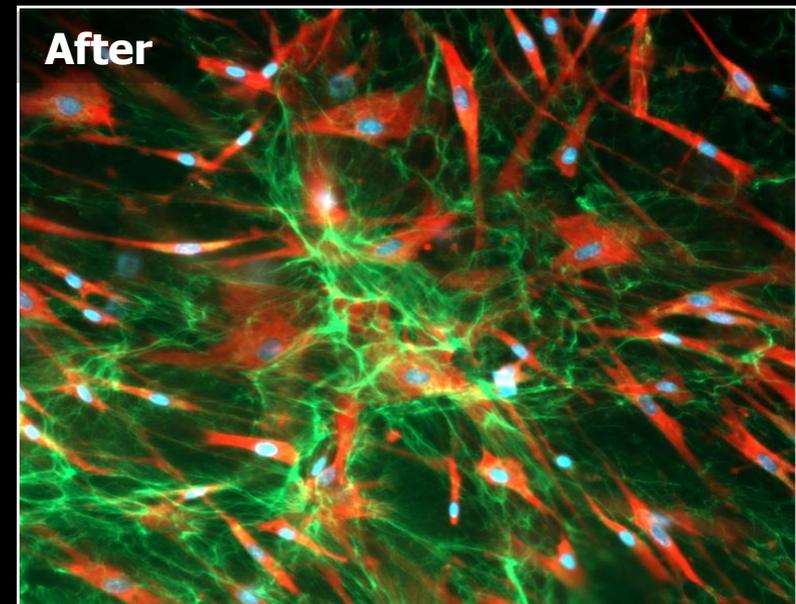
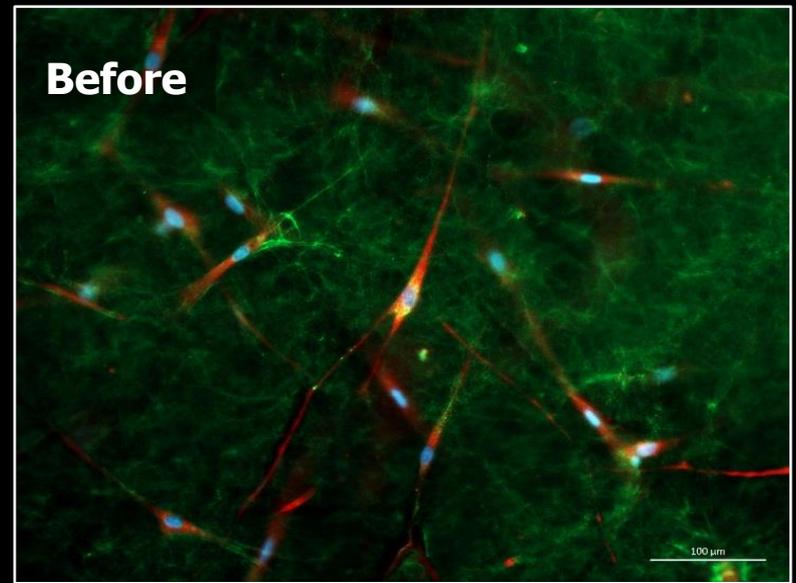


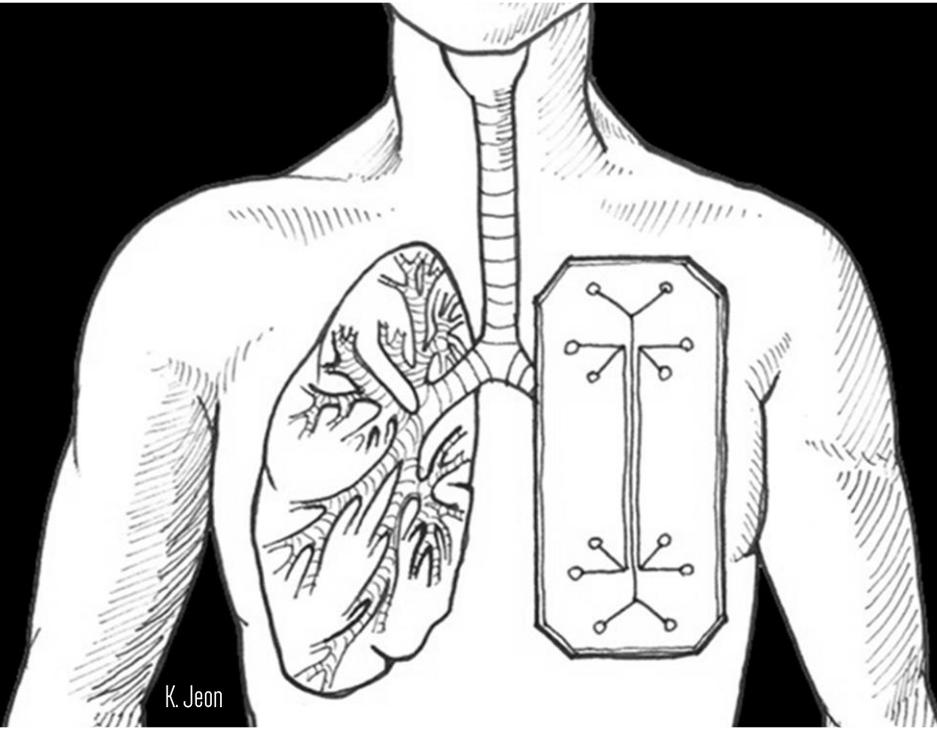
Airway tissue injury

Endoplasmic reticulum stress

Unfolded protein response

Airway remodeling





K. Jeon

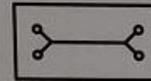
# Human lung-on-a-chip

# THIS IS FOR EVERYONE...

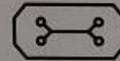
DESIGN EXPERIMENTS  
FOR THE COMMON GOOD

Design experiments are a way to explore new possibilities and create solutions that are both innovative and practical. They are a key part of the design process, allowing designers to test their ideas and learn from their mistakes. In this exhibition, we explore a range of design experiments that have been carried out by designers from around the world. These experiments have led to the development of new products, services and experiences that are designed to benefit everyone.

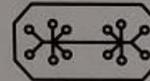




Liver



Gut



Lung

**Donald Elliot Ingber** (American, born 1956)  
**Dan Dongeun Huh** (Korean, born 1974)  
**Wyss Institute for Biologically Inspired Engineering at Harvard University** (est. 2009)  
**Boston Children's Hospital** (est. 1869)

## Human Organs-on-Chips 2008

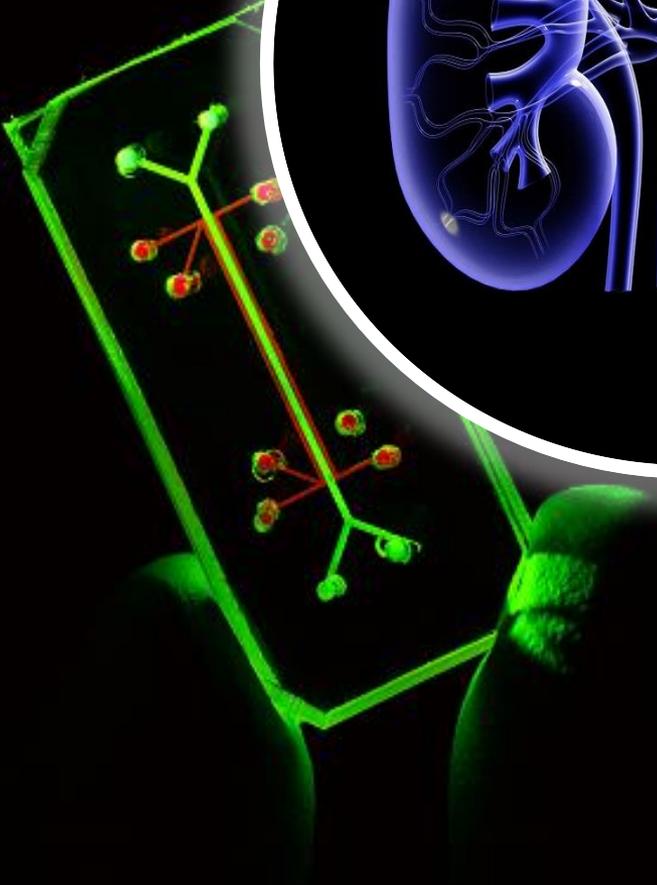
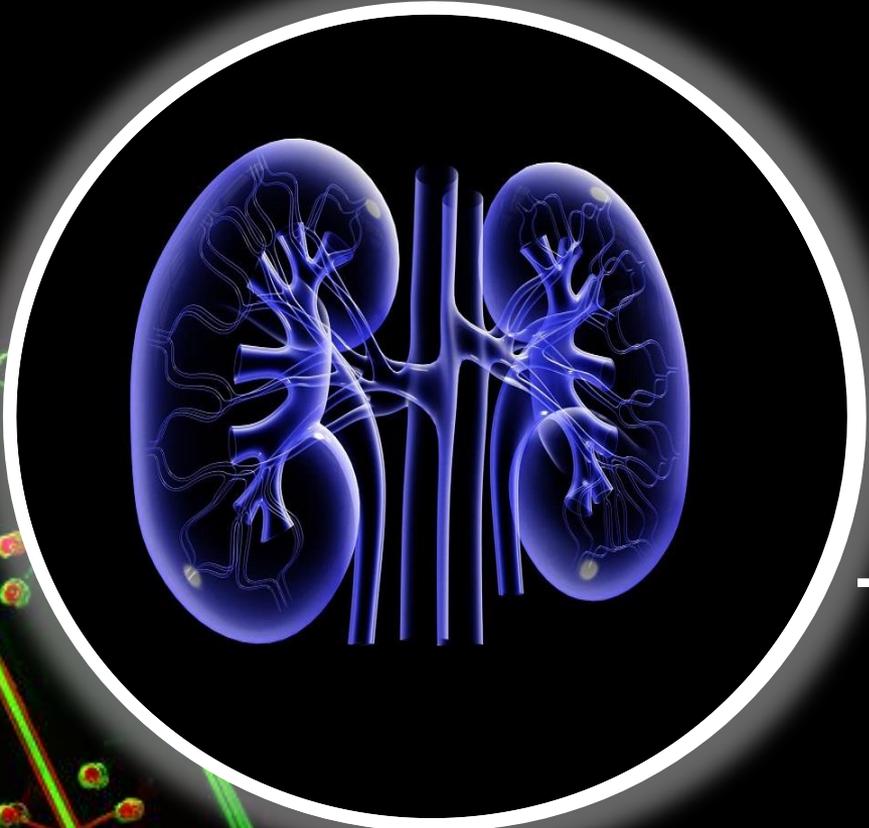
Silicone rubber

Gift of the Wyss Institute for Biologically Inspired Engineering at Harvard University, 2015

