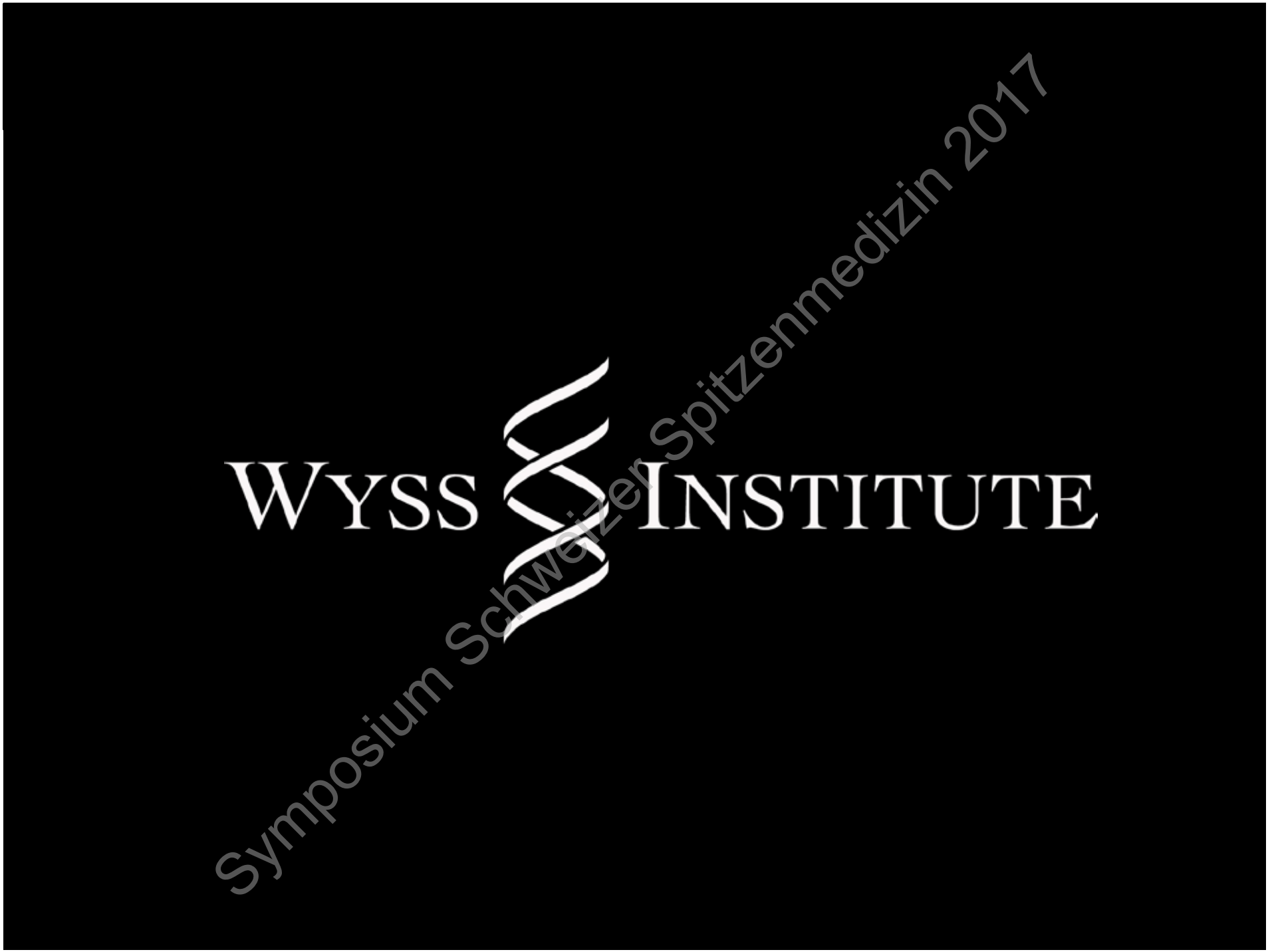

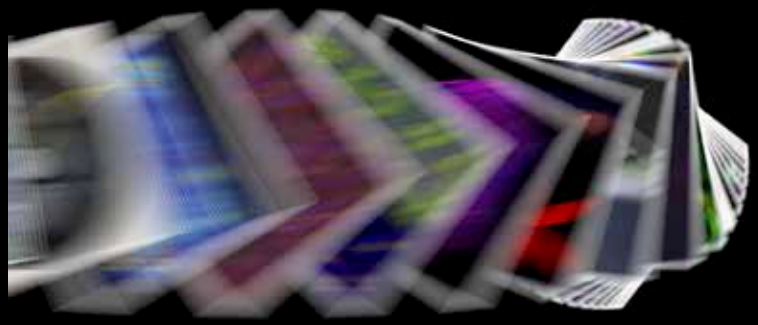

# Biologically Inspired Engineering: The Next Technology Wave


**Don Ingber, MD,PhD**

Founding Director, Wyss Institute
*Judah Folkman Professor of Vascular Biology*, Harvard Medical School & Children's Hospital
Professor of Bioengineering, Harvard School of Engineering and Applied Sciences

***Hansjörg Wyss Institute for Biologically Inspired Engineering at Harvard University***

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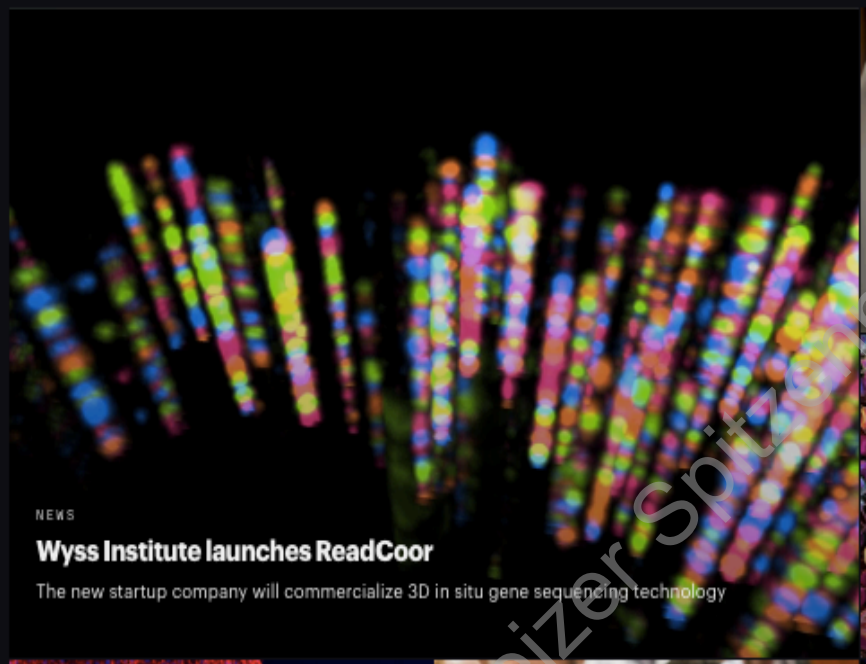
# our **Mission**

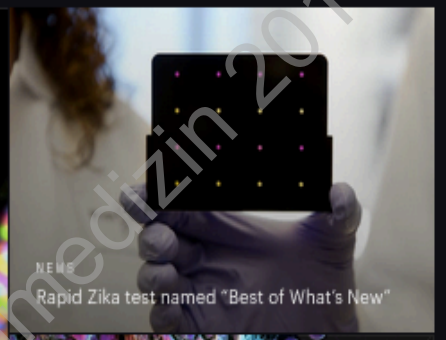
***To transform healthcare and the environment by emulating the way Nature builds***



NEWS

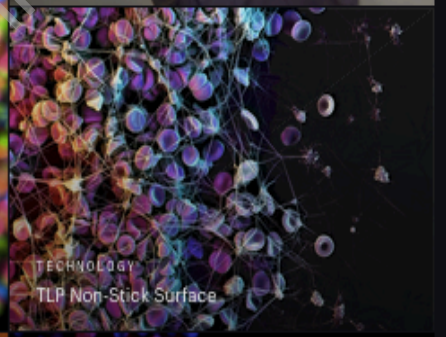
**Wyss Institute launches ReadCoor**

The new startup company will commercialize 3D in situ gene sequencing technology



NEWS

Rapid Zika test named "Best of What's New"



TECHNOLOGY

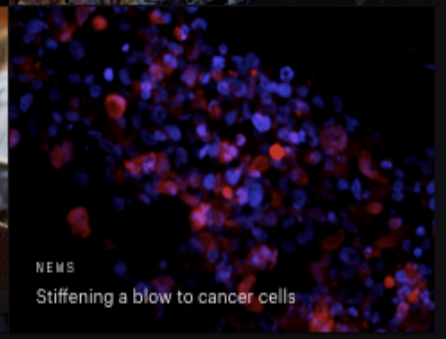
TLP Non-Stick Surface

NEWS

Towards building functional human tissues

EVENT

Embracing the Environment



NEWS

Stiffening a blow to cancer cells

# Breakthrough discoveries cannot change the world if they do not leave the lab

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# THE BIG CHALLENGE:
# Current Drug Development Model is Broken

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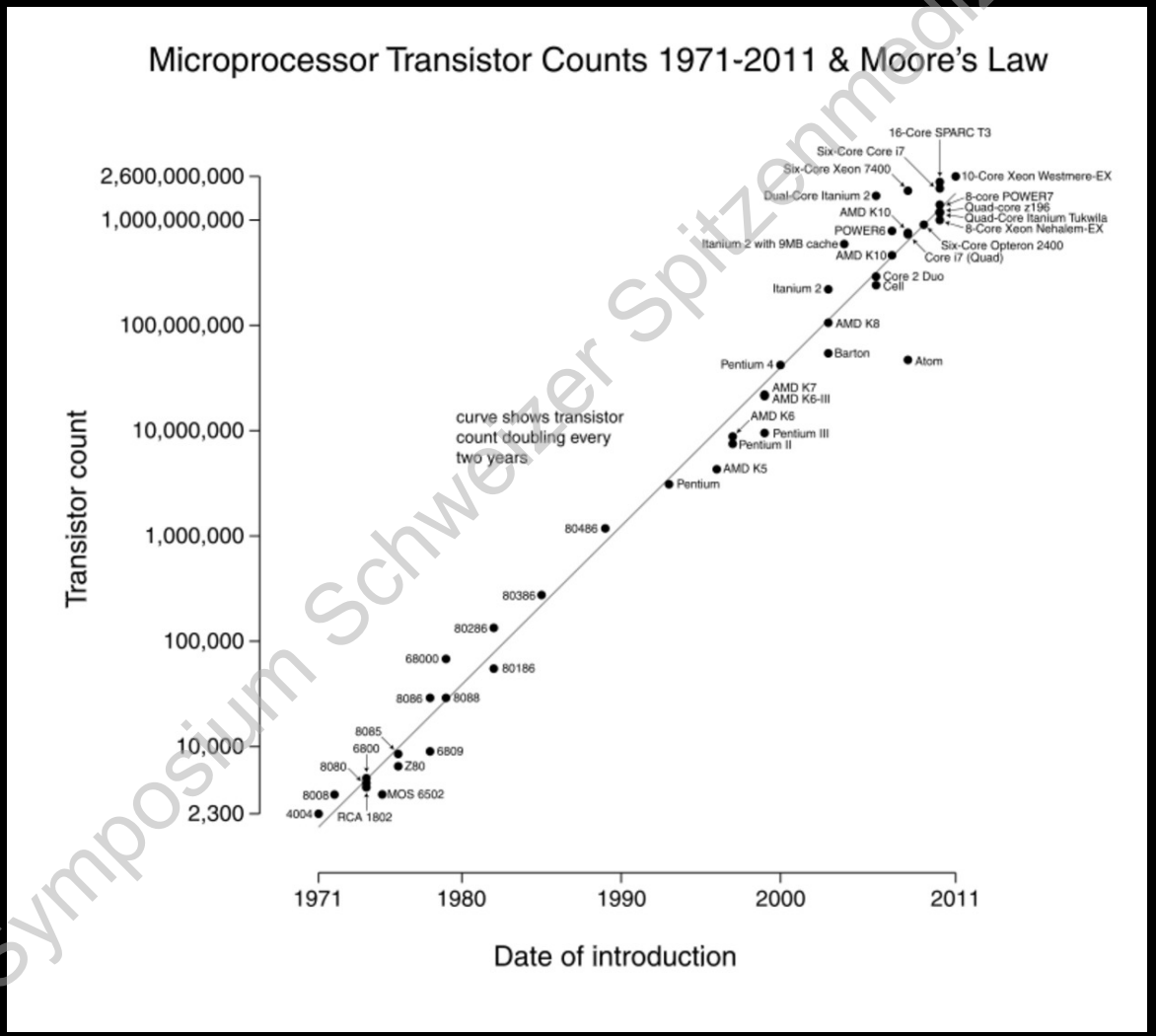
# Computer Power Doubles Every 18 Months

**Moore's Law**



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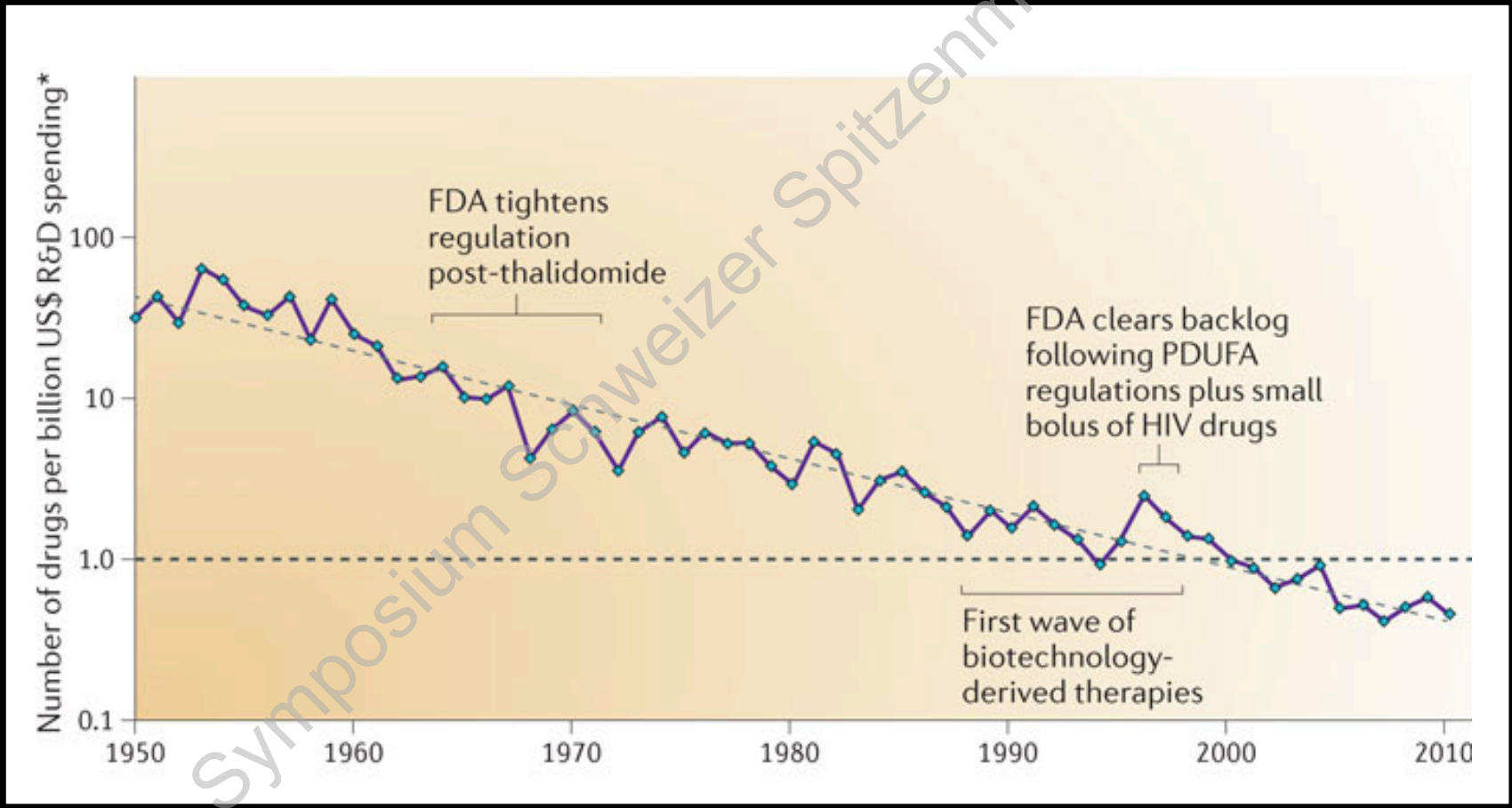
# Number of Medicines Invented HALVES Every 9 Years