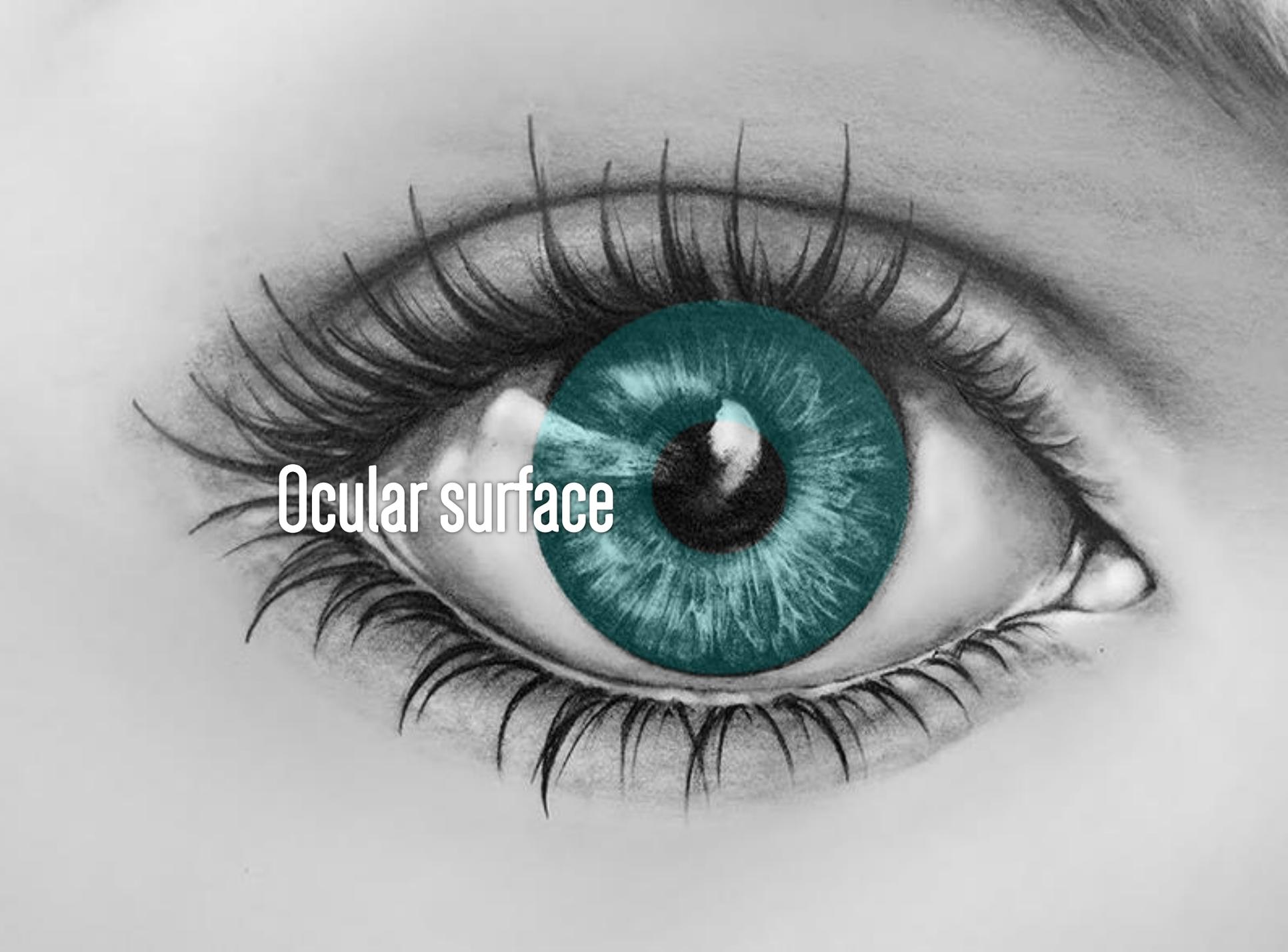
The Wyss Institute at Harvard University has developed ten different types of “organs-on-chips,” a still experimental technology designed to replace often expensive and ethically fraught human or animal testing in the pharmaceutical and medical industries. The chips—including the kidney-on-a-chip and the gut-on-a-chip—simulate human organ mechanical and biochemical functions, and can be used singly or in combinations to test the effects of new drug treatments on human physiology. For example, the lung-on-a-chip, a clear, flexible polymer lined with bioengineered human airway and capillary cells, is both better at predicting outcomes and less expensive than animal testing, as demonstrated in the *Pharmaceutical Journal*. Removing some of the pitfalls associated with human and animal testing means, theoretically, that drug trials could be conducted faster and their viable results disseminated more quickly.



**310** English only



-on-a-chip



Ocular surface

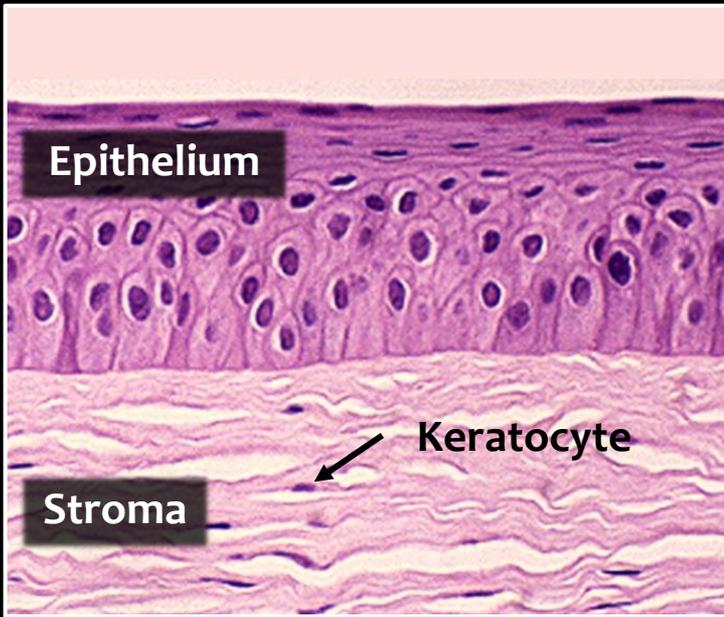


Cornea

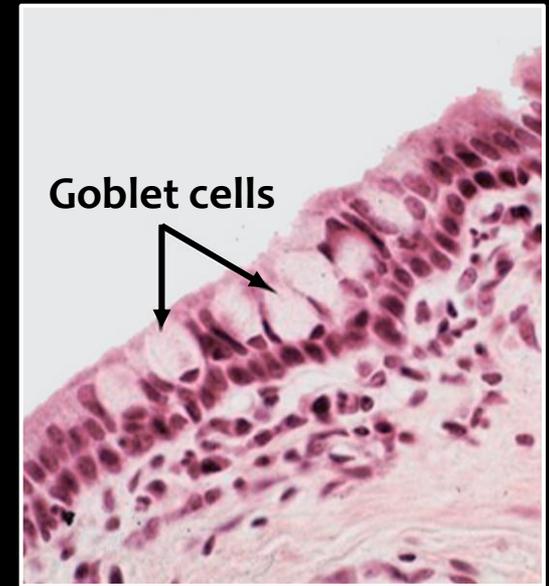
Conjunctiva

Ocular surface

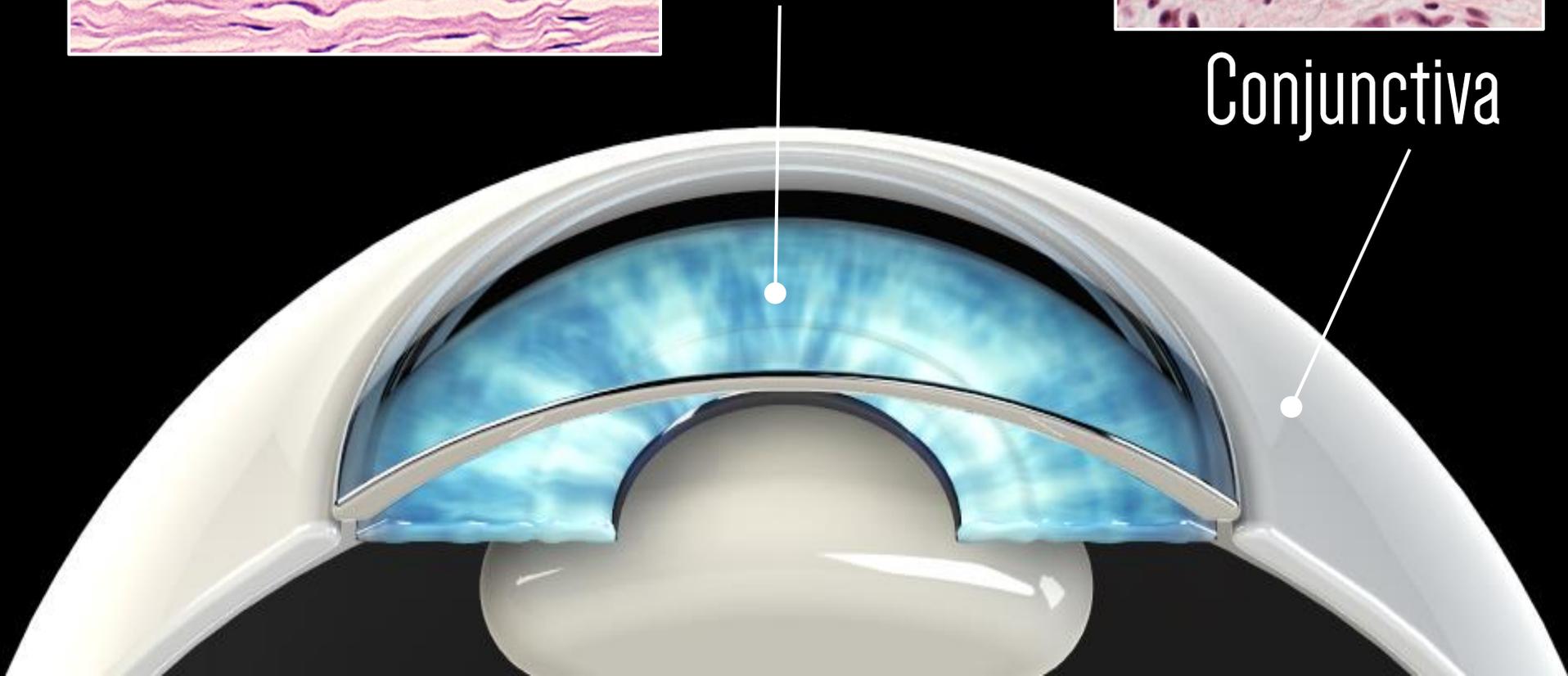


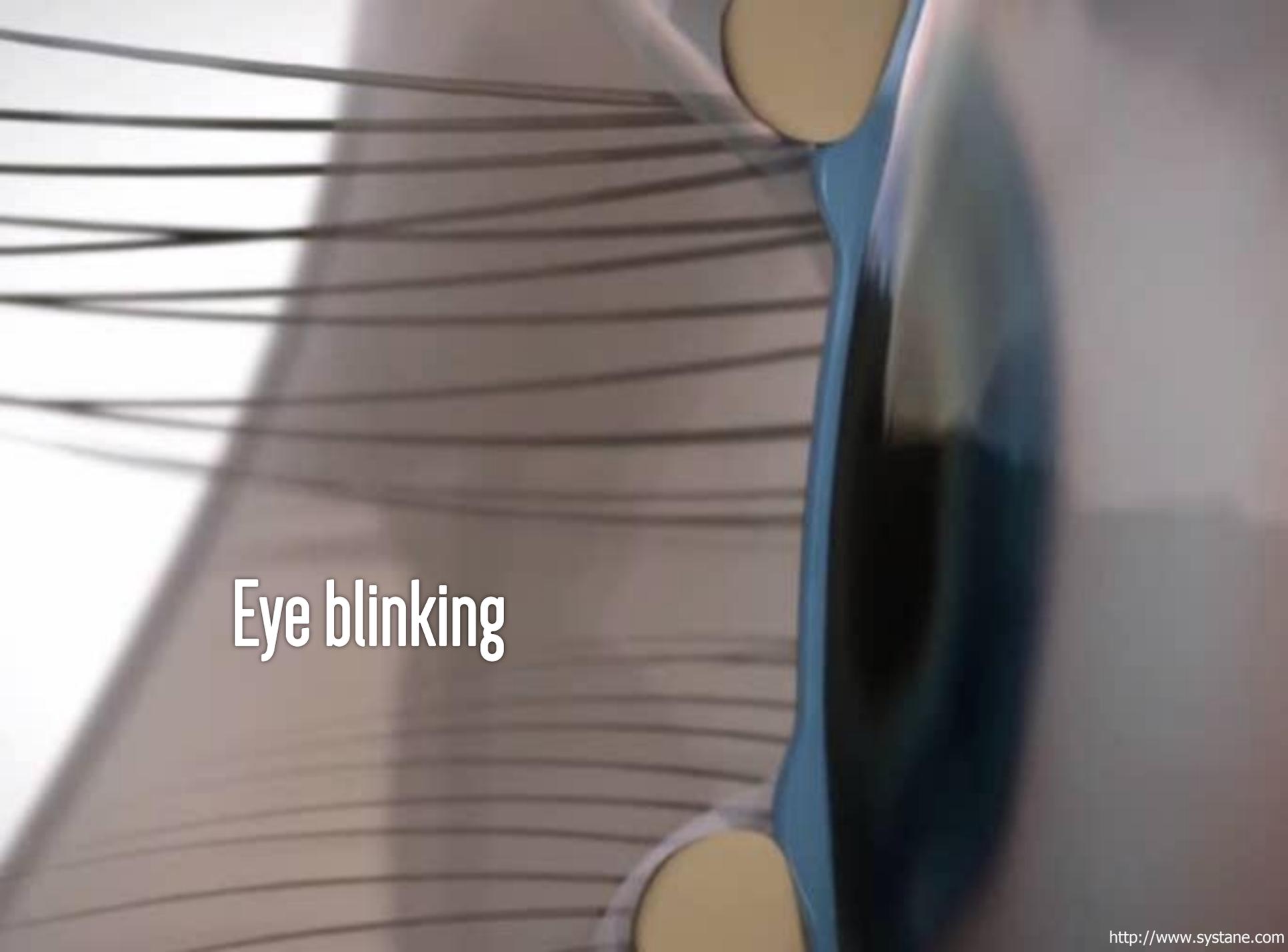


Cornea



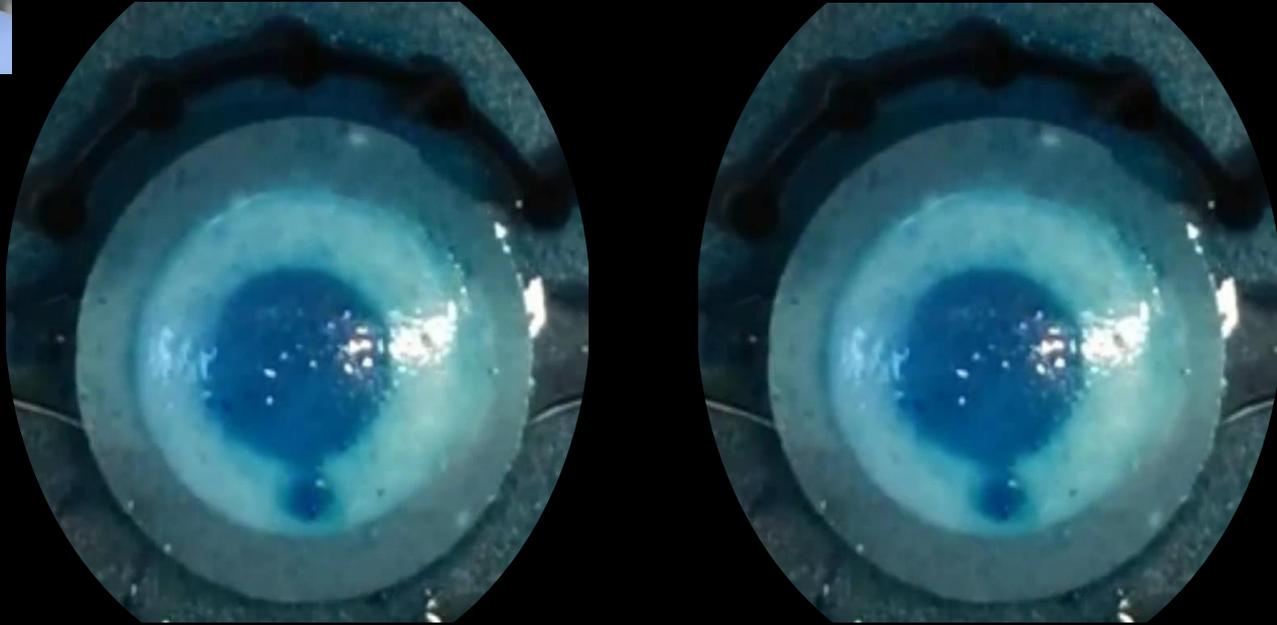
Conjunctiva



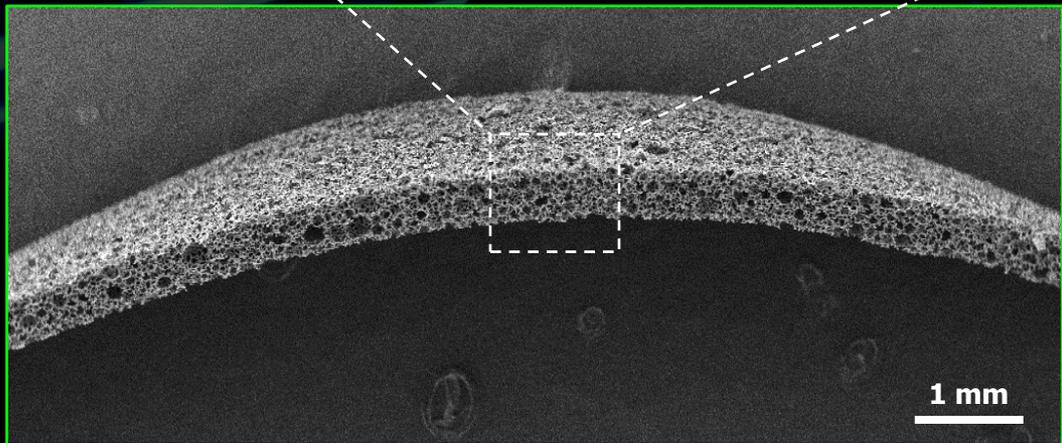
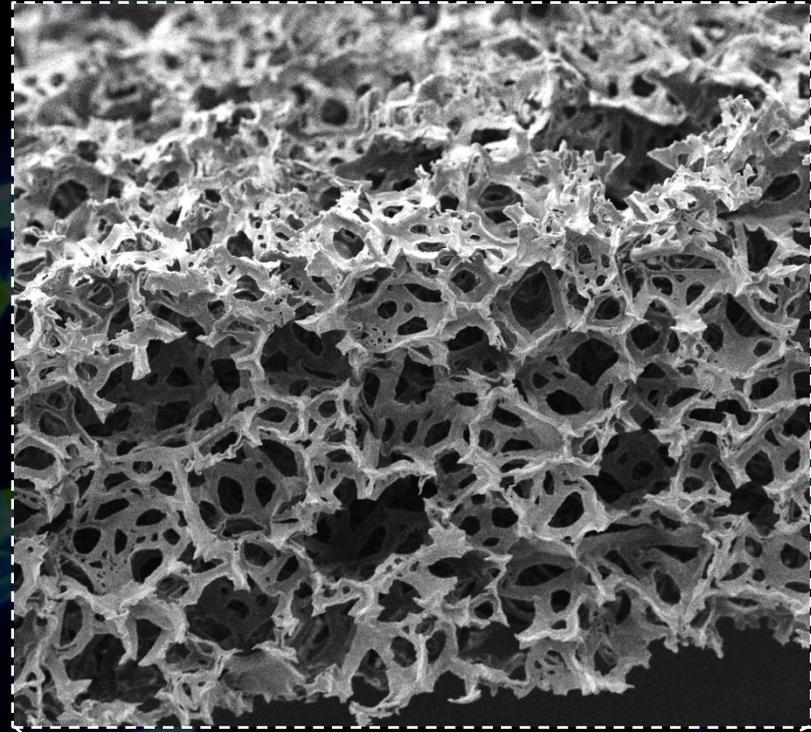
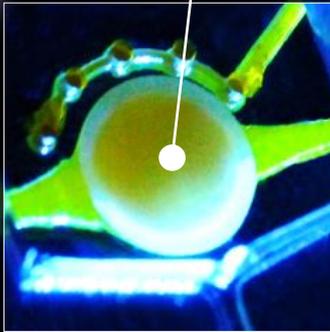
A close-up photograph of a person's eye. The eye is looking slightly to the right. The eyelashes are dark and long, and are in focus. A blue contact lens is visible on the eye. The background is a blurred, light-colored surface, possibly a wall or a ceiling.

Eye blinking

Jeongyun Seo

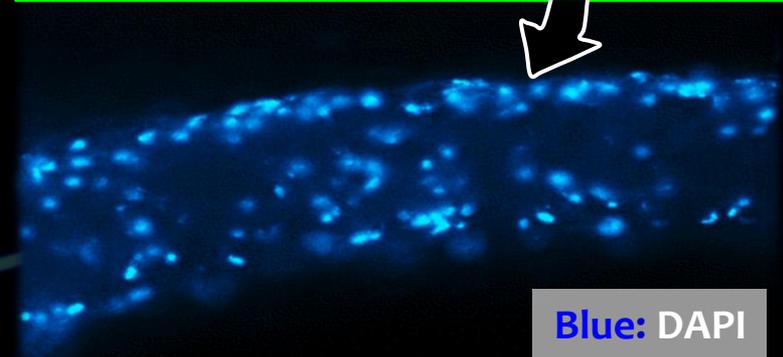
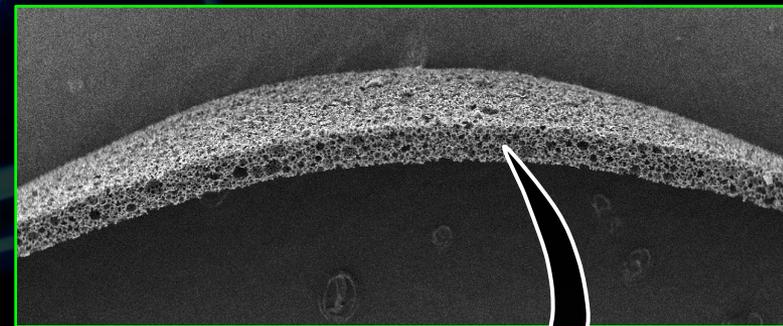
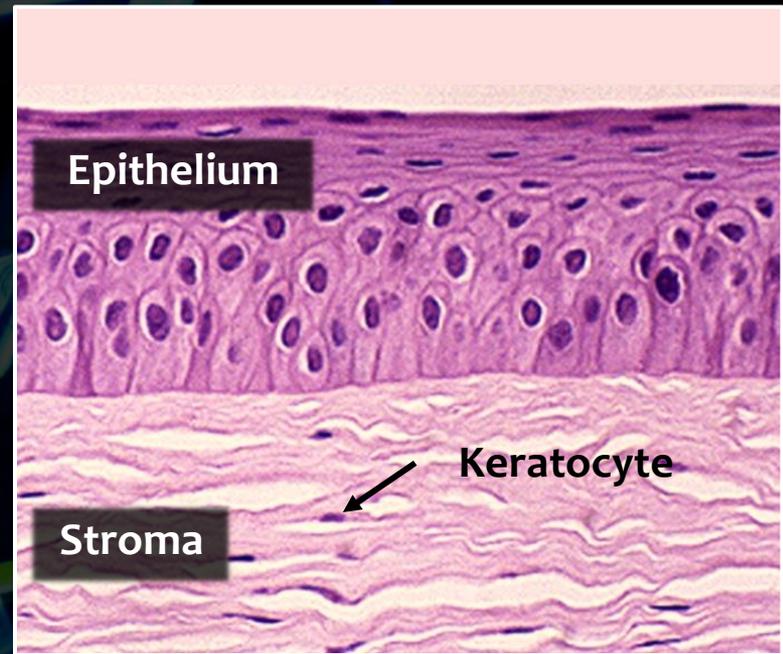
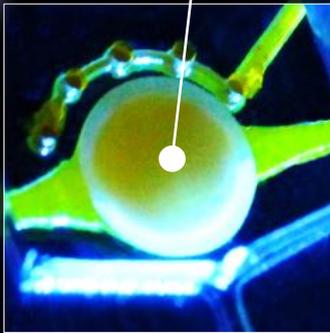