## Eroom's Law (Moore's law backwards)




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

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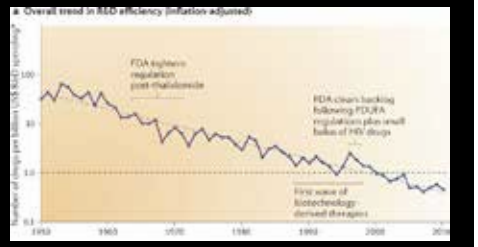
# The Drug Development Model is Broken

- Cost to develop & approve a new drug > $2.6 Billion
- Cells cultured in dishes don't function like in our bodies
- Animal studies take years to complete
- Innumerable animal lives are lost
- Results often don't predict clinical responses!
- Lack of new drugs reaching patients



***Need better lab models that mimic whole human organ function***

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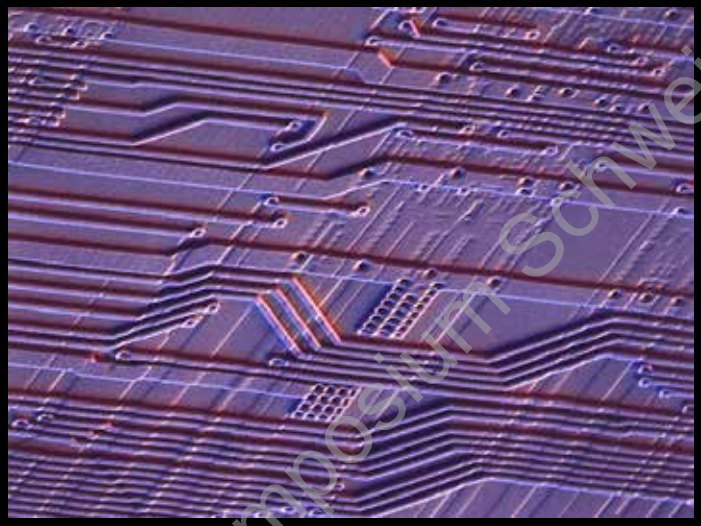
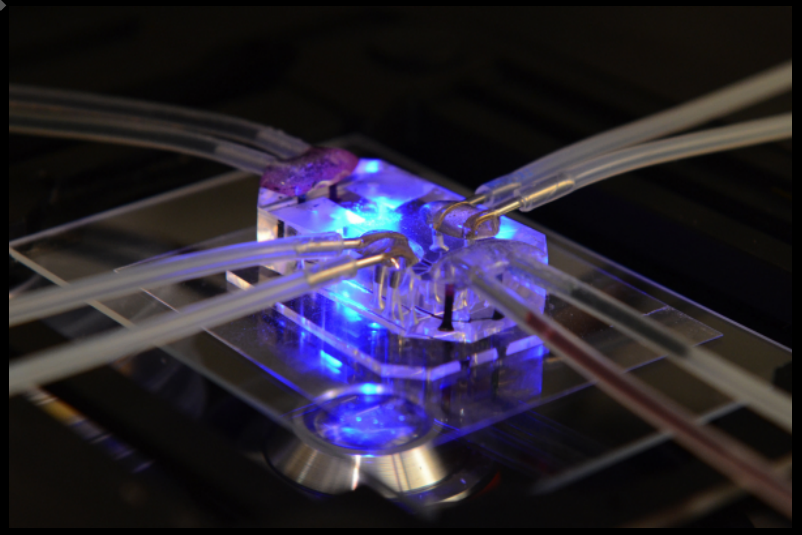
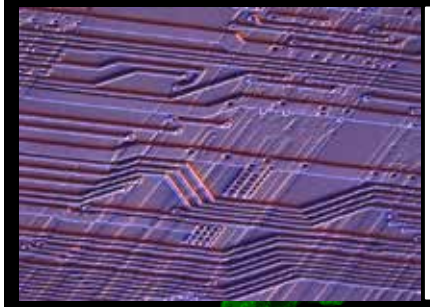
# Biomimetic Microsystems

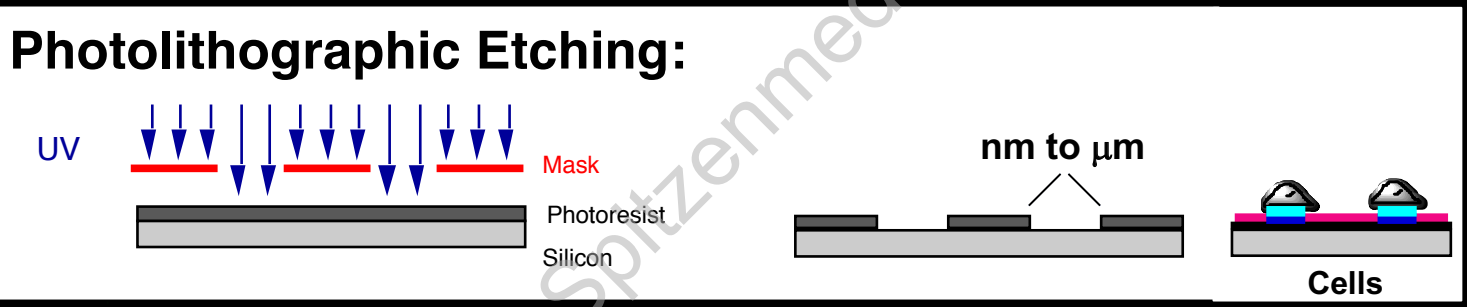
- Engineer microchips containing living human cells that reconstitute **organ-level functions**
- ***ACCELERATE drug development & REPLACE animal testing***

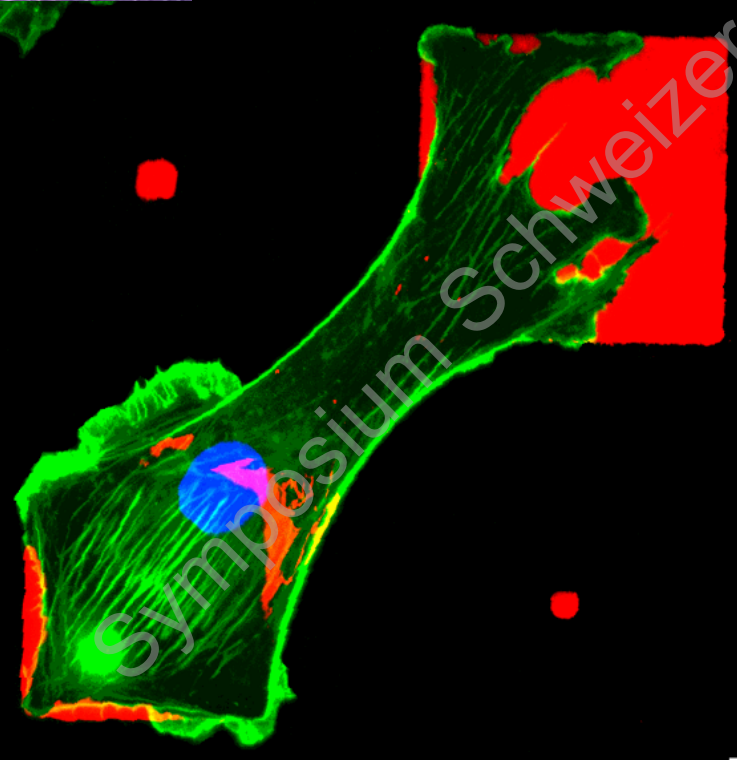




# Microchip Manufacturing offers control of features at same size scale of living cells





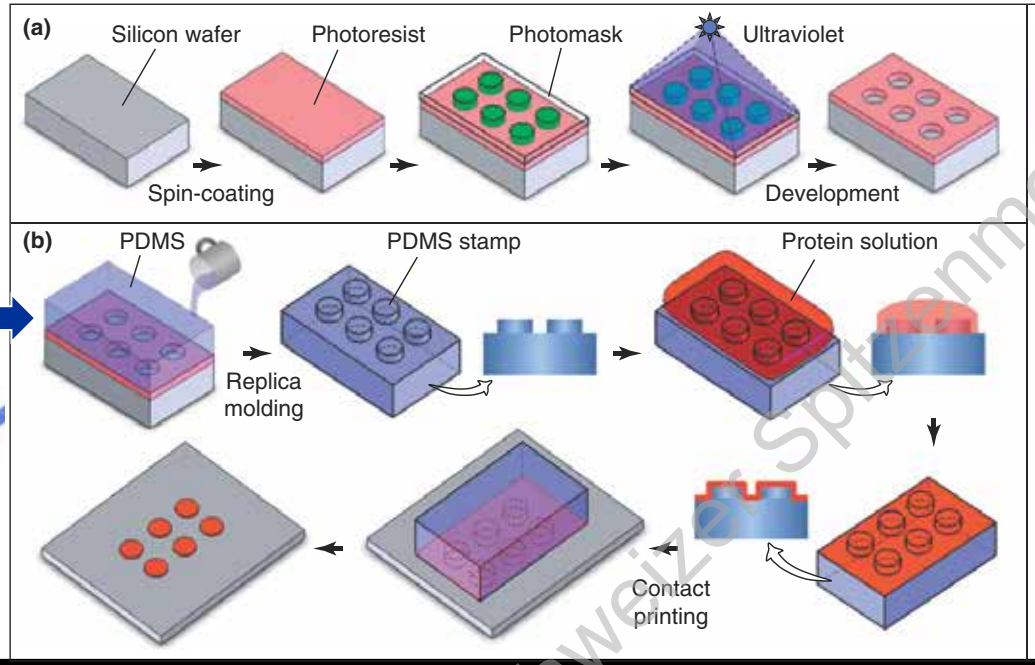



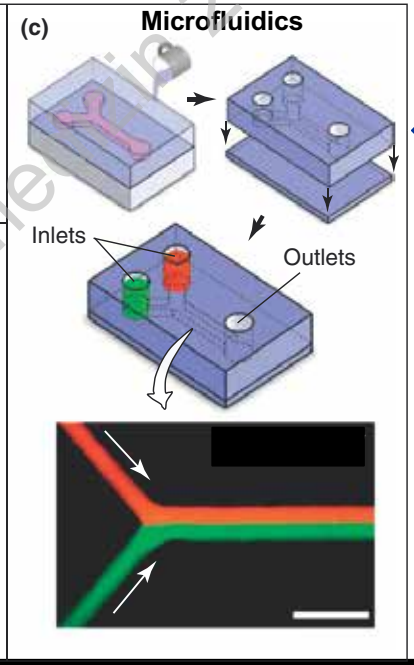
***1 nanometer is to 1 meter***
***as a Blueberry's width is to the Earth's***

# ‘Soft’ Lithography Produces Surface Replicas

*(developed with George Whitesides)*

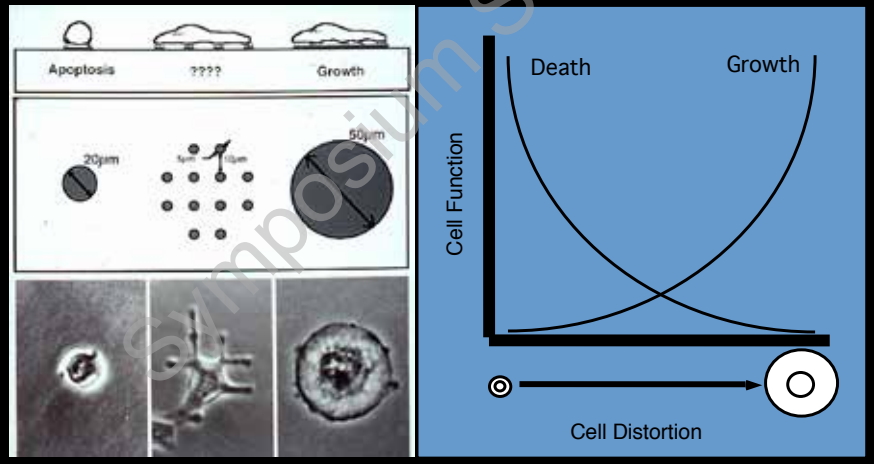
**Silicone Rubber Stamp**



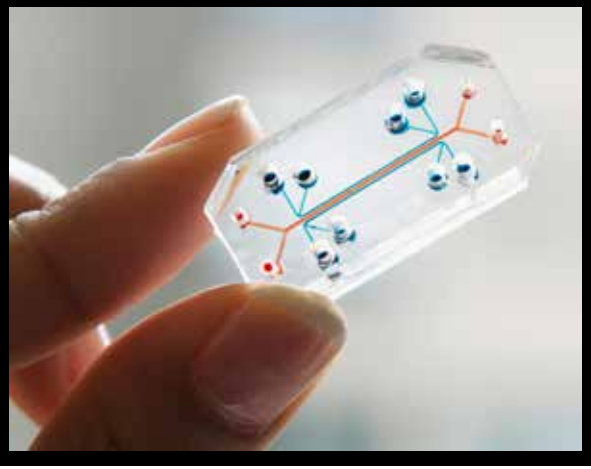

**Silicone Rubber Negative Imprint**

## *Control Cell Shape & Function*




(Chen et al., ***Science*** 1997)

## Fluidic Flow *at Cell Scale*



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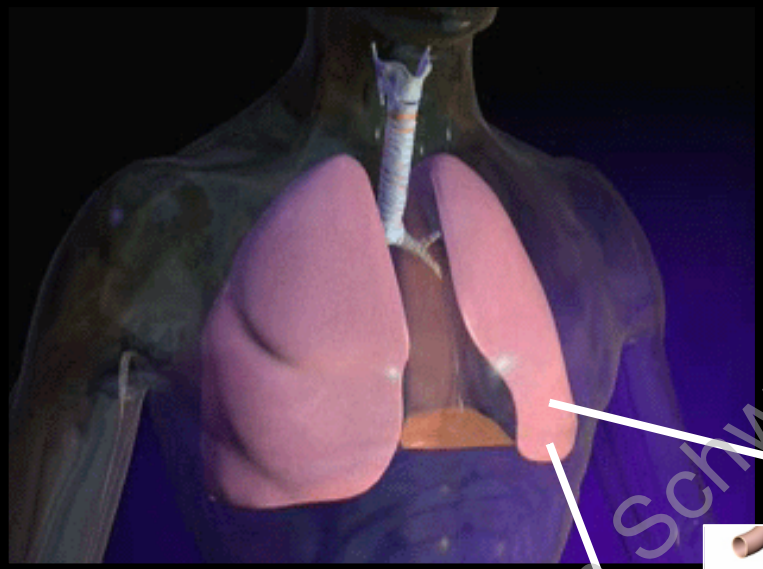
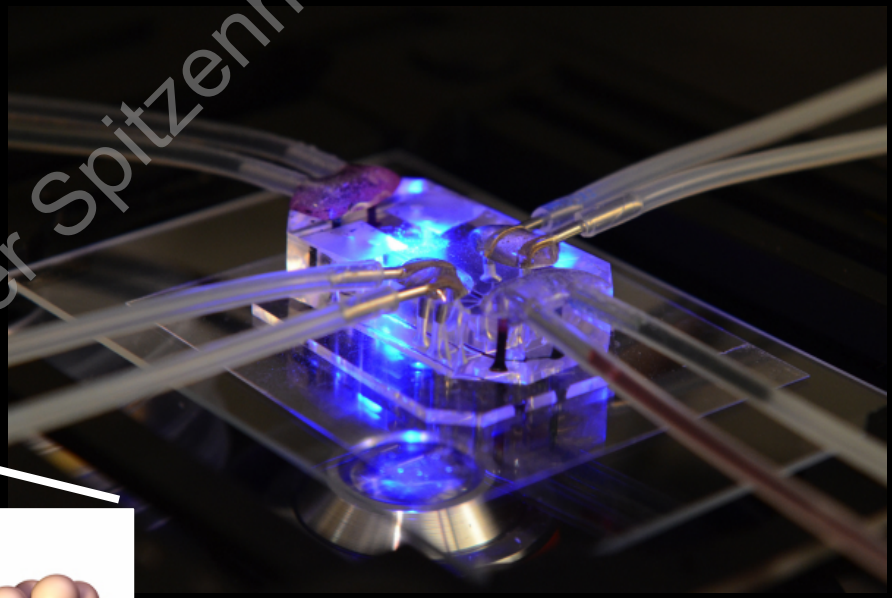
# A Human Breathing Lung-on-a-Chip