Human **blinking** eye-on-a-chip



J. Seo et al., *in preparation*  
2015 Collegiate Inventors Competition,  
TEDx 2015

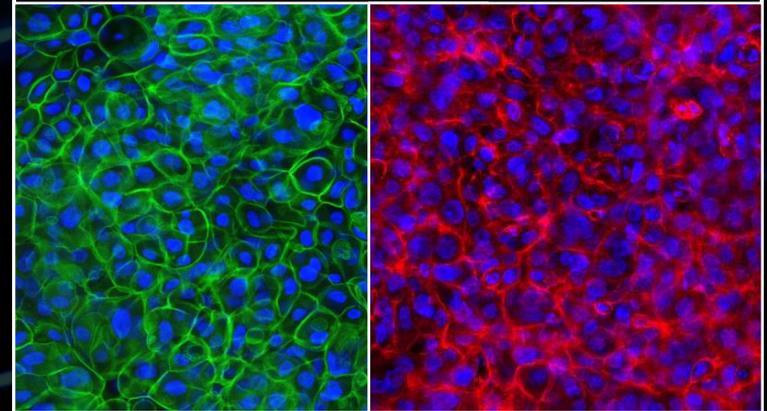
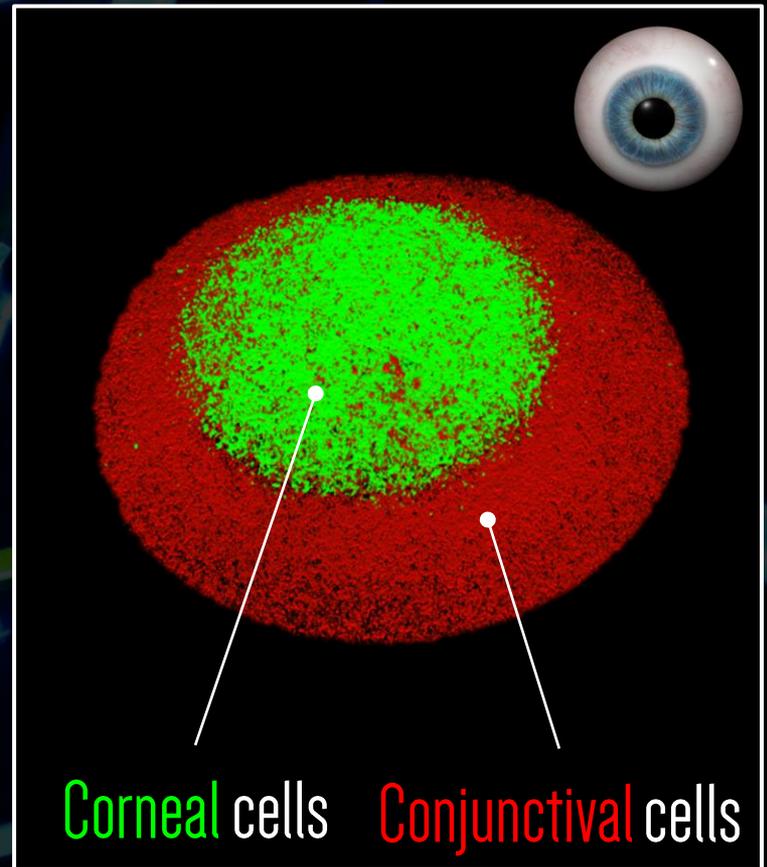
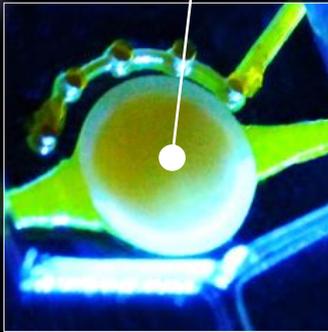
**BIOLines**



Blue: DAPI

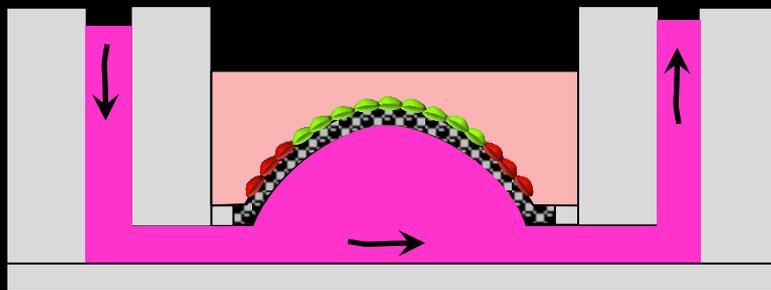
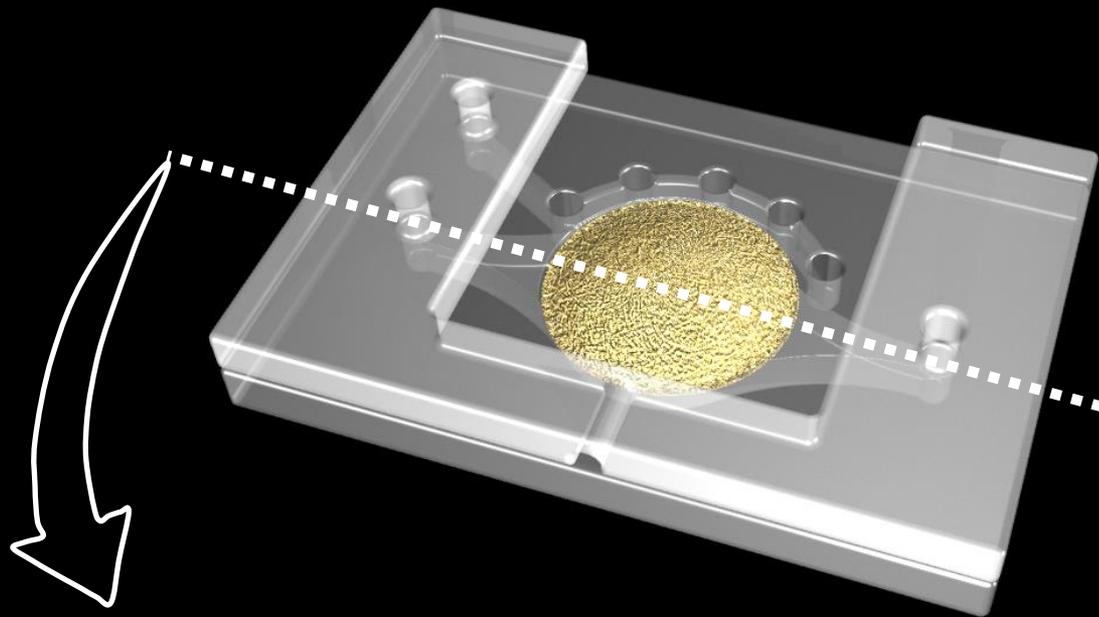
J. Seo et al., *in preparation*  
2015 Collegiate Inventors Competition,  
TEDx 2015



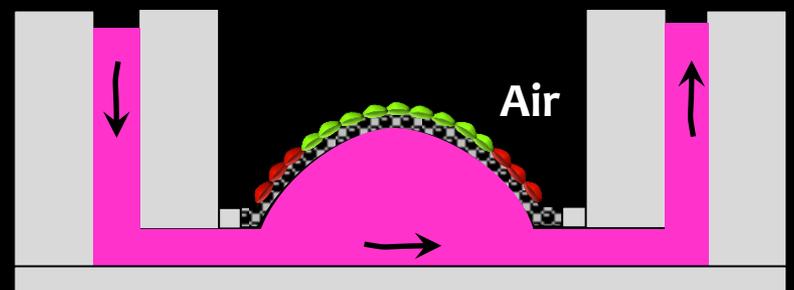
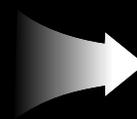


J. Seo et al., *in preparation*  
2015 Collegiate Inventors Competition,  
TEDx 2015

**BIOLines**

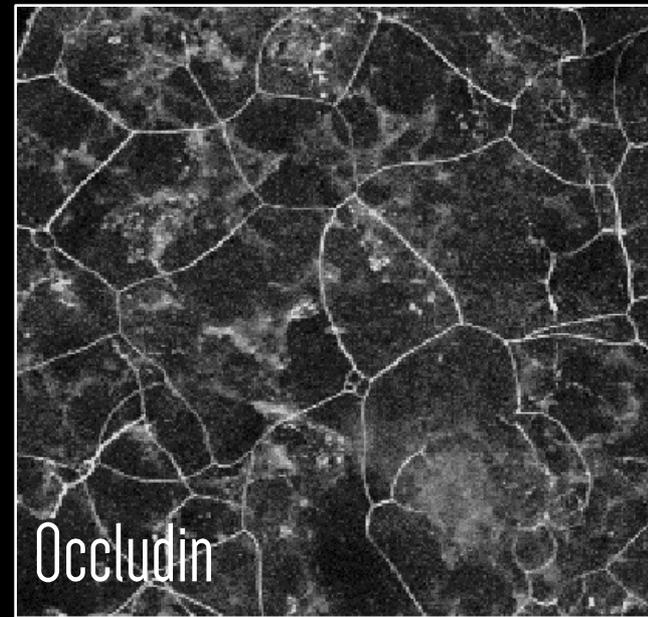
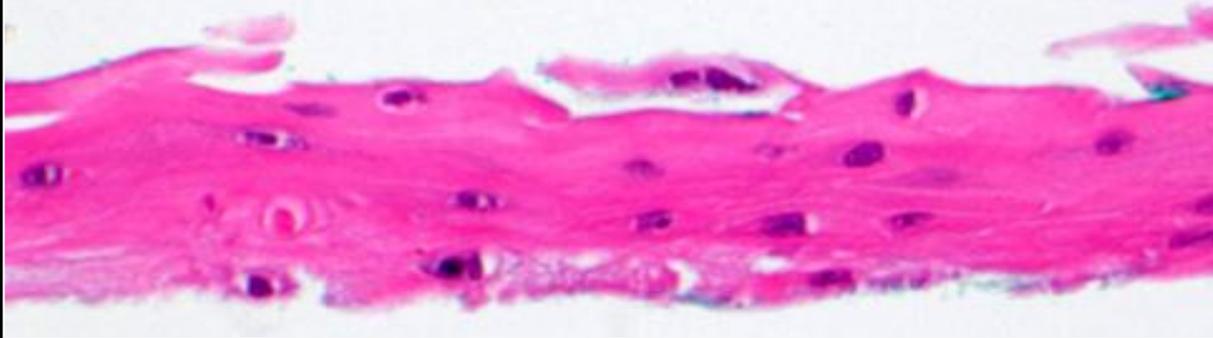


Submerged culture

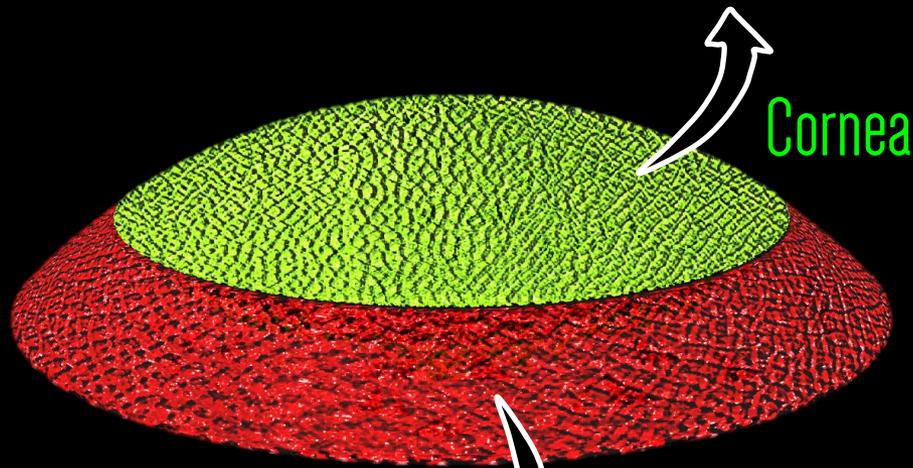


Air-liquid Interface (ALI) culture

Stratification

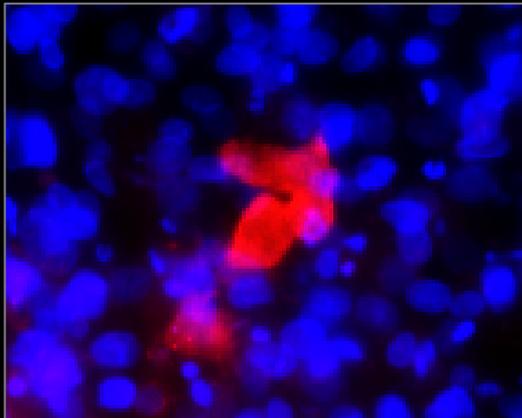


Occludin

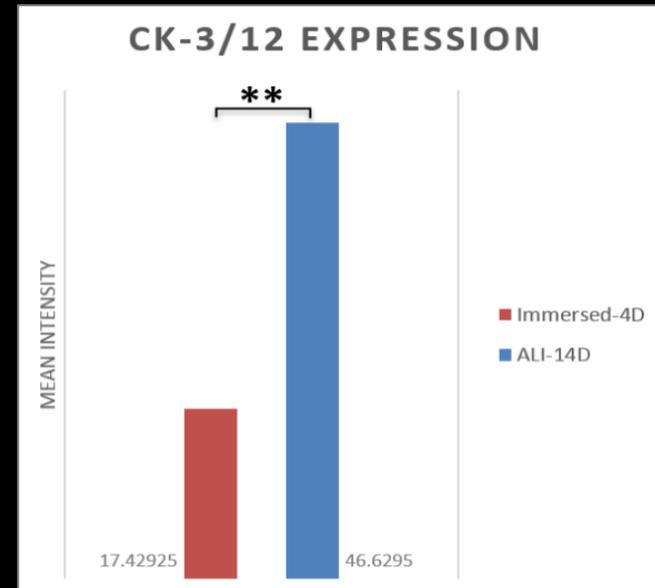


Cornea

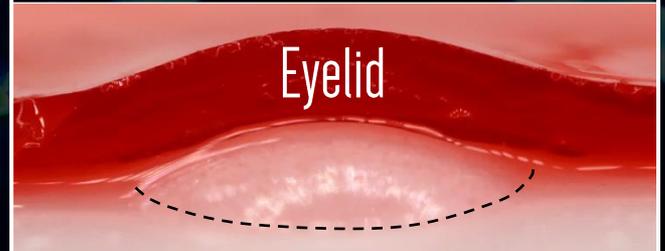
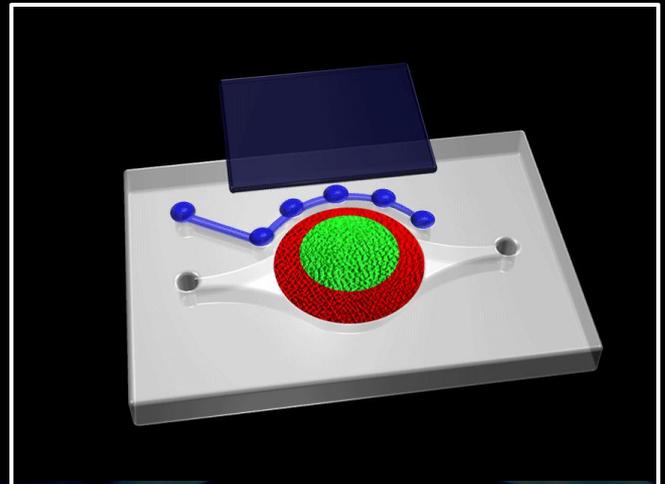
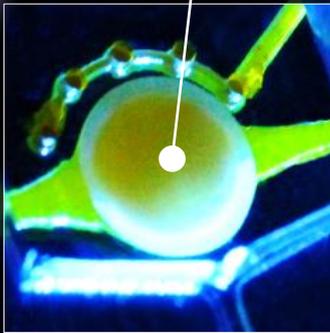
Conjunctiva



Goblet cells (MUC5AC)

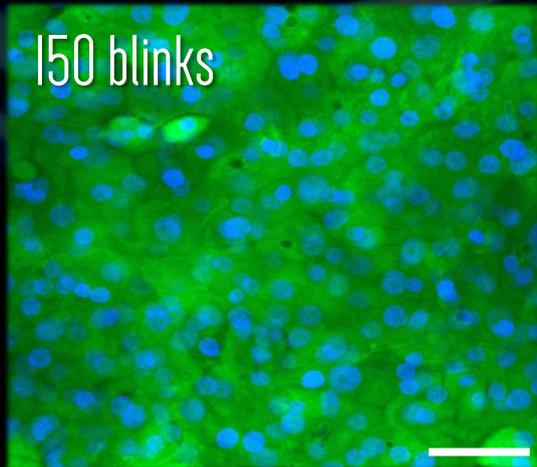
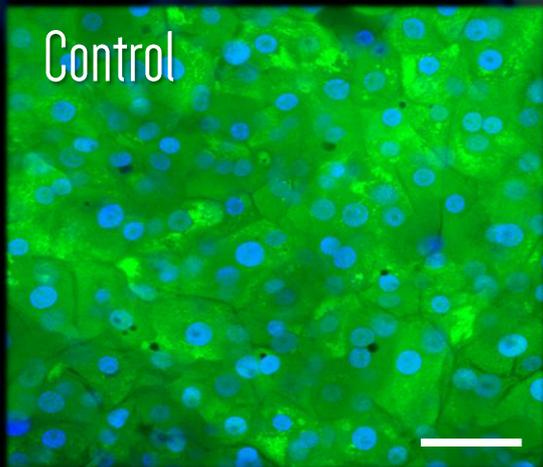
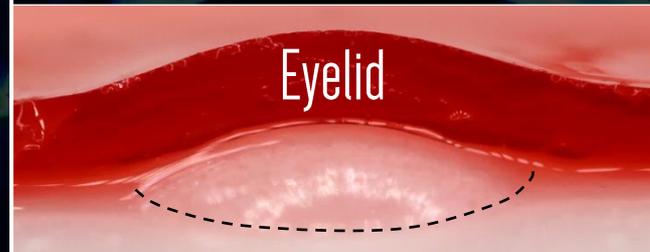
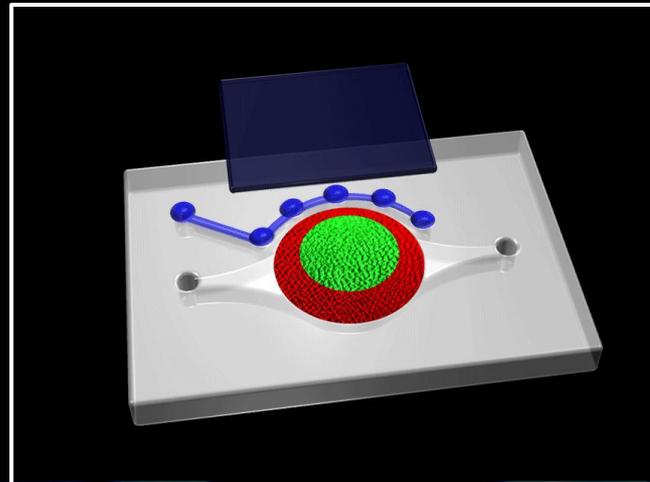
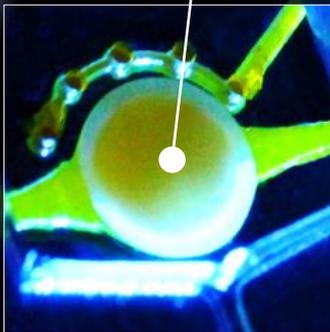


Corneal epithelial marker



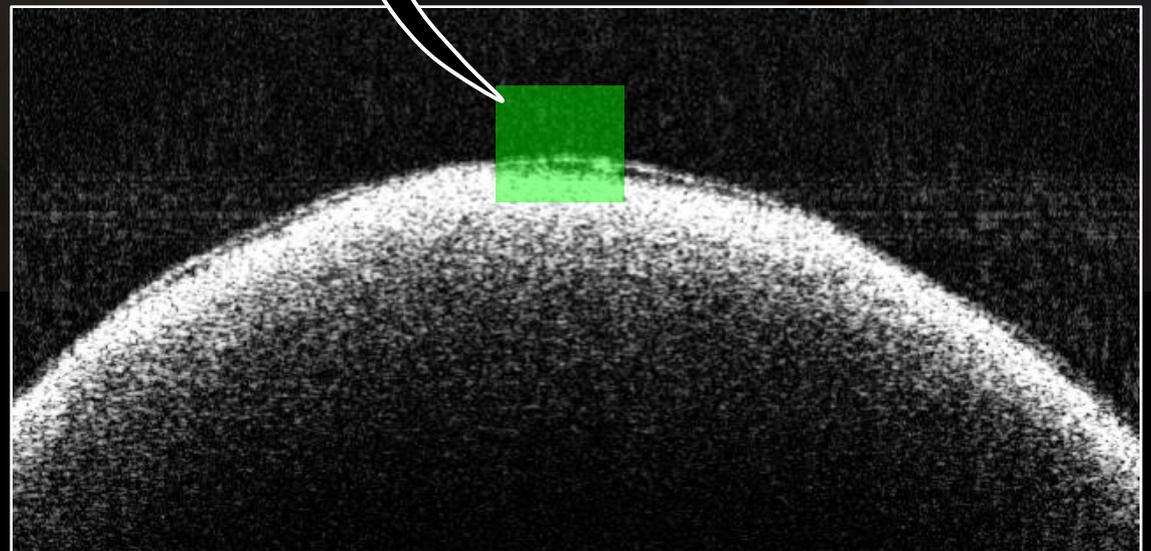
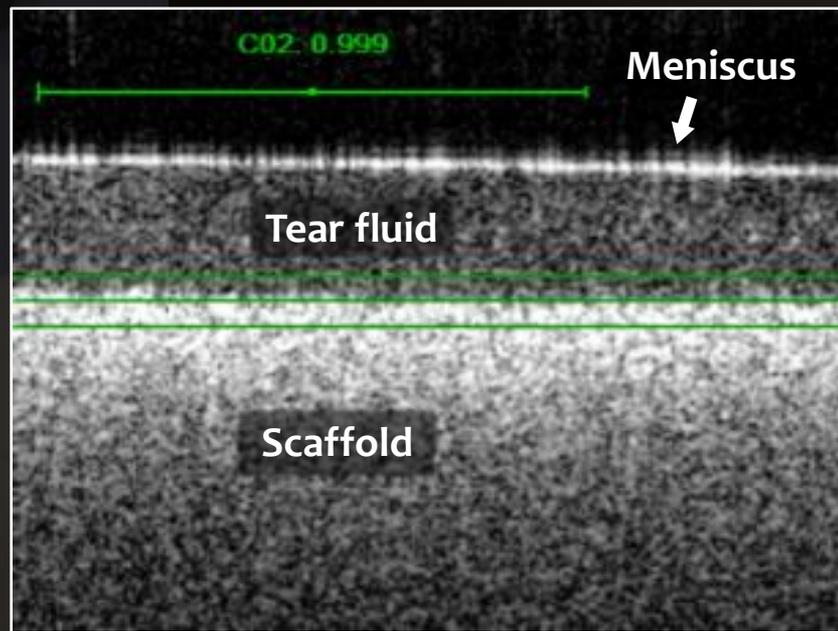
J. Seo et al., *in preparation*  
2015 Collegiate Inventors Competition,  
TEDx 2015