(Dan Huh, Wyss Institute; Huh et al., *Science* 2010)






Alveoli (air sacs)

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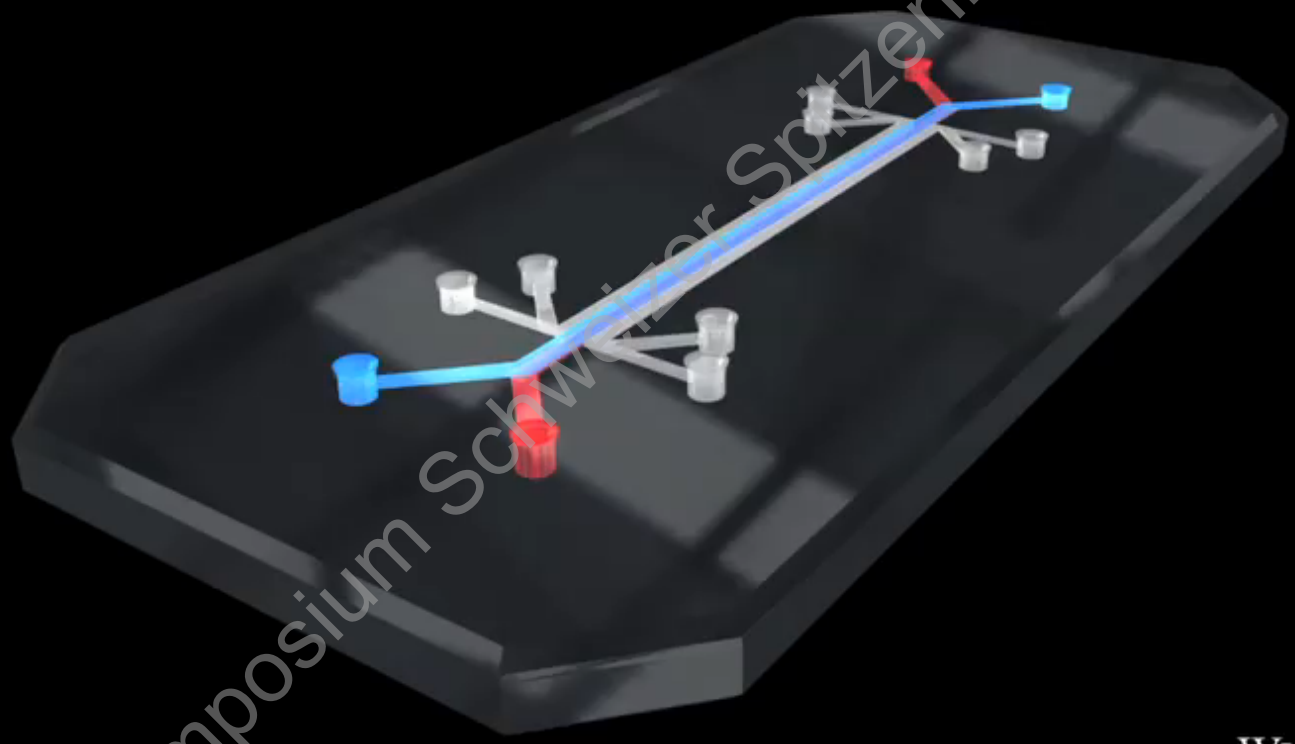



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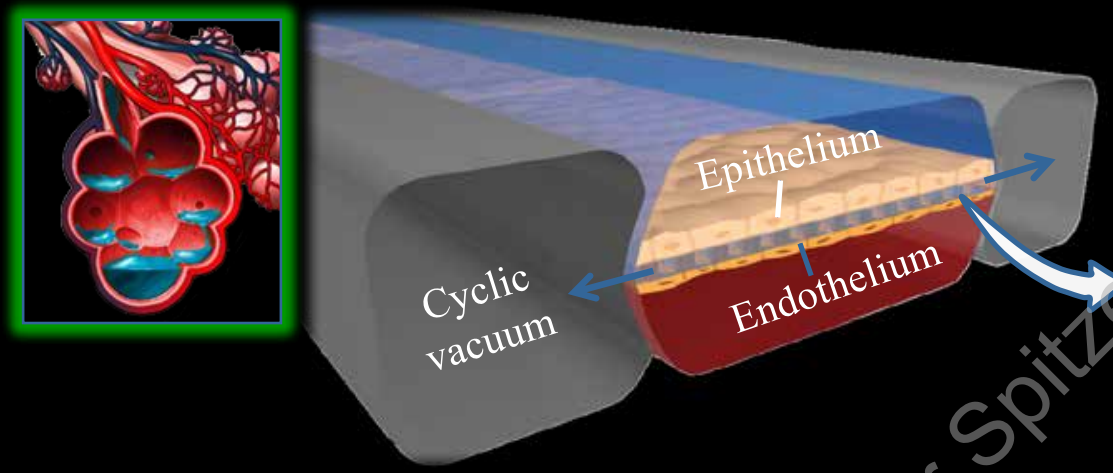
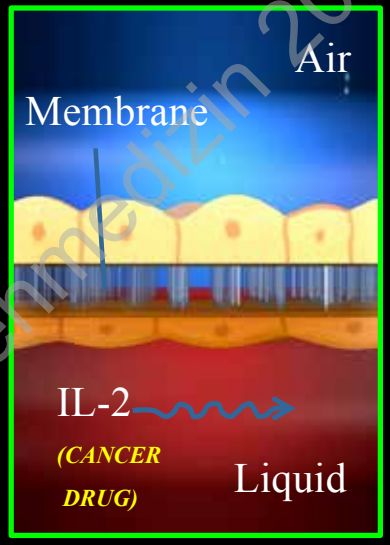
# Human Disease Model:

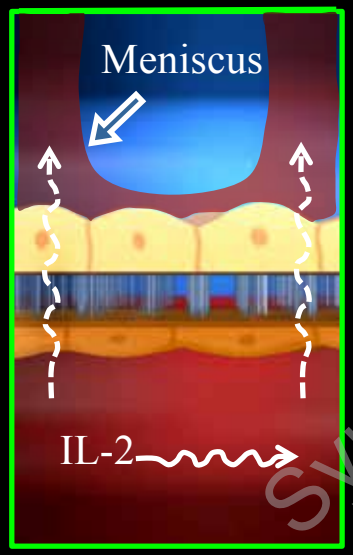
## Pulmonary Edema ('Fluid on the Lungs')-on-a-Chip

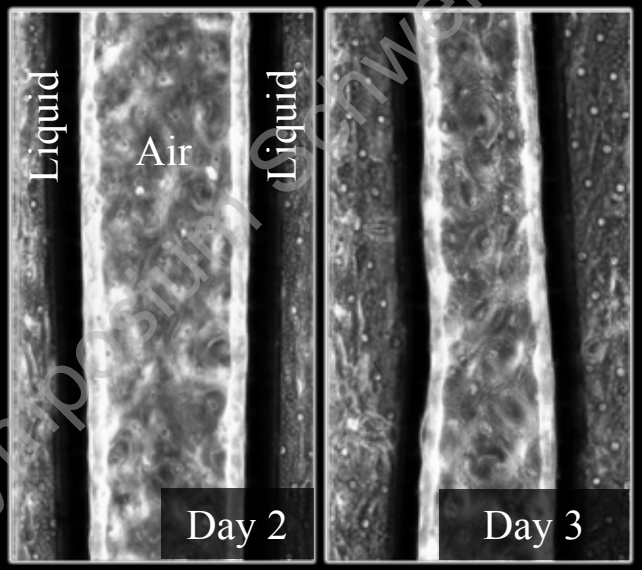


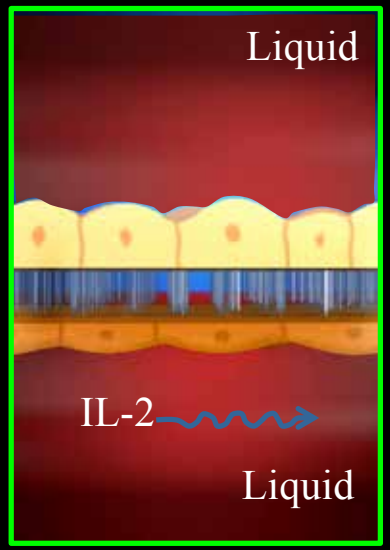



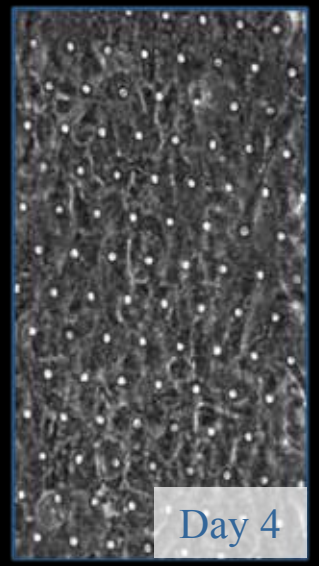


(Huh et al. ***Sci. Trans. Med.***, 2012)



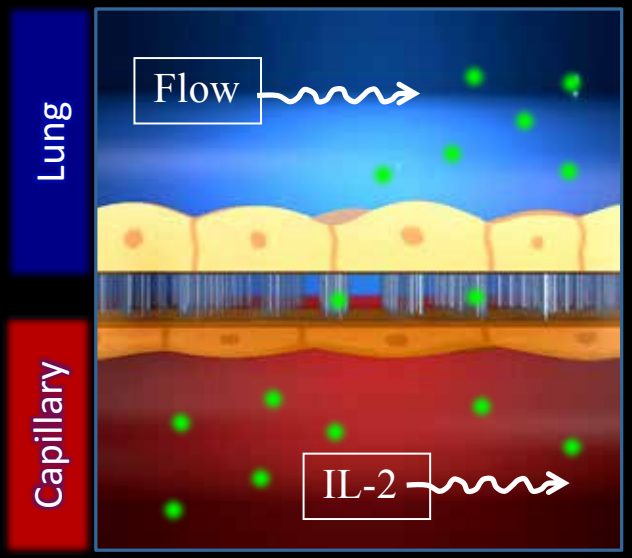



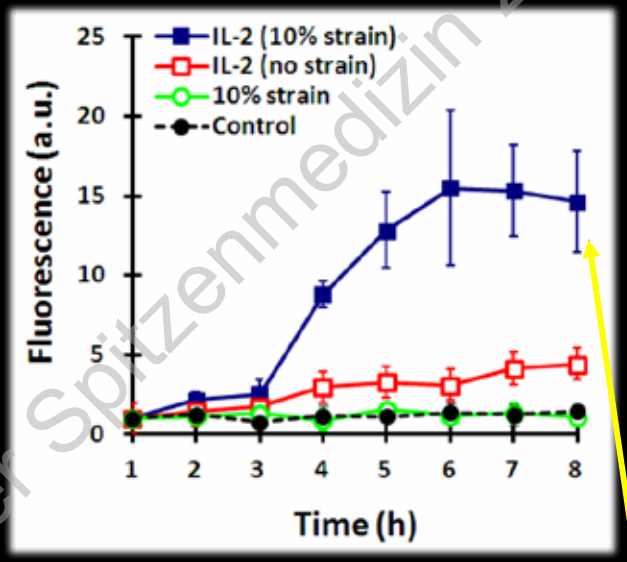



# Effects of IL-2 Cancer Drug on Lung Permeability

*(with GSK)*

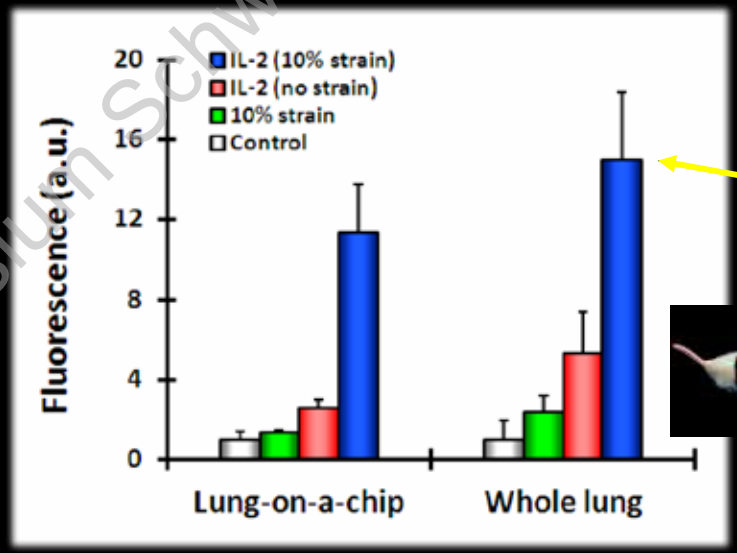
**Vascular Leakage Model**




**On-Chip**

**Prediction Confirmed *In Vivo***




***Breathing Motions Increase Drug Toxicity***

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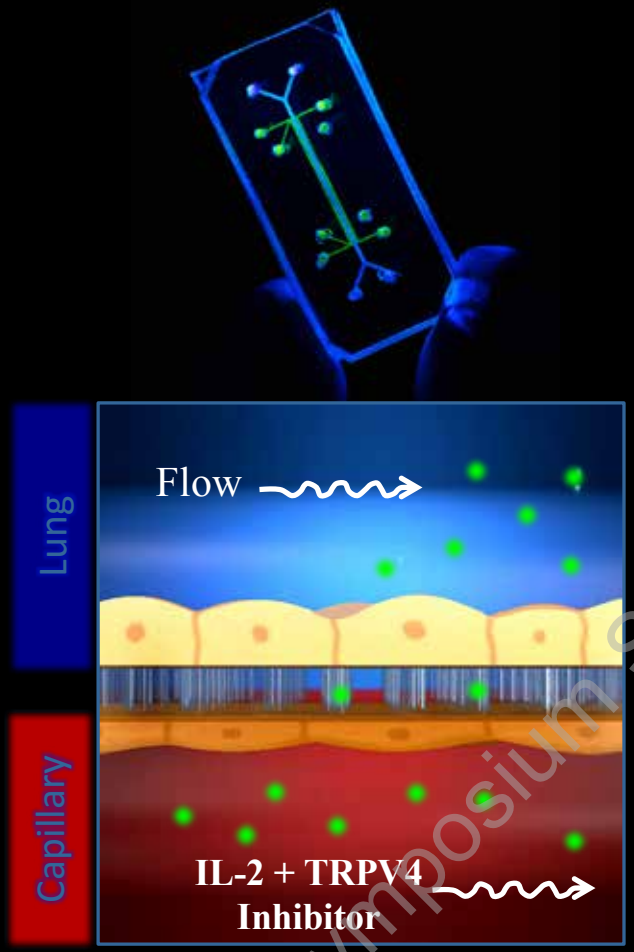
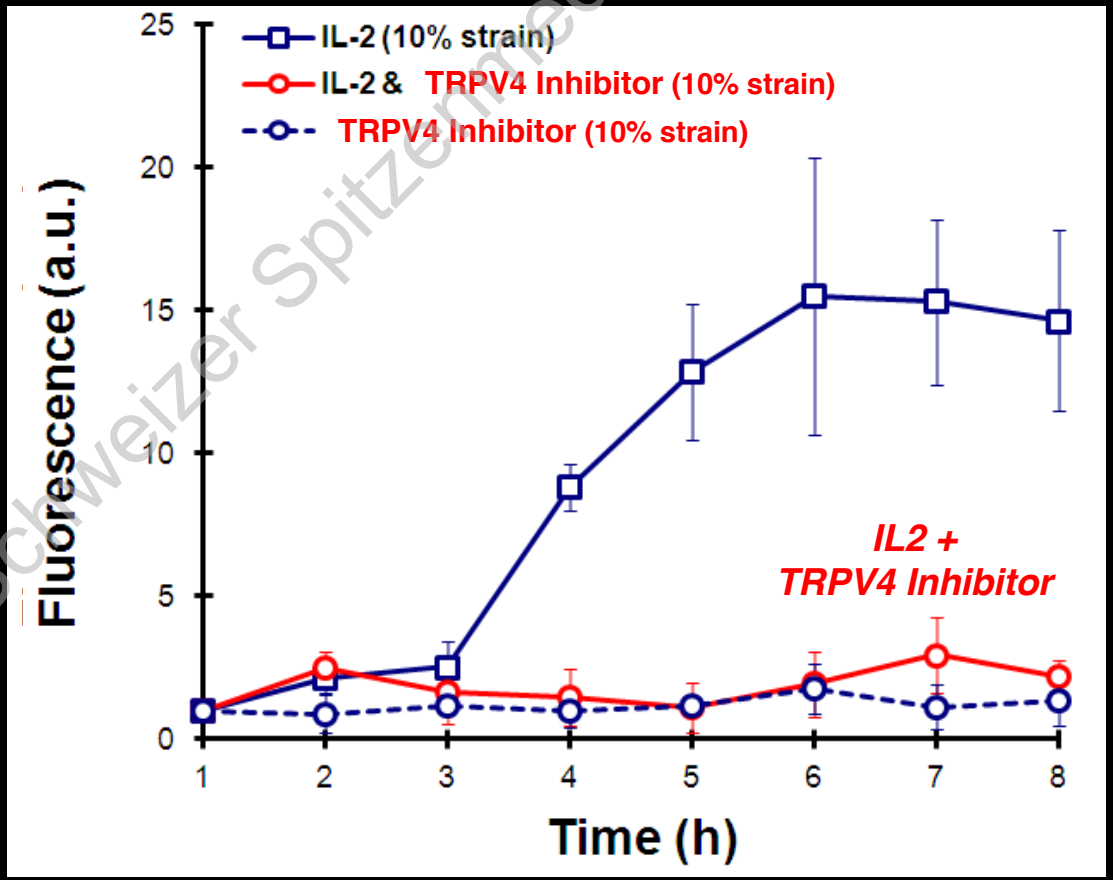
# Predicting Drug Efficacy and Toxicity

***+ Discovery of a Mechanotherapeutic***



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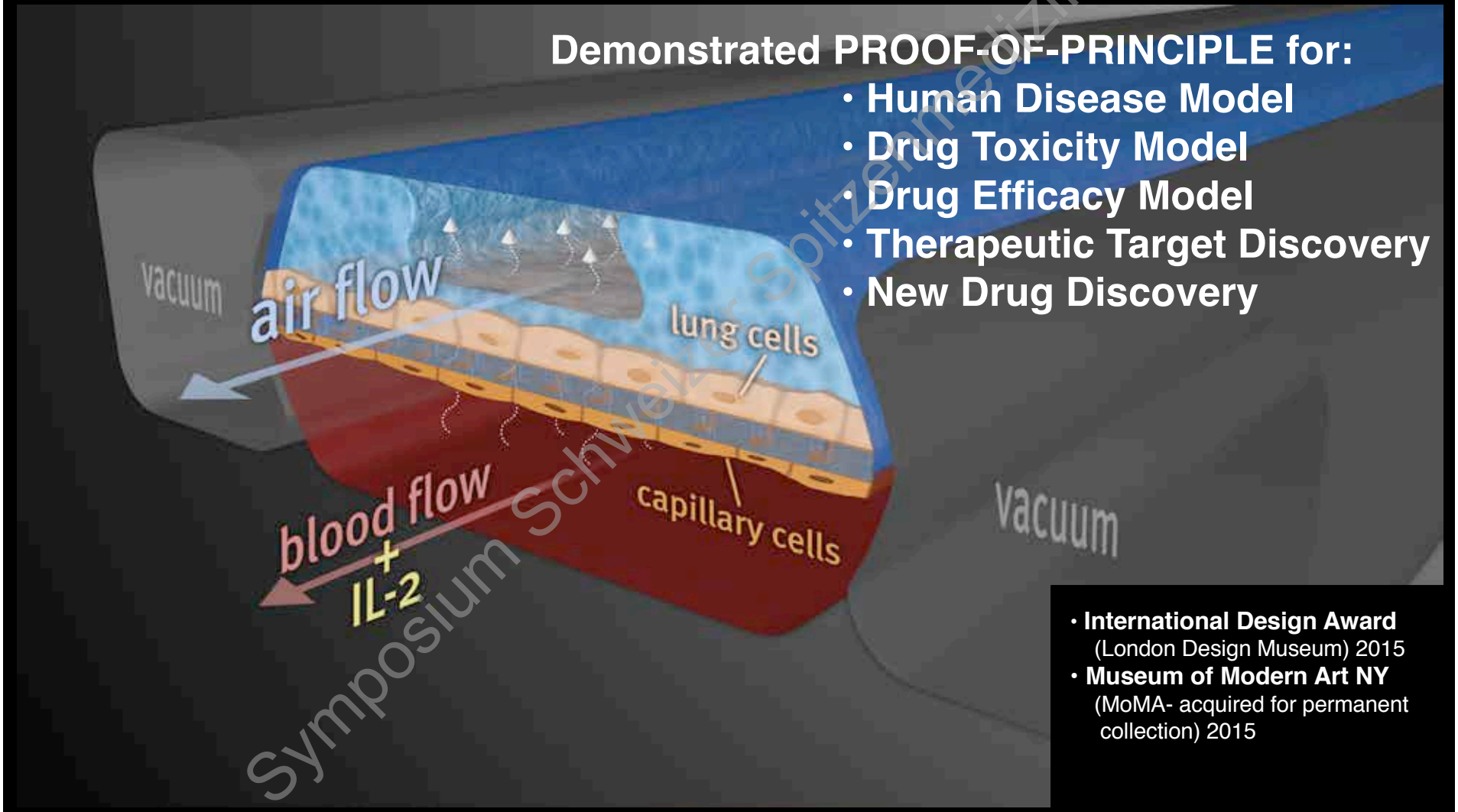
# Human Lung Alveolus Chip




**Demonstrated PROOF-OF-PRINCIPLE for:**

- **Human Disease Model**
- **Drug Toxicity Model**
- **Drug Efficacy Model**
- **Therapeutic Target Discovery**
- **New Drug Discovery**

- **International Design Award** (London Design Museum) 2015
- **Museum of Modern Art NY** (MoMA- acquired for permanent collection) 2015

(Huh et al., *Science* 2010 & *Sci. Trans. Med.* 2012)

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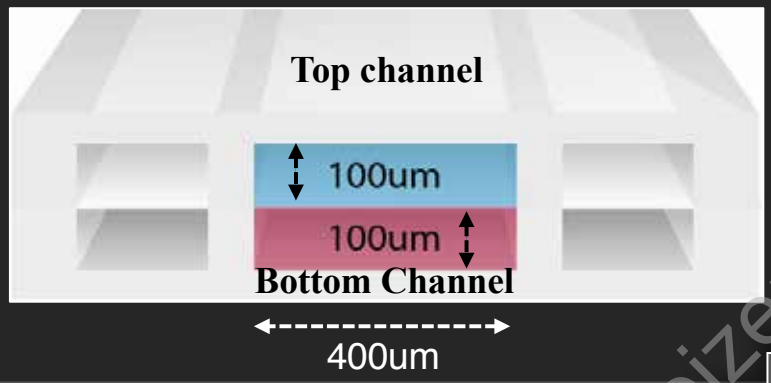
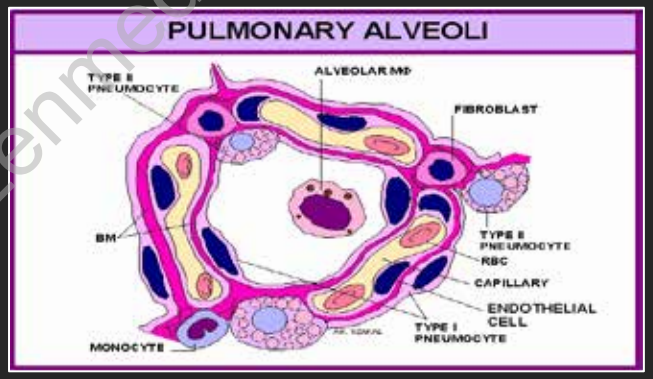
# Small Airway-On-A-Chip

**(Benam et al., *Nature Methods 2015 & Cell Systems 2016*)**

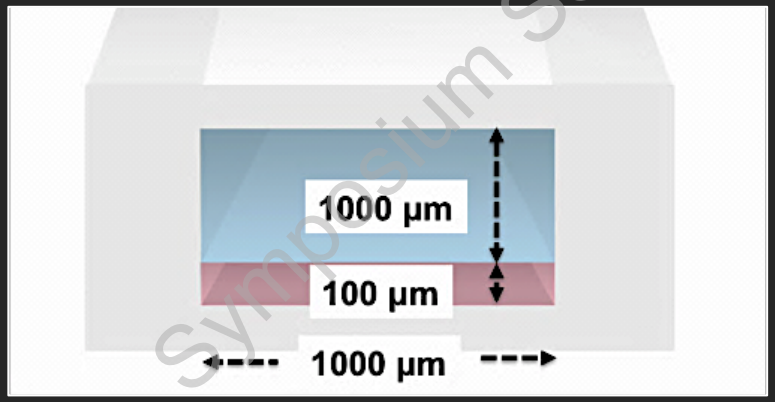


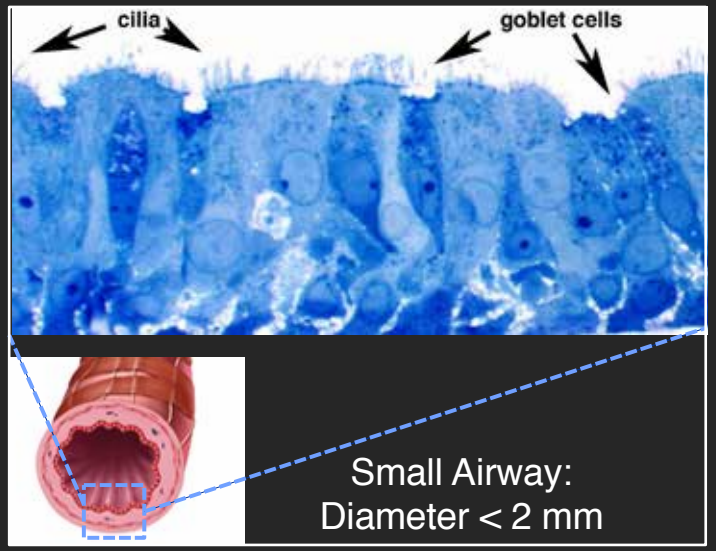
## ‘Classic’ Lung (Alveolus)-On-a-Chip




## Small Airway-On-a-Chip



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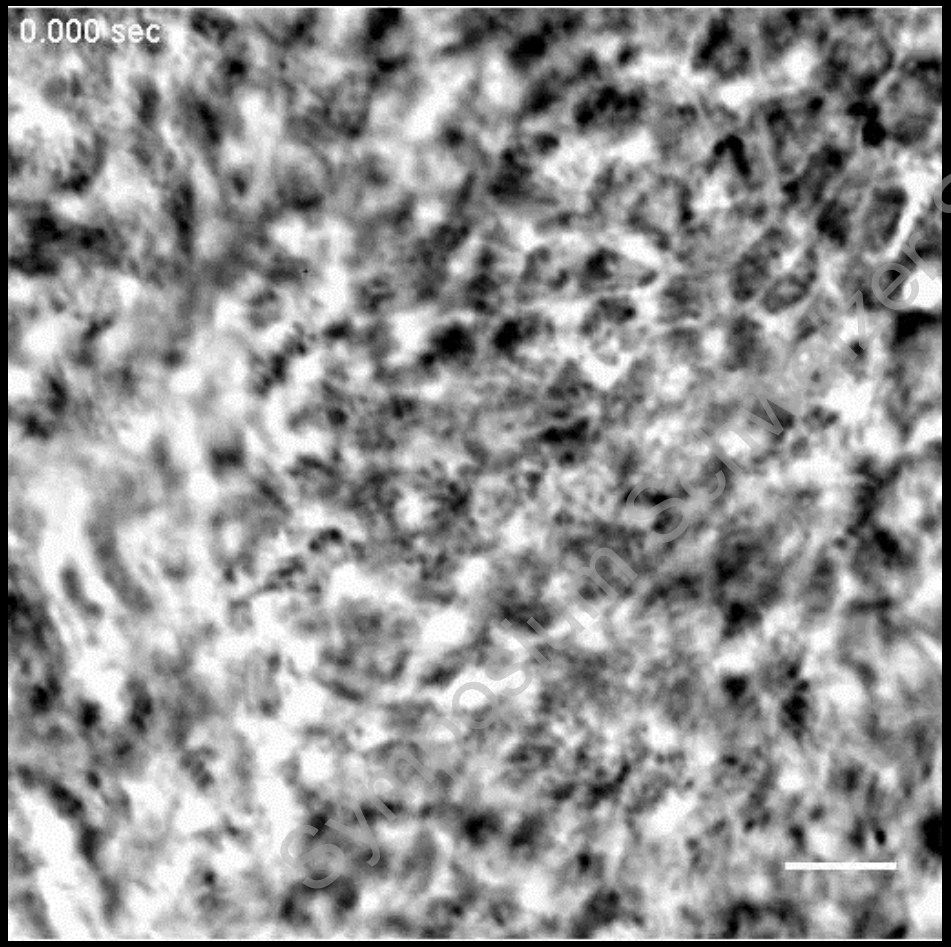
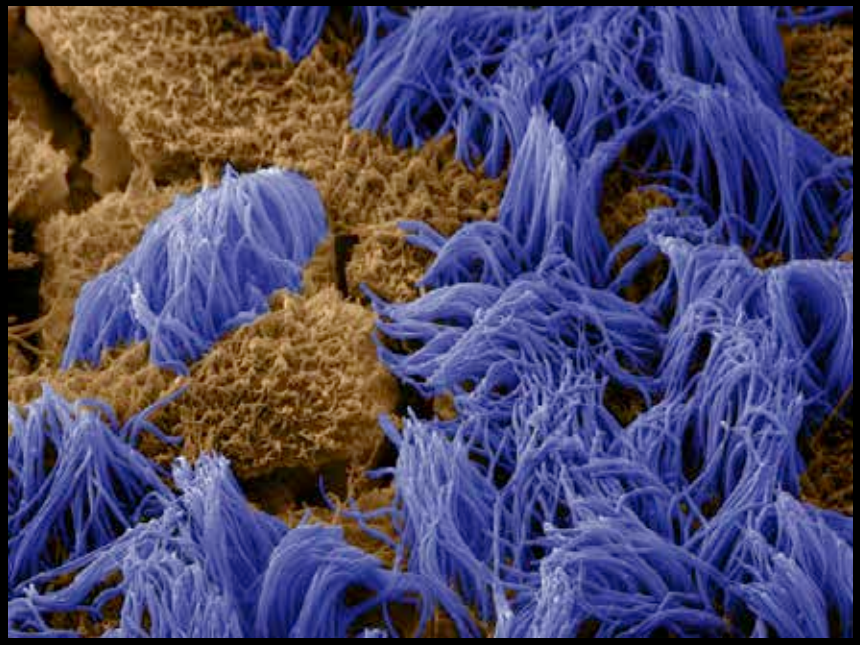
# Beating Cilia in the Airway-on-a-Chip