**BIOLines**

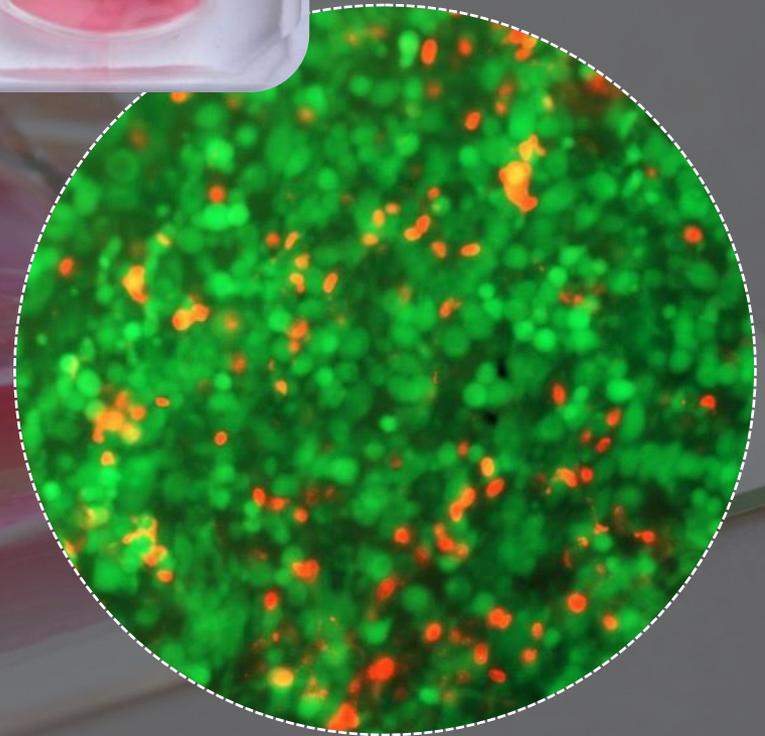
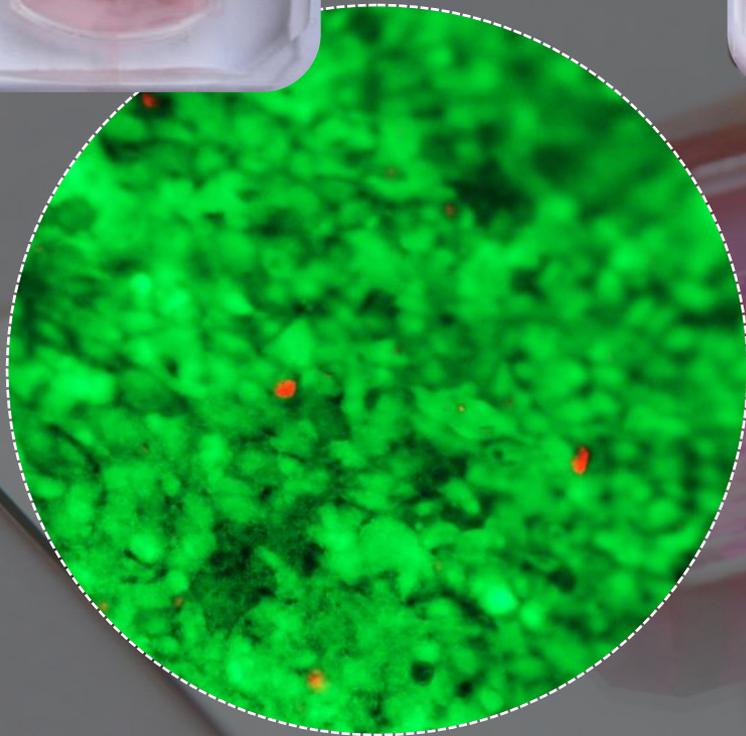
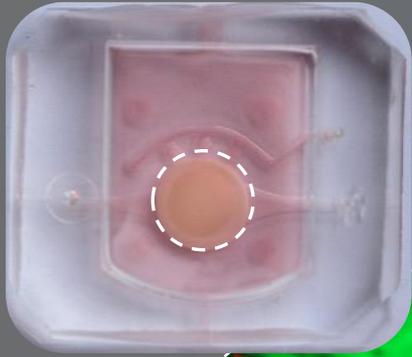
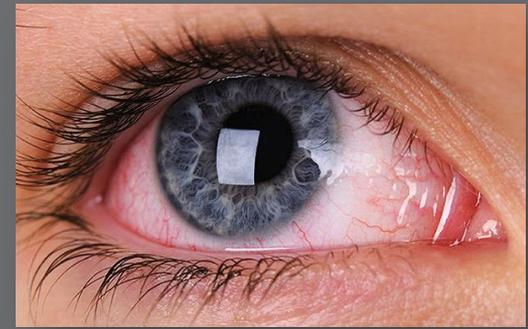




Optical coherence tomography (OCT)



# Ocular toxicity screening



Untreated

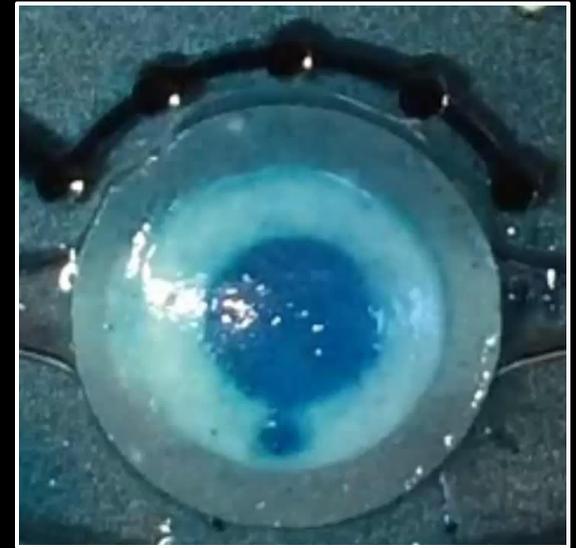
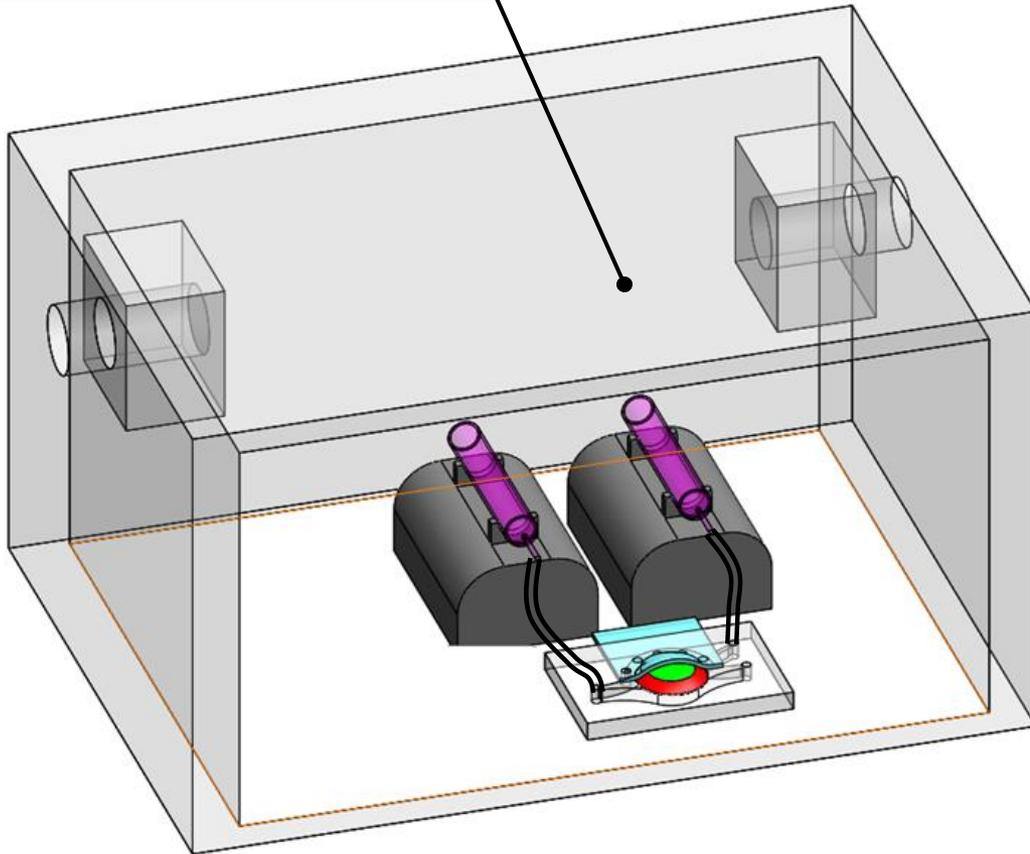
Treated with 1% EDTA

Dry eye disease (DED)