***(time-lapse at 1/7th normal rate)***

**Top View**




**Side View**



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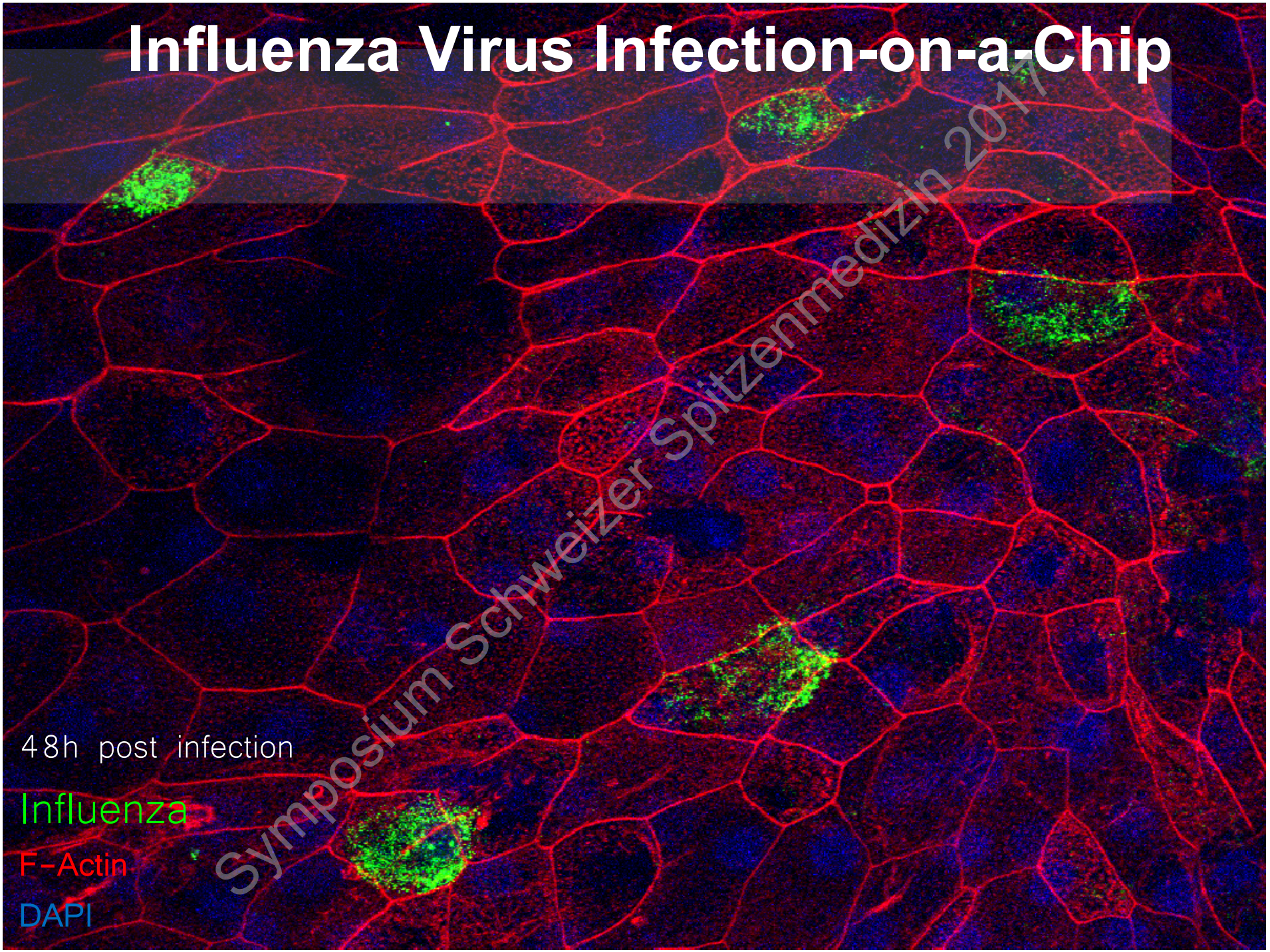
# Visualization of Mucociliary Transport

***(Real-Time Imaging)***

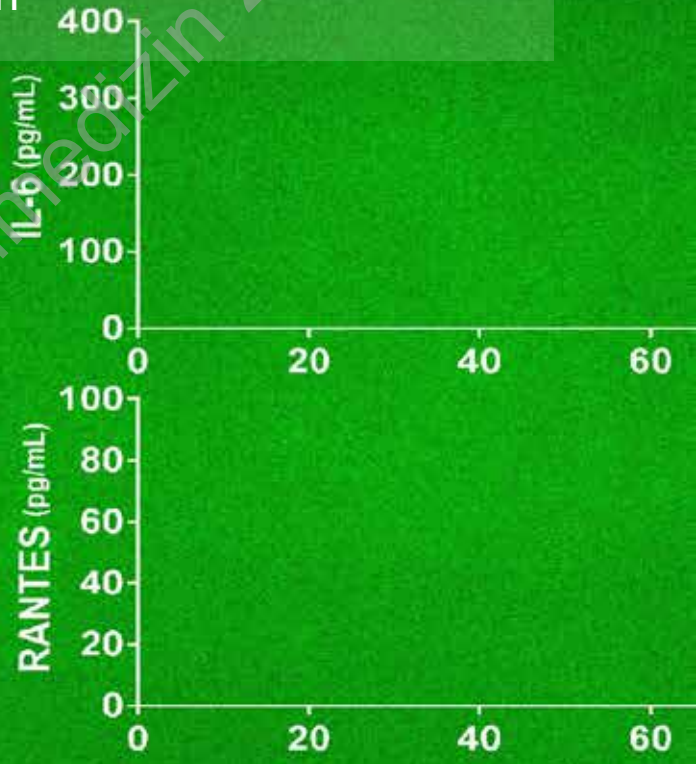
# Influenza Virus Infection-on-a-Chip



00:00 h

# Infectious Disease Platform (sendai-GFP)

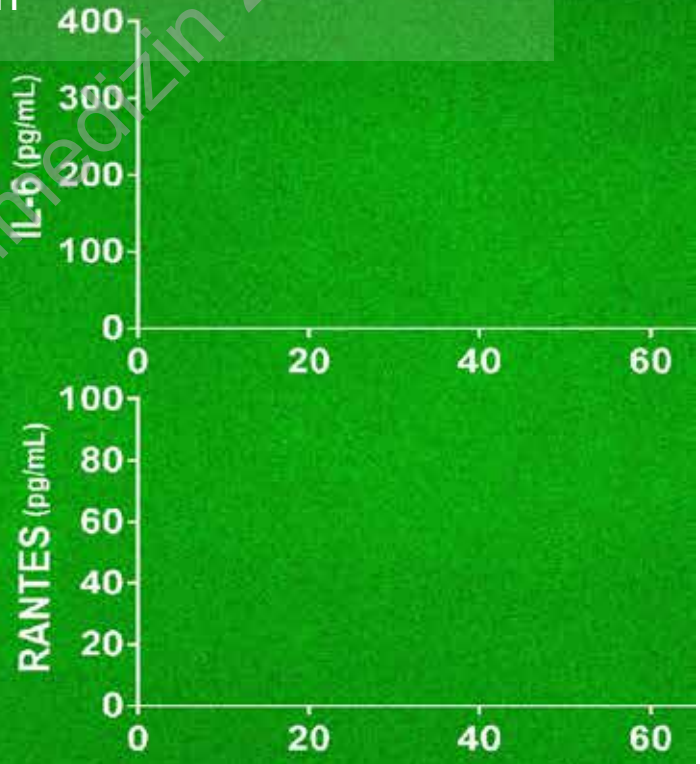
Real time imaging and high resolution cytokine titration



00:00 h

# Infectious Disease Platform (sendai-GFP)

Real time imaging and high resolution cytokine titration



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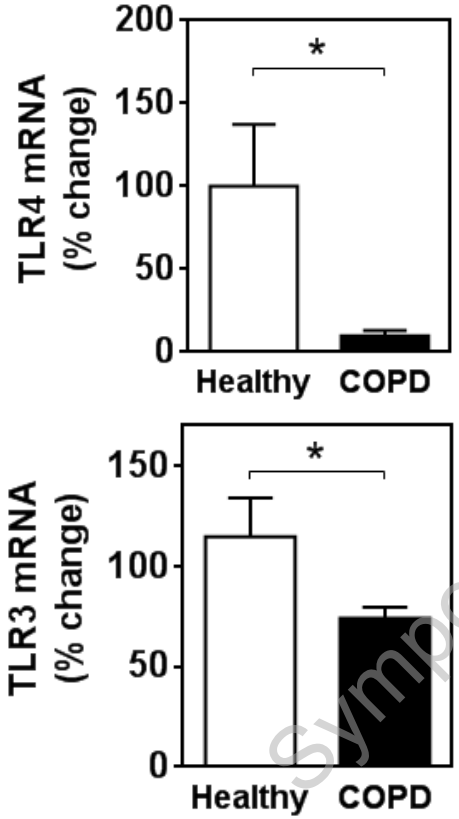
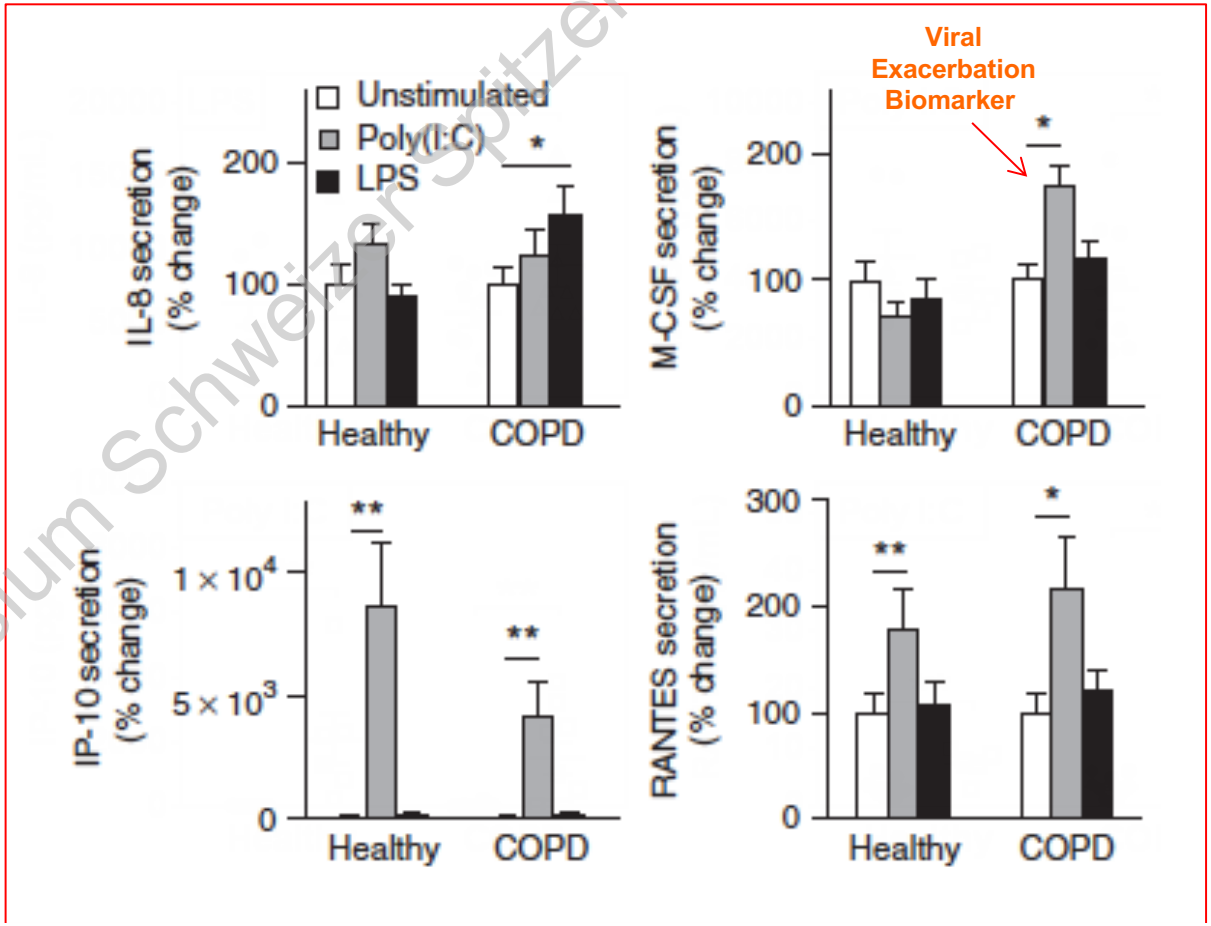
## *Chips Lined by Cells from COPD Patients*

***(COPD = Chronic Obstructive Pulmonary Disease)***

(Benam et al., *Nature Methods* 2015)

# Human COPD Lung Response & *Exacerbations* are Recapitulated On-Chip



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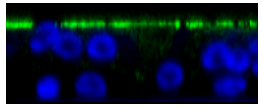
# Testing Effects of Cigarette Smoke on Lung Chips

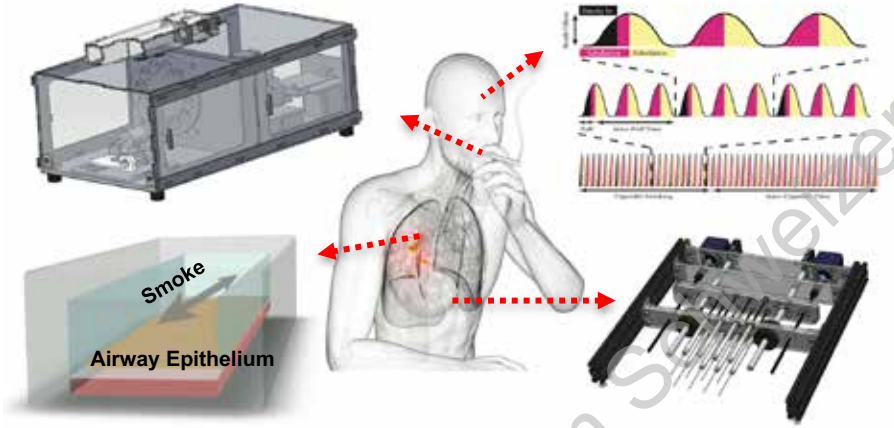
(Benam et al. *Cell Systems* 2016)



A

B




C

D

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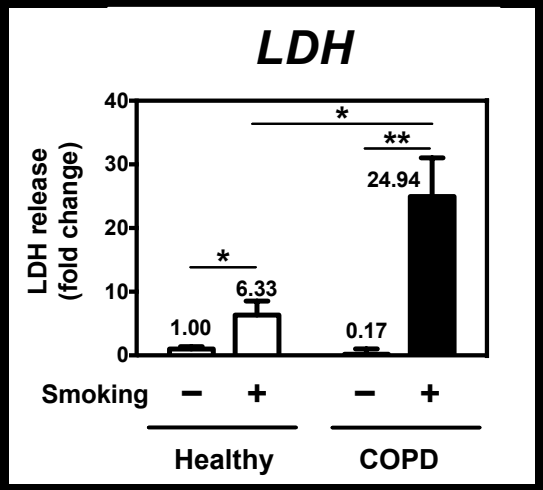
# Cigarette Smoke: Matched Comparative Modeling in Lung Chips

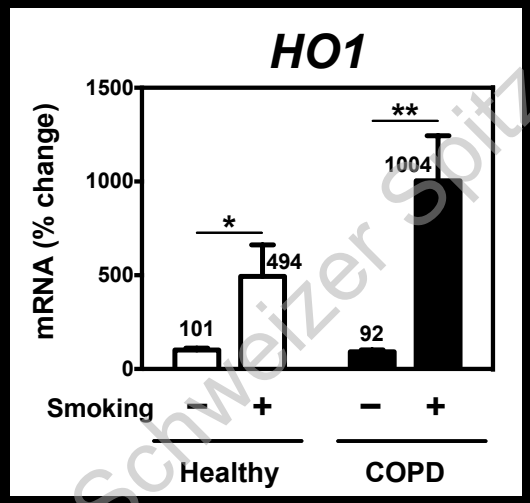
(Benam et al. *Cell Systems* 2016)