5% CO<sub>2</sub>, 37 °C

Humidity: 50%



**Normal**

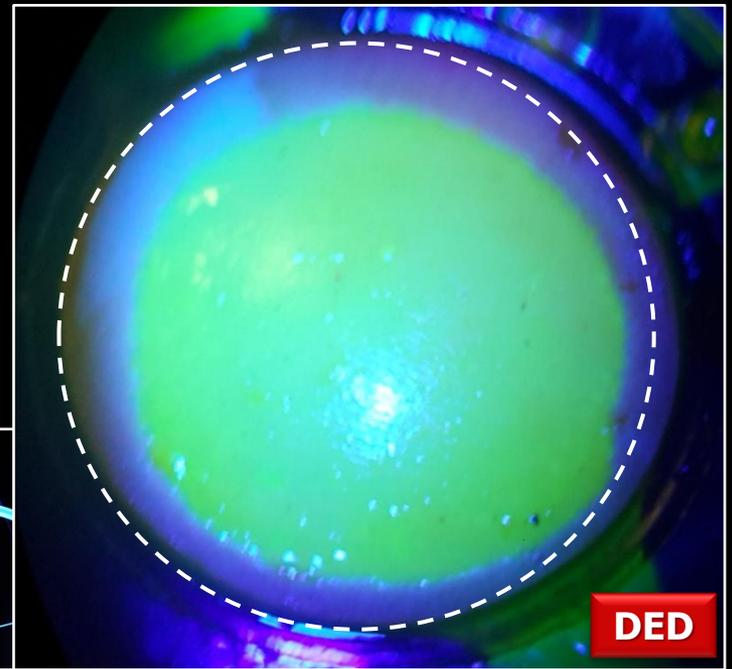
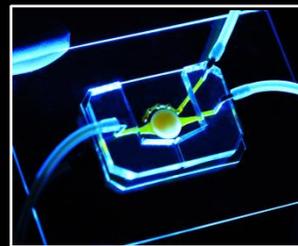
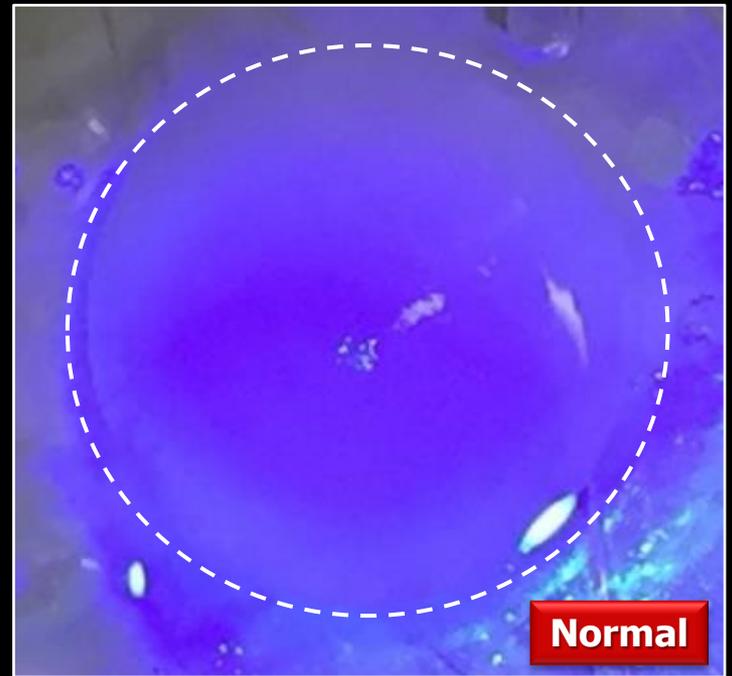
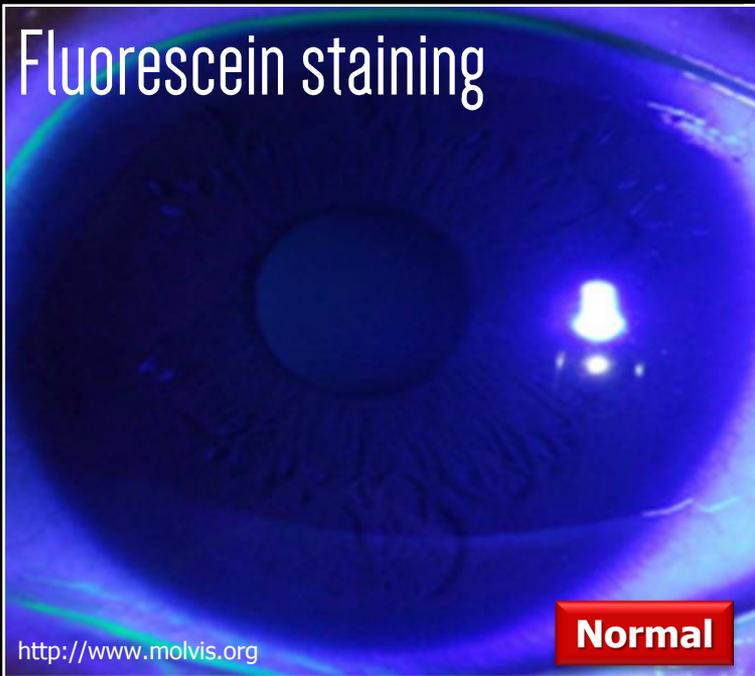
Blinking frequency: 0.2 Hz



**Dry eye disease (DED)**

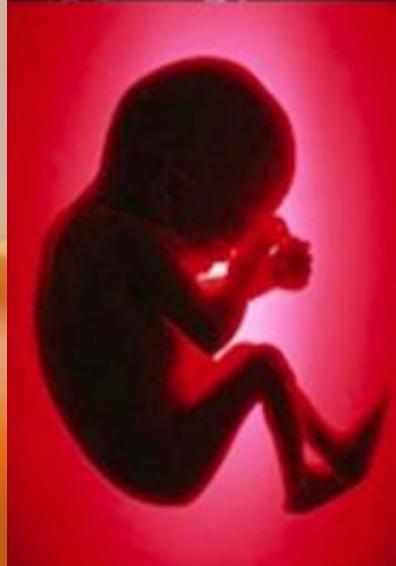
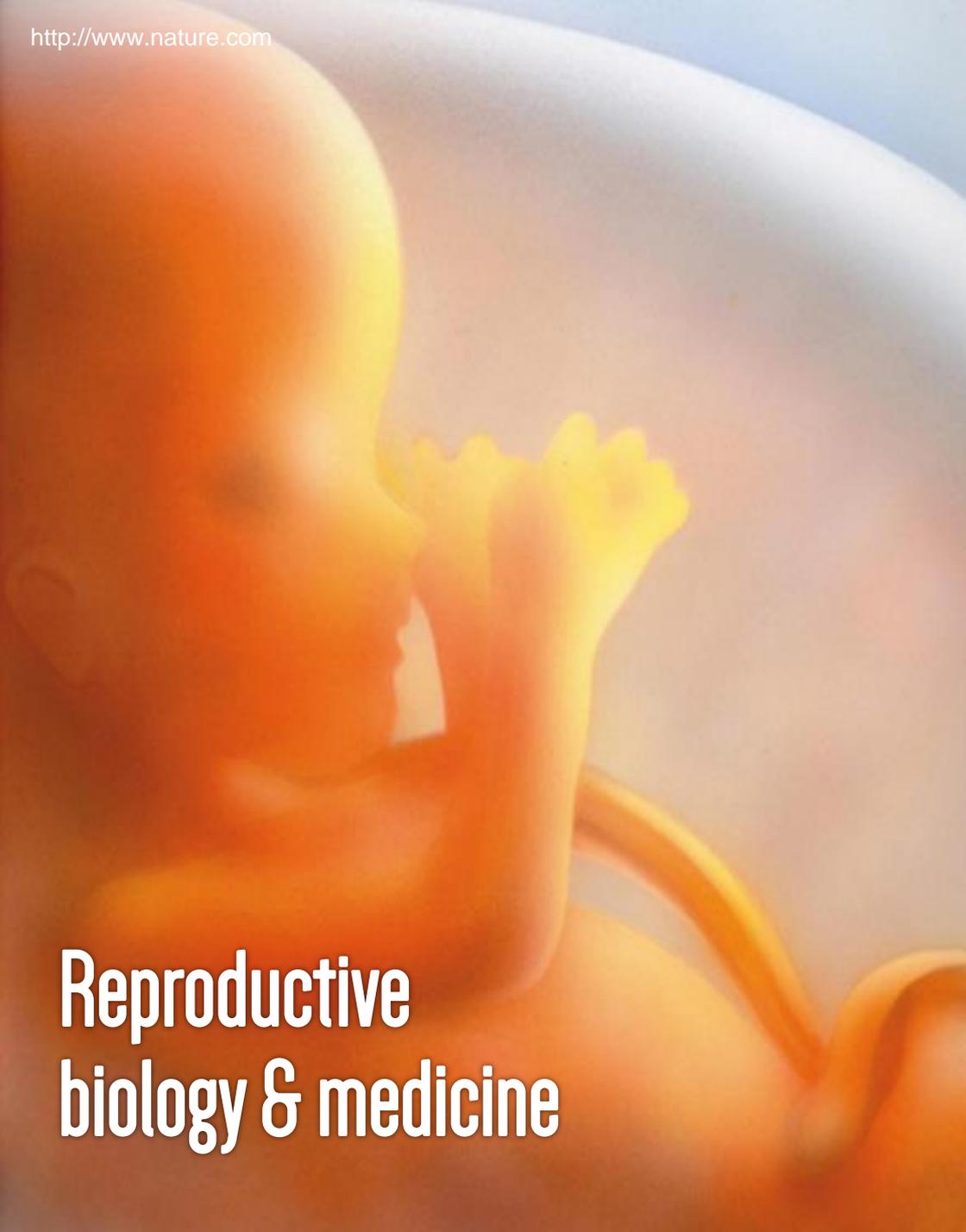
Blinking frequency: 0.1 Hz

# Fluorescein staining

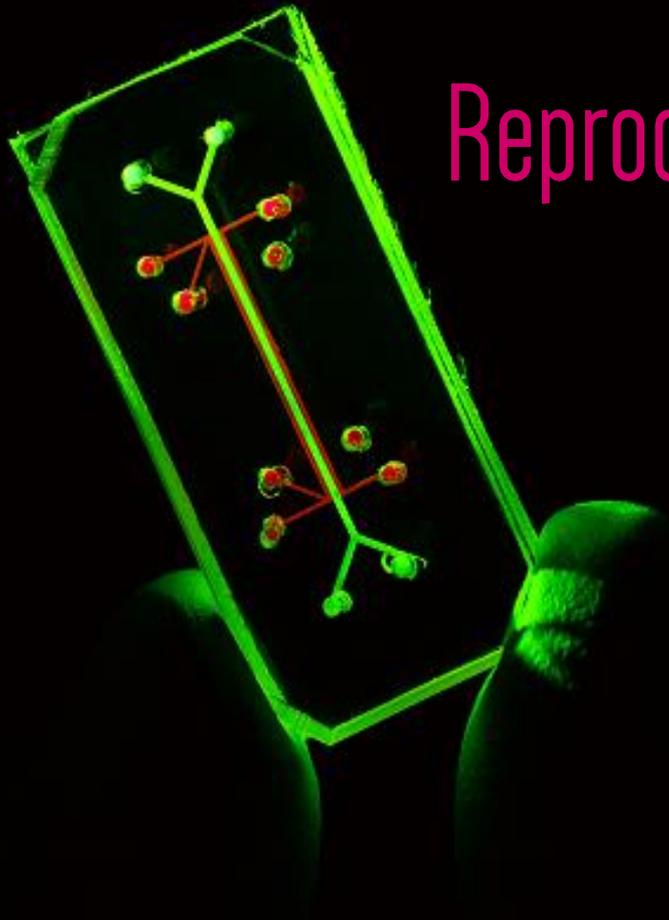




Human blinking eye-on-a-chip

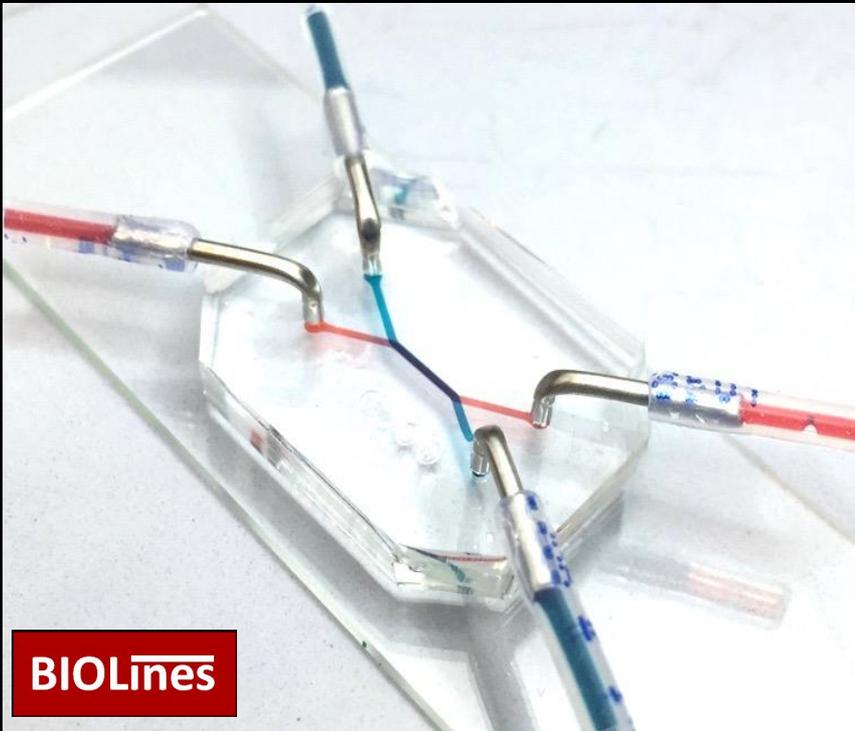


# Reproductive biology & medicine



# Reproductive organs-on-a-chip

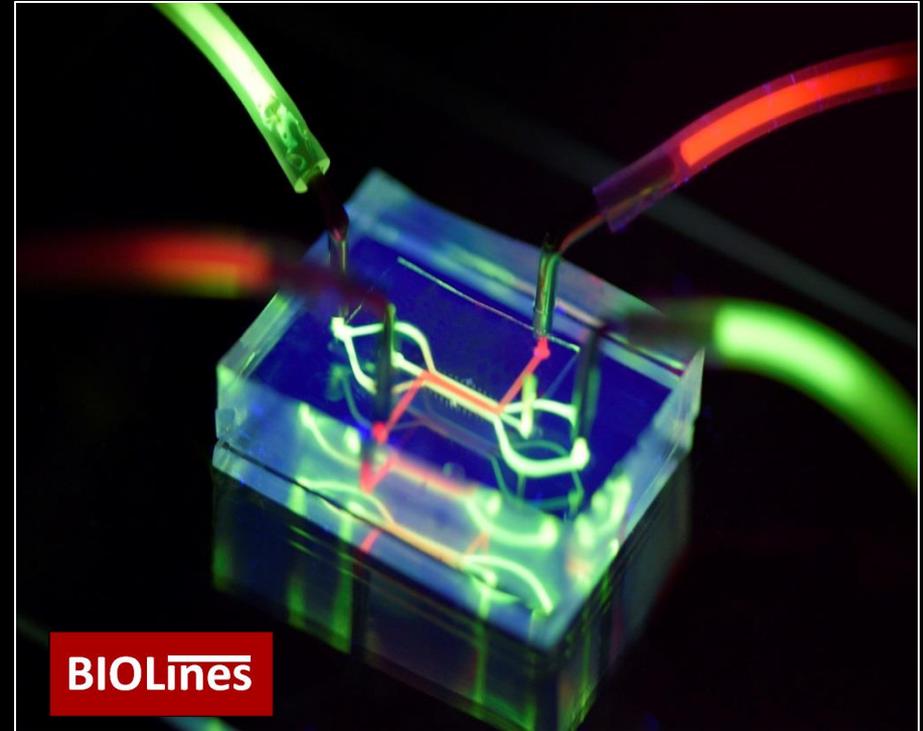
# Placenta-on-a-chip



BIOLines

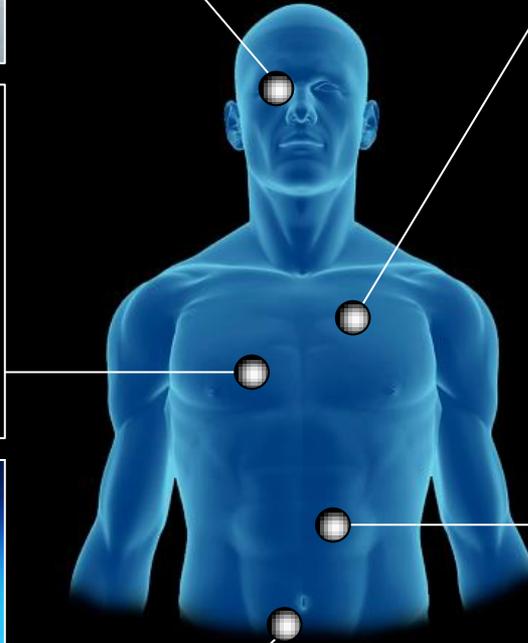
C. Blundell, E. Tess, A. Schanzer, C. Coutifaris, E.J. Su, S. Parry, D. Huh, *Lab Chip* 2016  
J.S. Lee, R. Romero, Y.M. Han, H.C. Kim, C.J. Kim, J.S. Hong, D. Huh, *JMFNM* 2015

# Cervix-on-a-chip

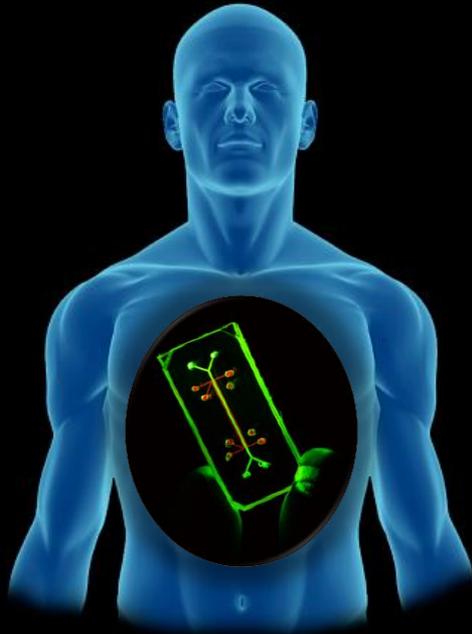


BIOLines

J. Seo, E. Tess, S. Mark, A. Brown, L. Anton-Farrington, M. Elovitz, D. Huh



Microengineered  
**biomimicry** of human organs



“ This work completely changed the way we think about *in vitro* model systems, and became a basis for launching new funding programs”

*NIH & FDA (Aug. 2011)*

## Human breathing lung-on-a-chip



“ NIH will collaborate with DARPA and FDA to develop a chip to screen for safe and effective drugs far more swiftly and efficiently than current methods, and before they are tested in humans”

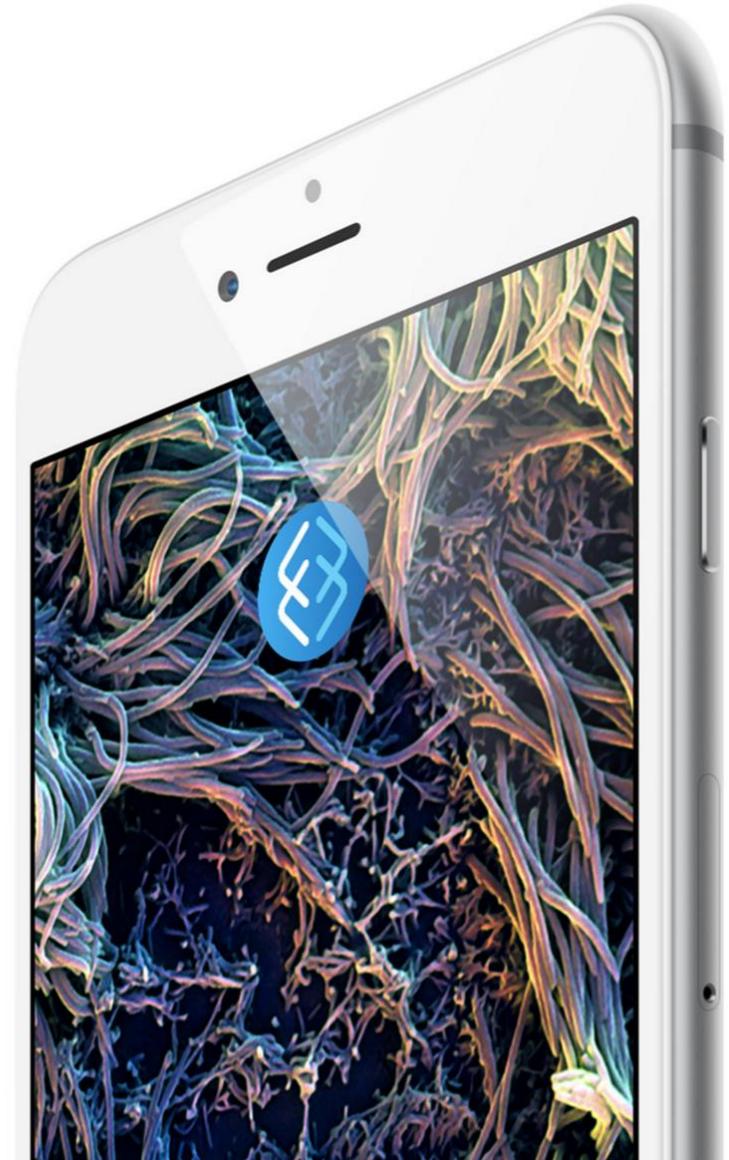
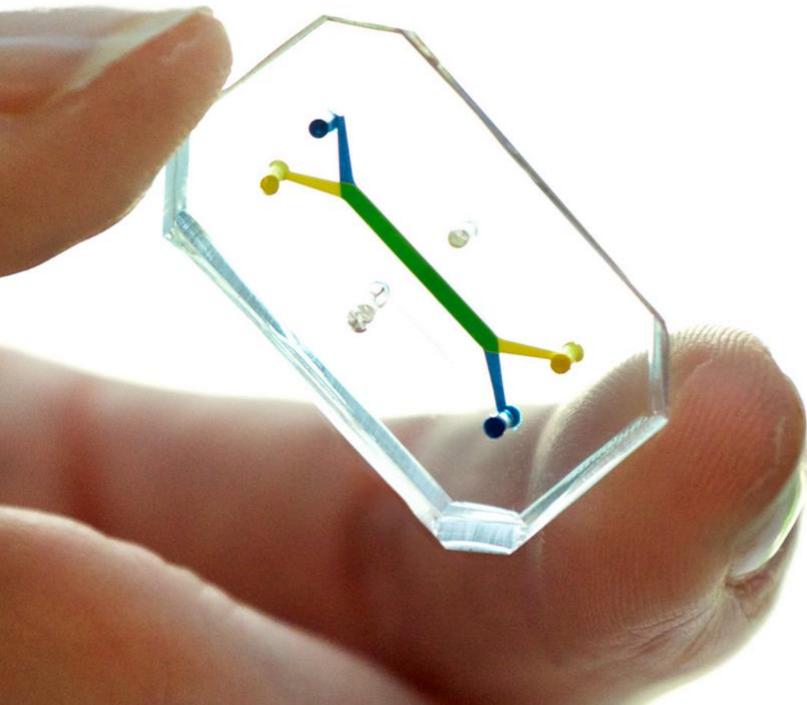
*Obama (Sep. 2011)*



emulate

We emulate human biology  
to understand how diseases,  
medicines, chemicals, and foods  
affect human health.

## Living Human Emulation



*Nature Reviews Drug Discovery* | AOP, published online 20 March 2015; doi:10.1038/nrd4539

## PERSPECTIVES

### INNOVATION

# Organs-on-chips at the frontiers of drug discovery

*Eric W. Esch, Anthony Bahinski and Dongeun Huh*

In recent years, this biomimetic micro-systems approach has been used to establish microengineered models that recapitulate the structural and functional complexity of human organs such as the liver, heart, lung, intestine, kidney, brain and bone<sup>1,18–20</sup>. A representative example is the lung-on-a-chip microdevice that reconstitutes the mechanically active alveolar–capillary barrier in the

**BIOLines**



Jeongyun Seo  
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Cassidy Blundell  
Jinny Cho  
Emily Tess  
Mark Mondrinos  
Megan Farrell  
Jungwook Paek  
Keon Woo Kwon  
Yooni Yi  
Summer Ding  
Woo Yul Byun  
Nan-Kun Wu  
Ariana Schanzer  
Andi Frank  
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Vivian Lee  
Sam Parry  
Michal Elovitz  
Emily Su  
Christos Coutifaris  
Becky Simmons  
Rita Leite  
Nicholas Illsley  
Monica Mainigi  
Reza Dana  
Amy Brown  
Lauren Anton Farrington



National Heart, Lung,  
and Blood Institute



National Institute of  
Diabetes and Digestive  
and Kidney Diseases



Institute for Regenerative Medicine  
Penn IRM



National Research  
Foundation of Korea



Alternatives Research & Development  
FOUNDATION