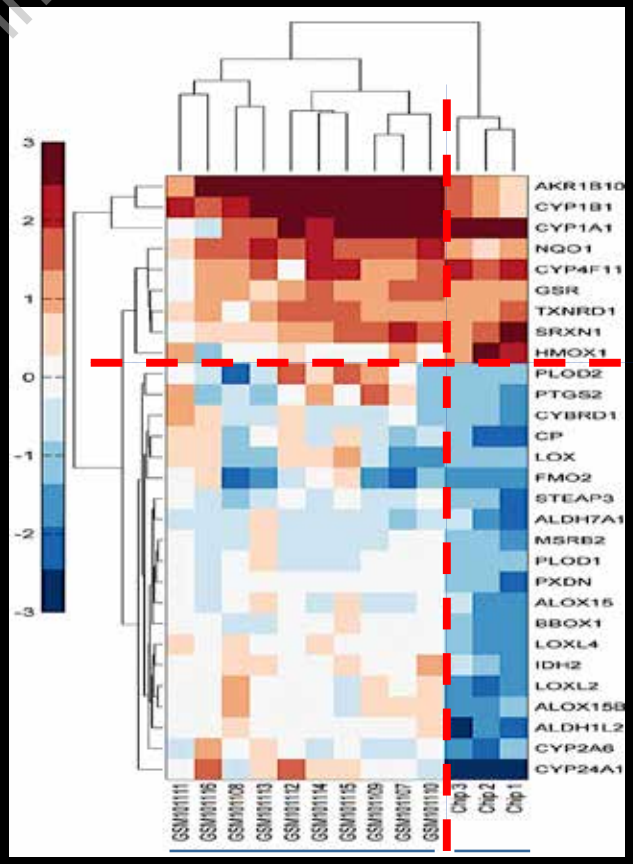
## Cytotoxicity




## Cell Stress



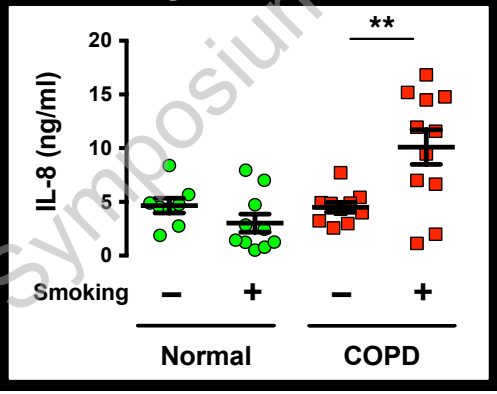

## Gene Microarrays




Normal smokers

Smoking chips

## Cytokines



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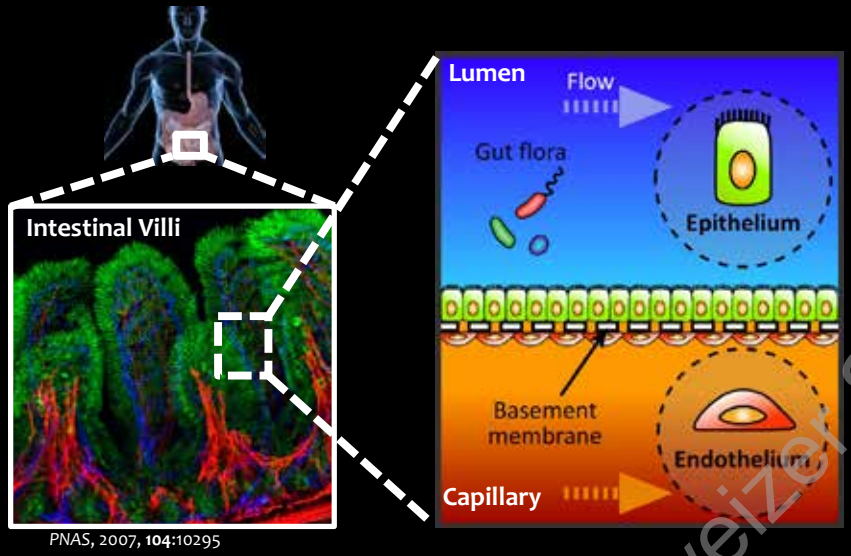
# Peristaltic Human Gut-on-a-Chip

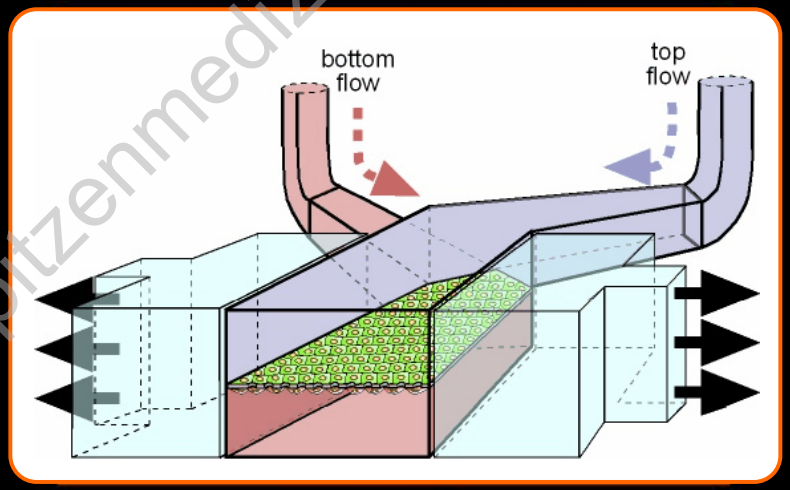
(Kim et al., ***Lab Chip*** 2012, ***Integ. Biol.*** 2013, ***PNAS*** 2016)

## Human Intestine

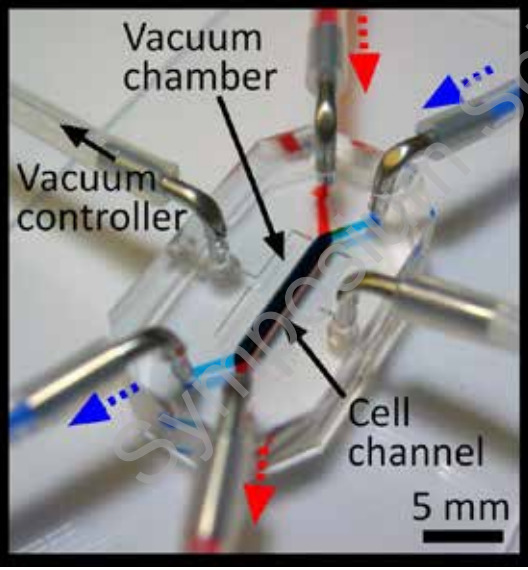



PNAS, 2007, **104**:10295

## Microfluidic Platform

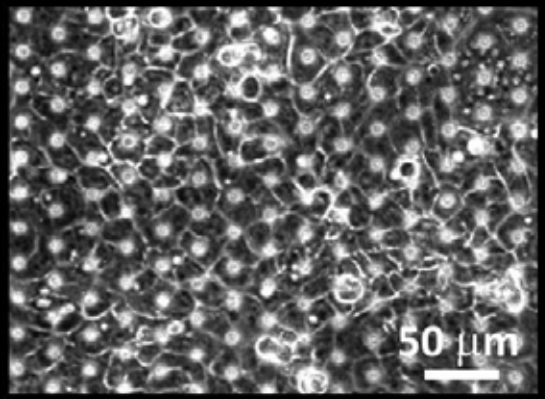



**Gut Chip**

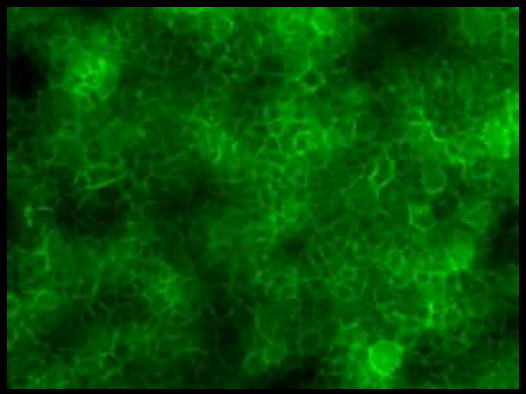



## Human Gut Epithelium

**(Exposed to Flow + Cyclic Deformation)**




24 hr after seeding



+ Peristaltic-like motions

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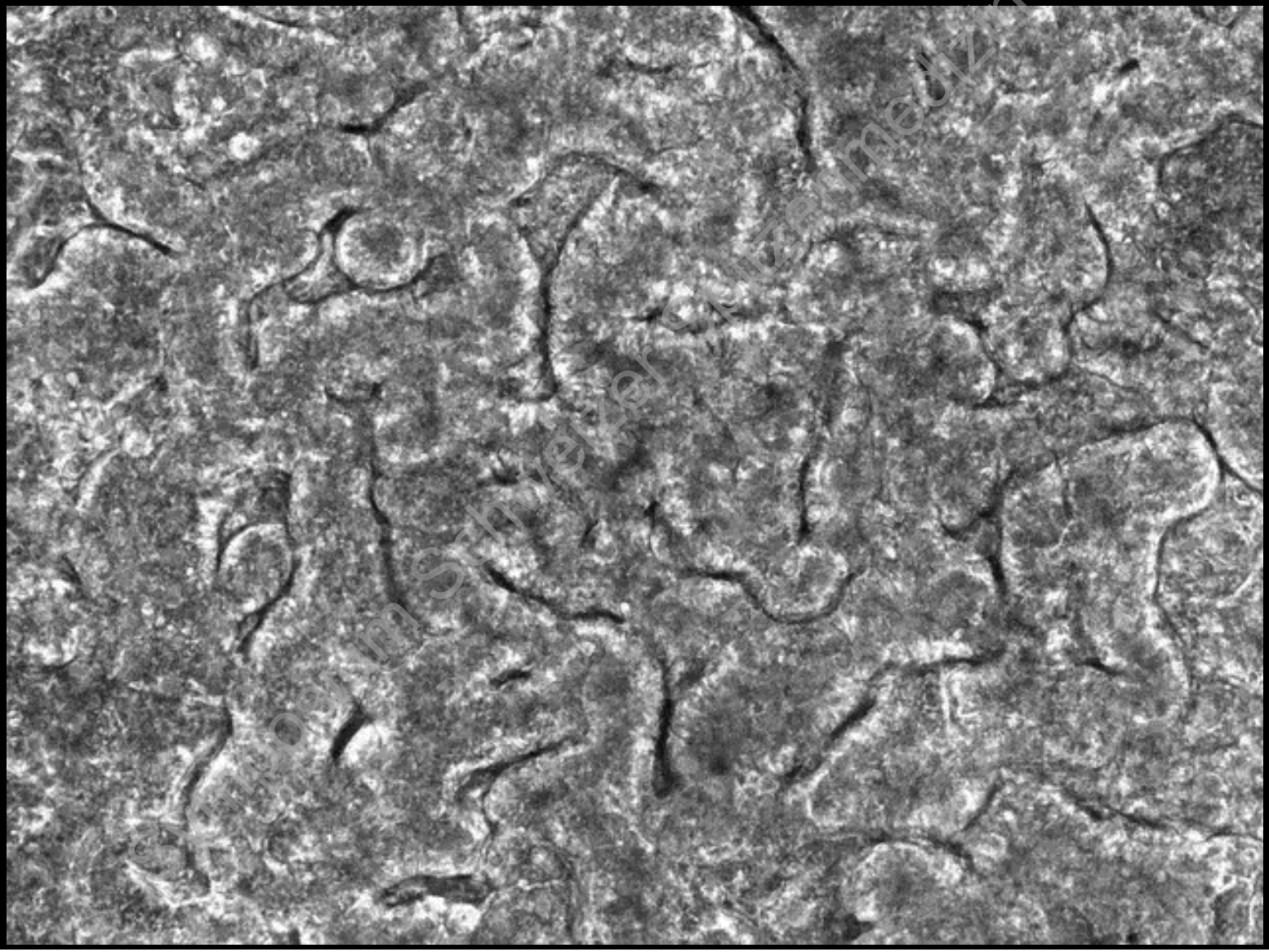
# Induction of Intestinal Villi Formation



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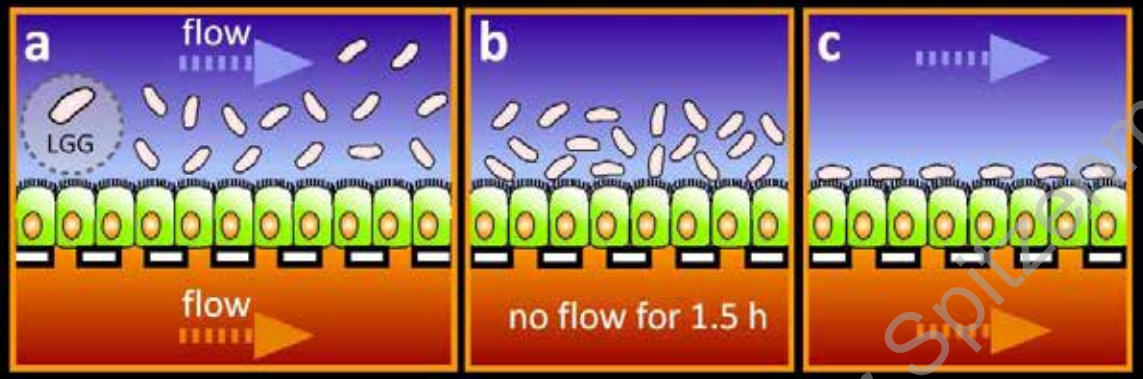
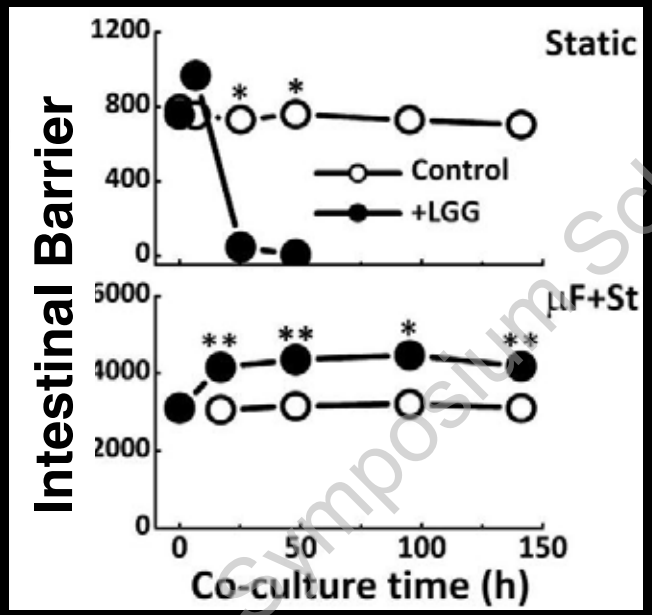
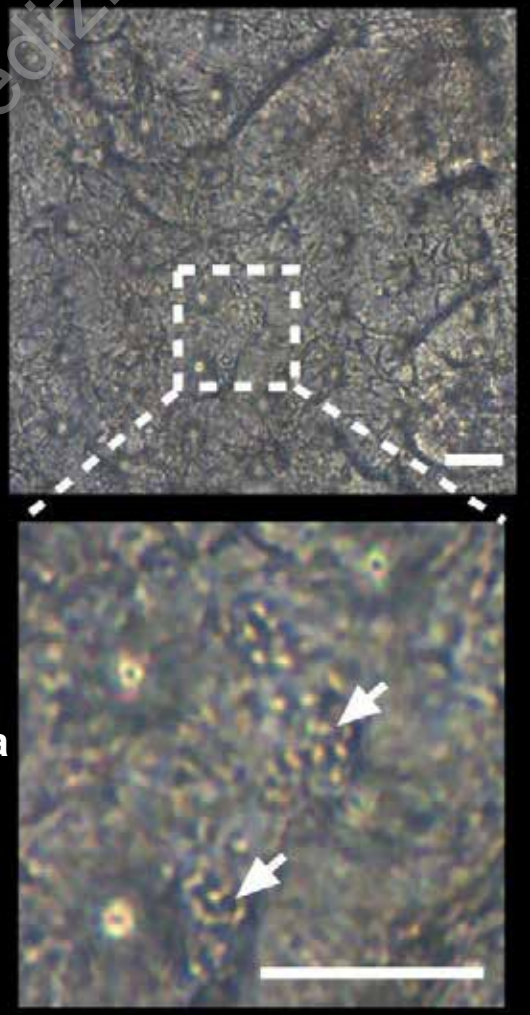
# Co-Culture with Intestinal Microbiome




(Kim *et al.*, ***Lab Chip*** 2012)



**Probiotic Bacteria**
**(Lactobacillus GG)**

Bar, 50 μm

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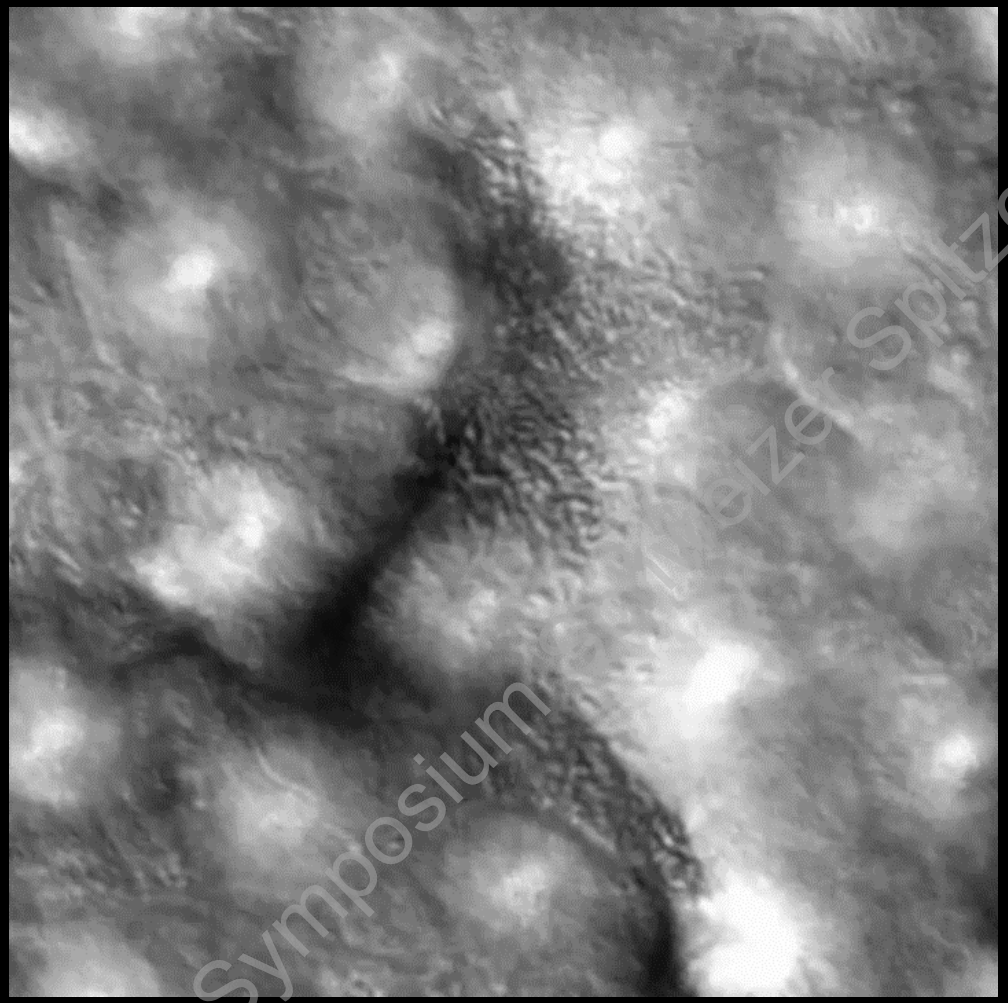
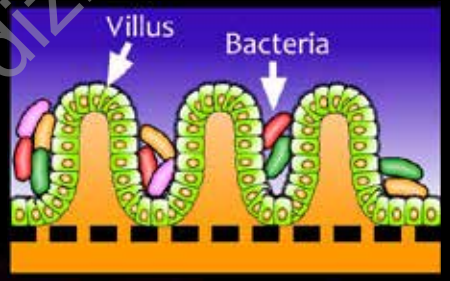
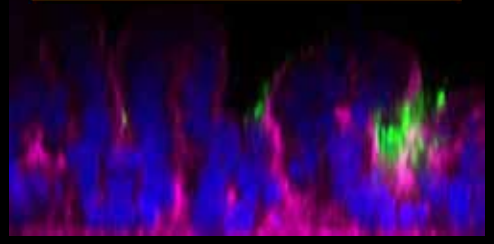
# Gut-on-a-chip with Normal Microbiome

***(8 different probiotic strains)***

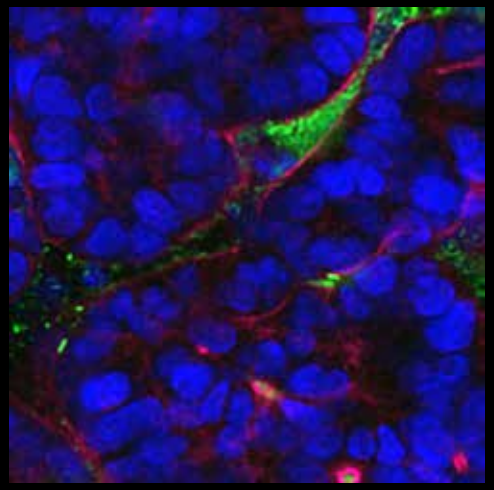





Side view



Top view



GFP-*E. coli*, F-actin Nuclei

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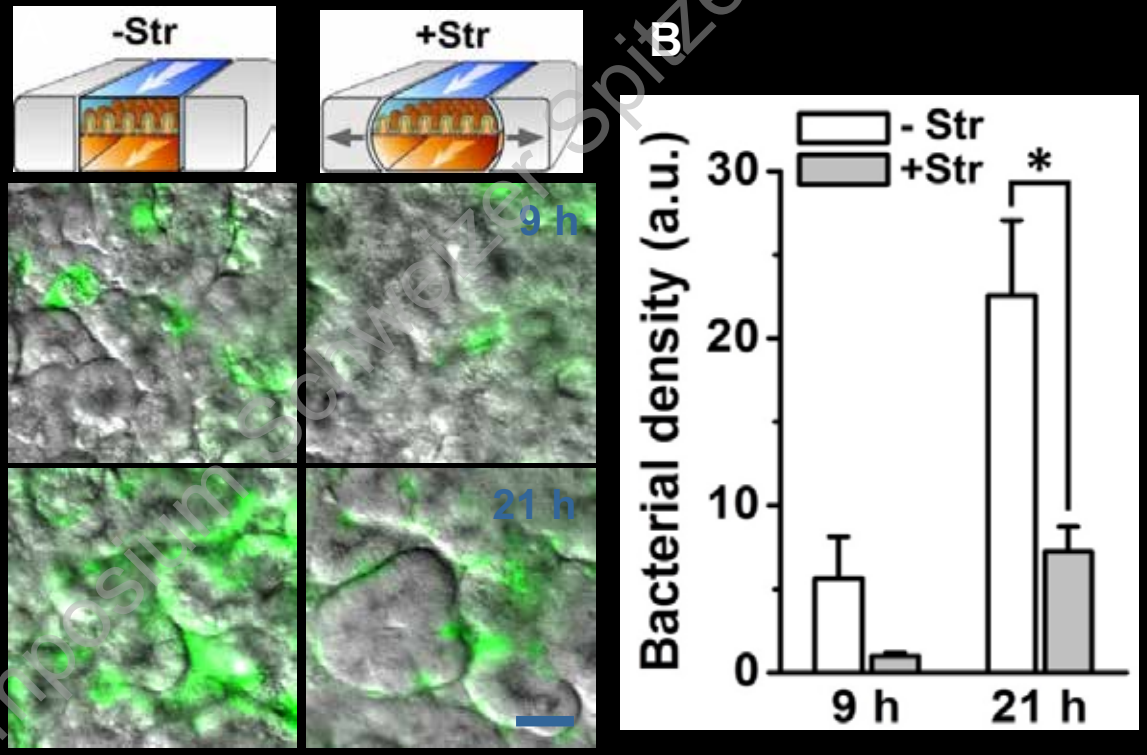
# Overgrowth of Commensal Bacteria is caused by a change in Mechanics

*(similar to patients with 'Ileus')*



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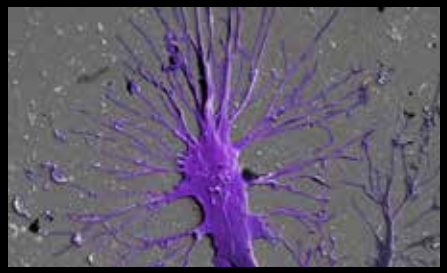
# Human Kidney Glomerulus-on-a-Chip

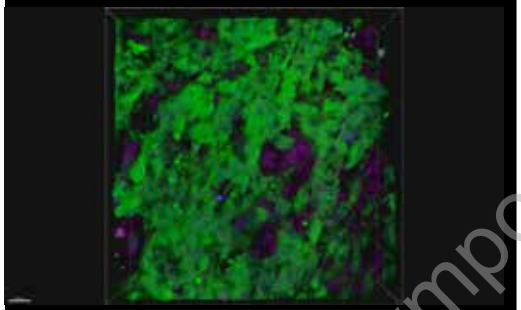
(Musah et al., *Nature Biomed. Engin.* 2017)

**Organ Chip Lined by:**

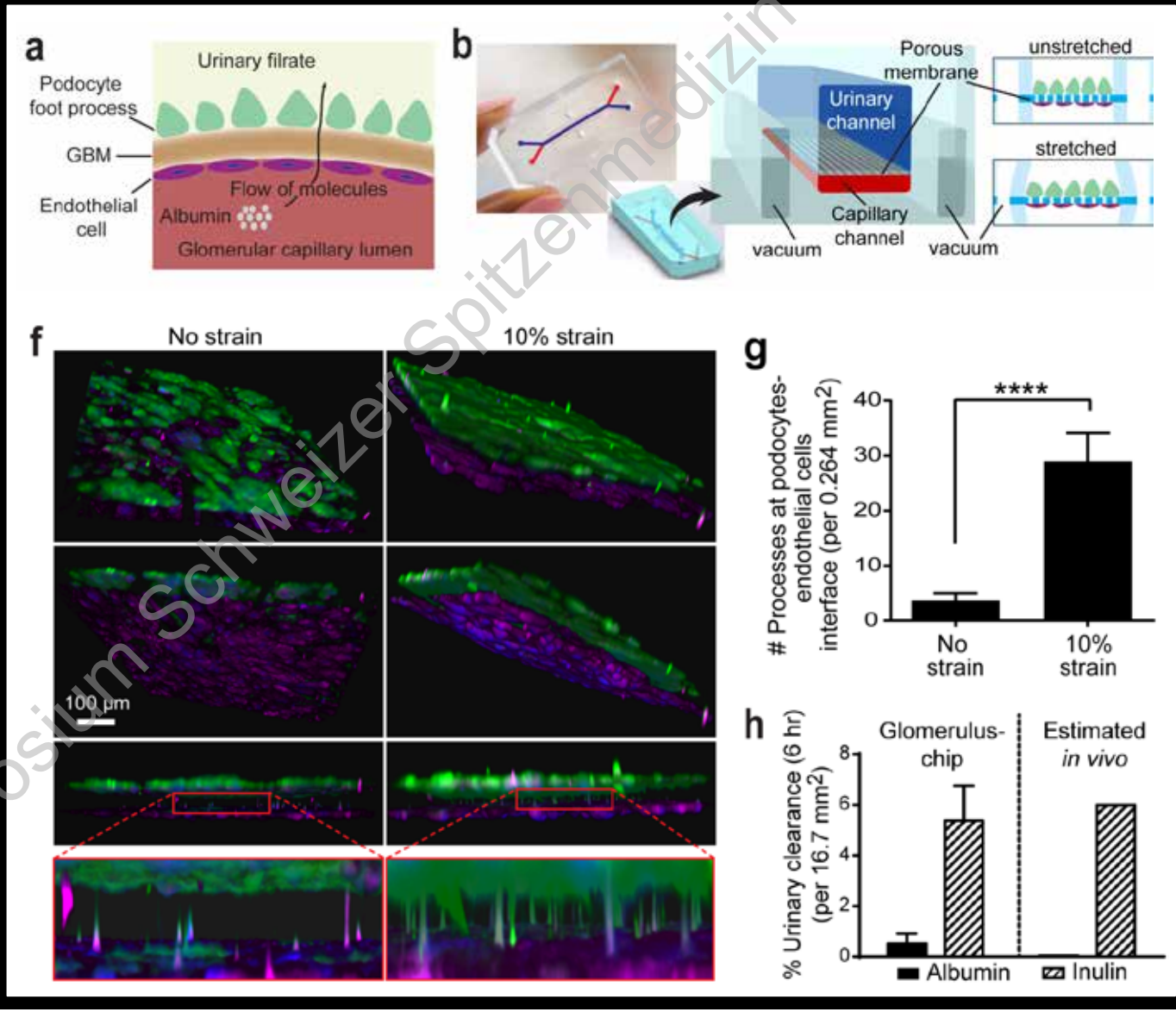
**Human iPS-derived Kidney Podocytes + Human Glomerular Microvascular Endothelium**



Mature iPS-derived Podocyte



**Podocyte Foot Process Extensions**



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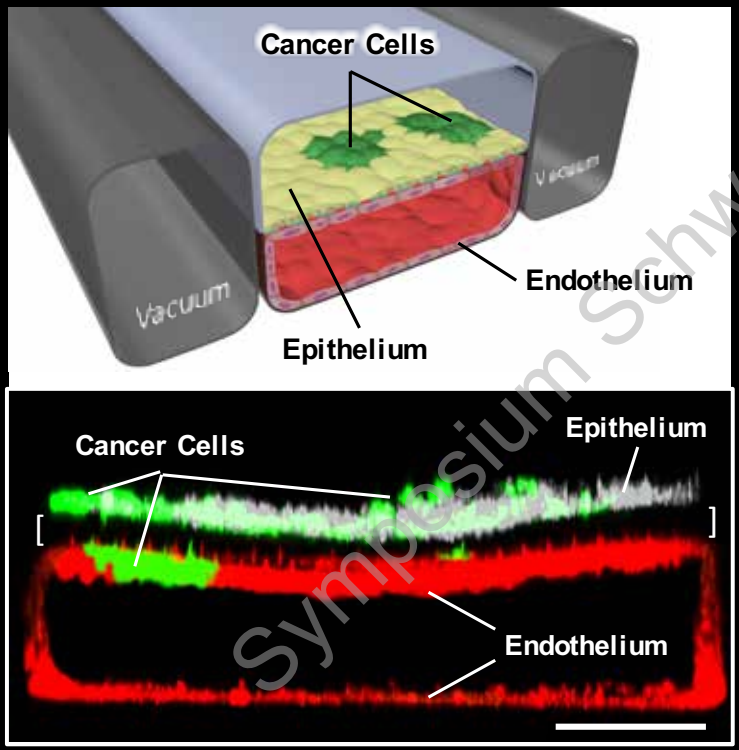
# Human Orthotopic Lung Cancer Chips

(Hassell et al., *Cell Reports*– in press)

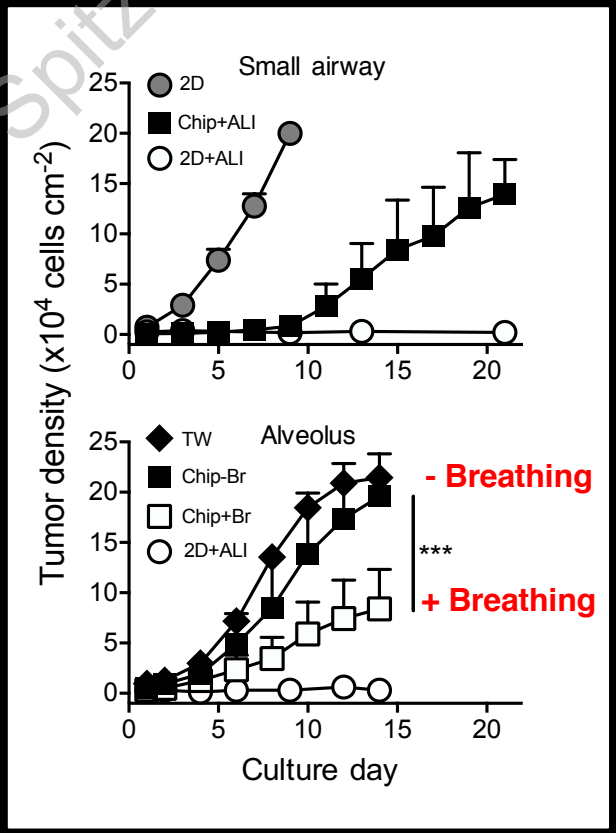


## Human Non-Small Cell Lung Cancer (NSCLC) 'adenocarcinoma'

***Emerges in distant bronchiole but preferentially grows in alveoli in vivo***




**GFP-H1975 NSCLC cells**




***Recapitulates Orthotopic Cancer Growth Patterns in vitro***

**+**

***Breathing Motions Suppress Lung Cancer Growth***

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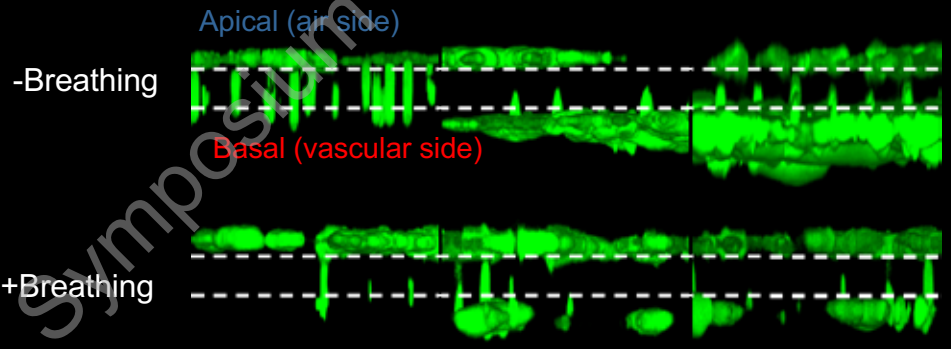
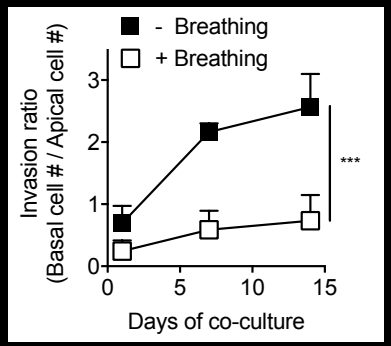
# NSCLC Adenocarcinoma in Lung ALVEOLUS Chip


**Tumor Invasion On-Chip**




**Breathing Inhibits Invasion**

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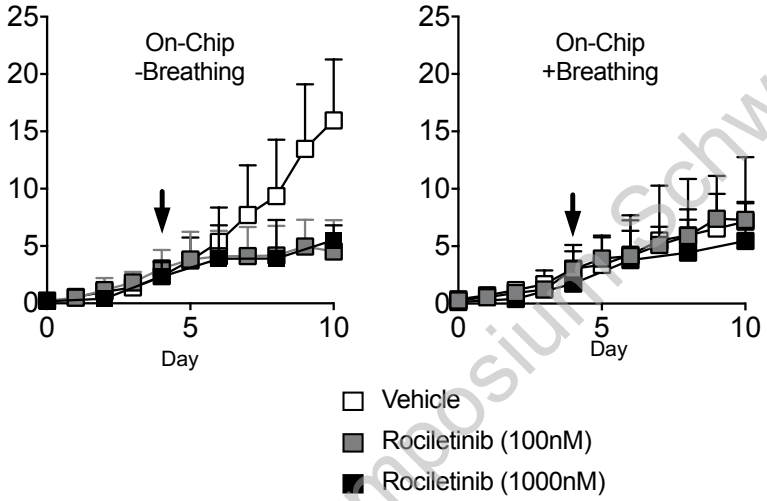
# Tumor Cells are LESS Responsive to Therapy in Orthotopic Chips with Breathing

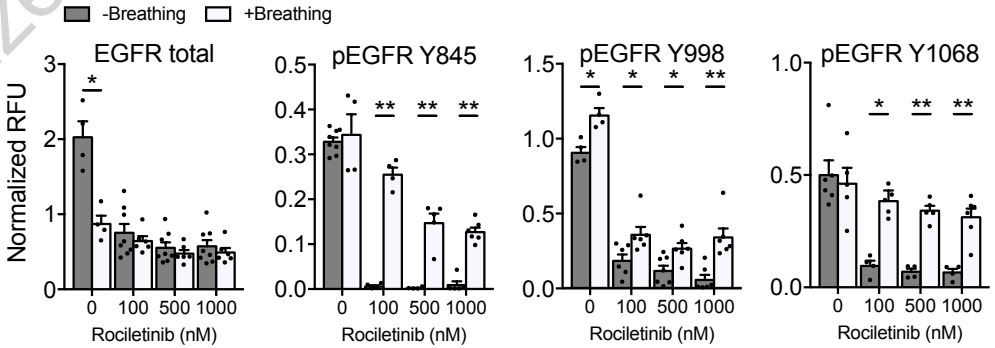
***(mediated by altered EGFR Phosphorylation)***



## *Breathing Regulates Therapeutic Response*




## *Breathing Regulates EGFR Signaling*



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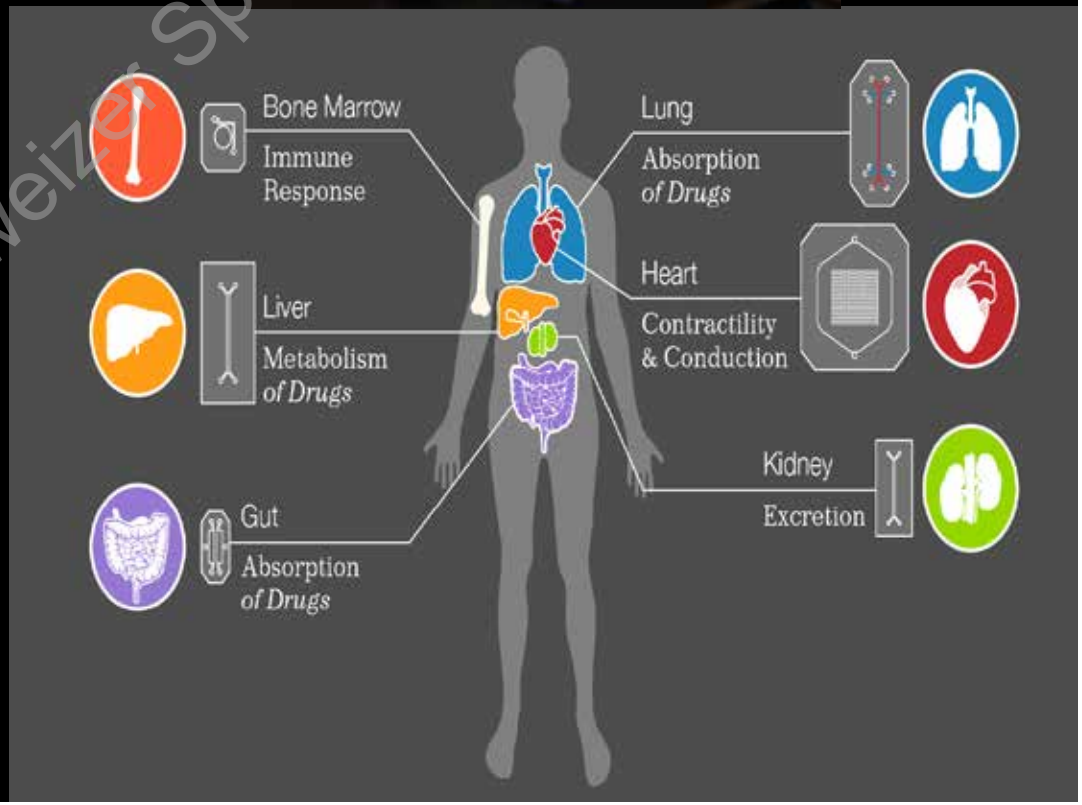
# Organ-on-Chip Technology Pipeline

- **Ongoing projects**
  - Lung Alveolus
  - Lung Small Airway
  - Liver
  - Small Intestine
  - Large Intestine
  - Kidney Proximal Tubule
  - Kidney Glomerulus
  - Bone marrow
  - Skin
  - Blood-Brain Barrier
  - Orthotopic Cancers
  - Heart *(Kit Parker's group)*
  - Placenta *(Dan Huh's group)*
  - ……



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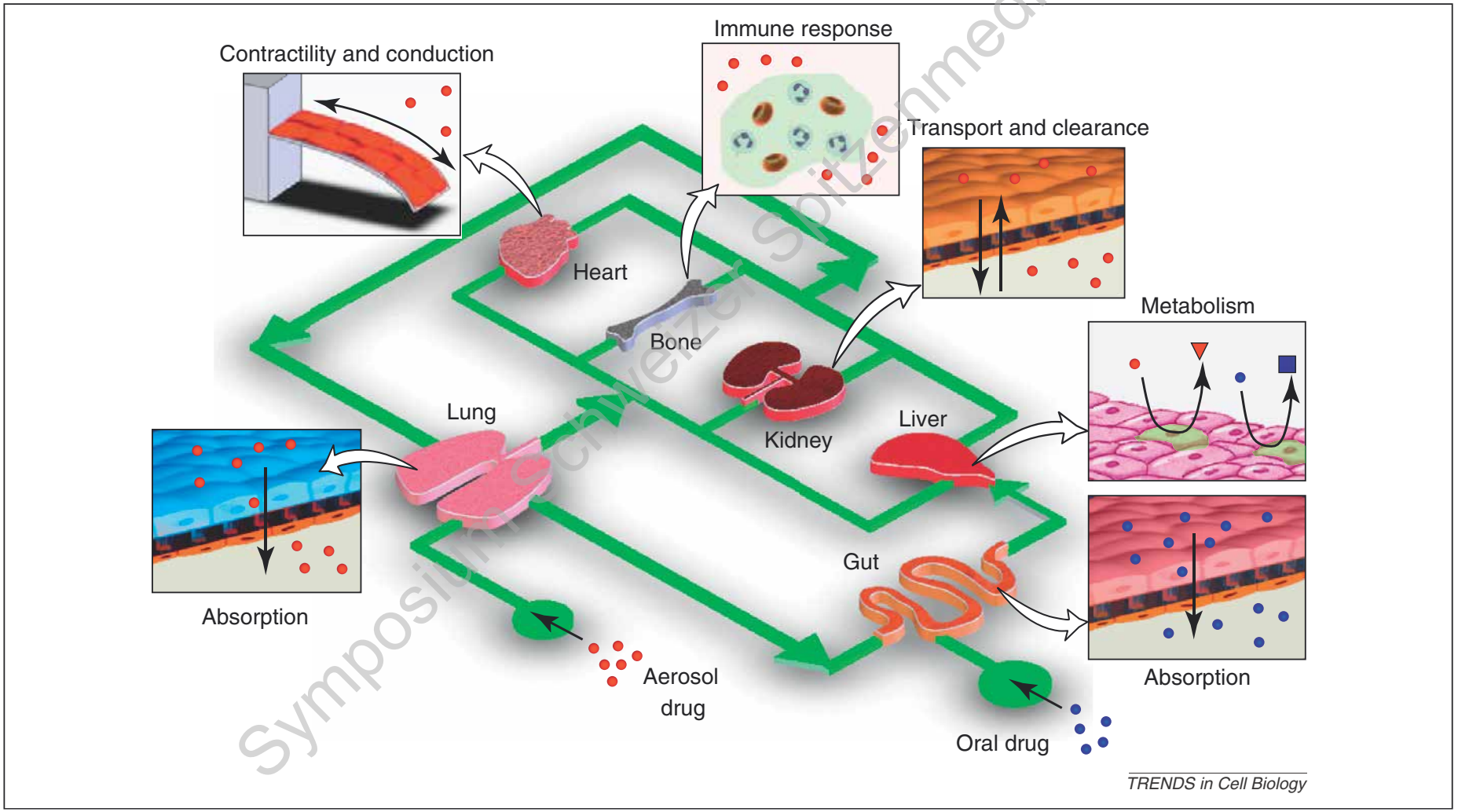
# Integrated Human Body-on-Chips



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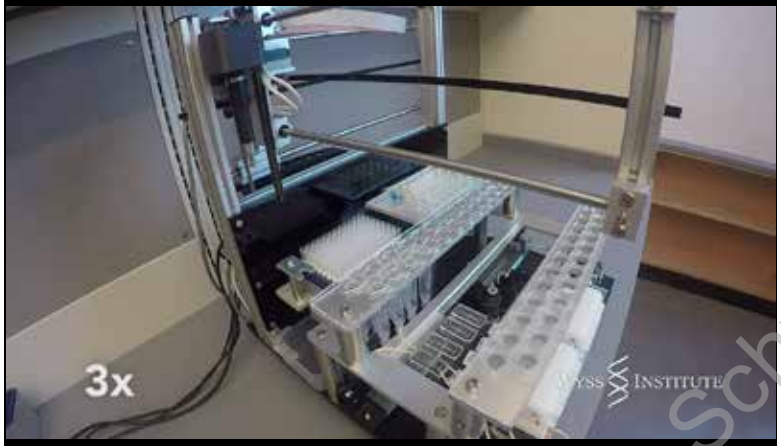
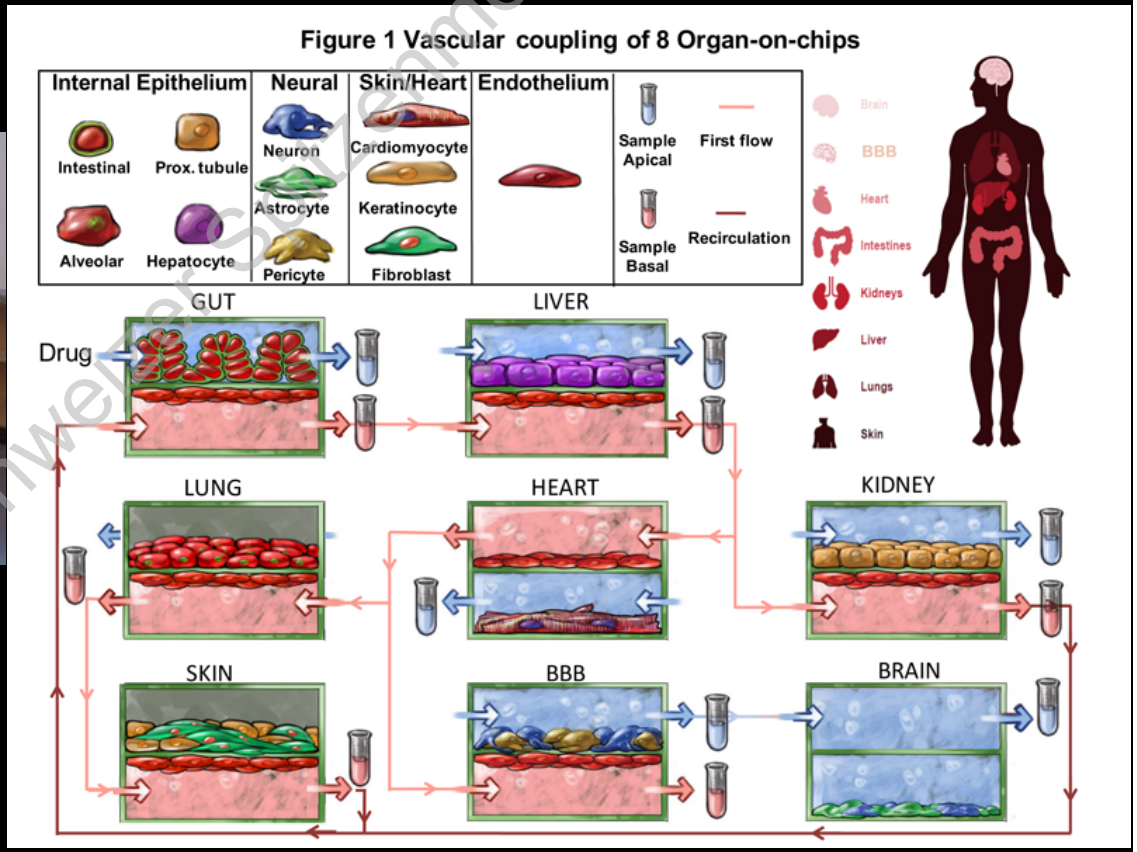
# Automated Coupling of 8 Organs for 3 Weeks



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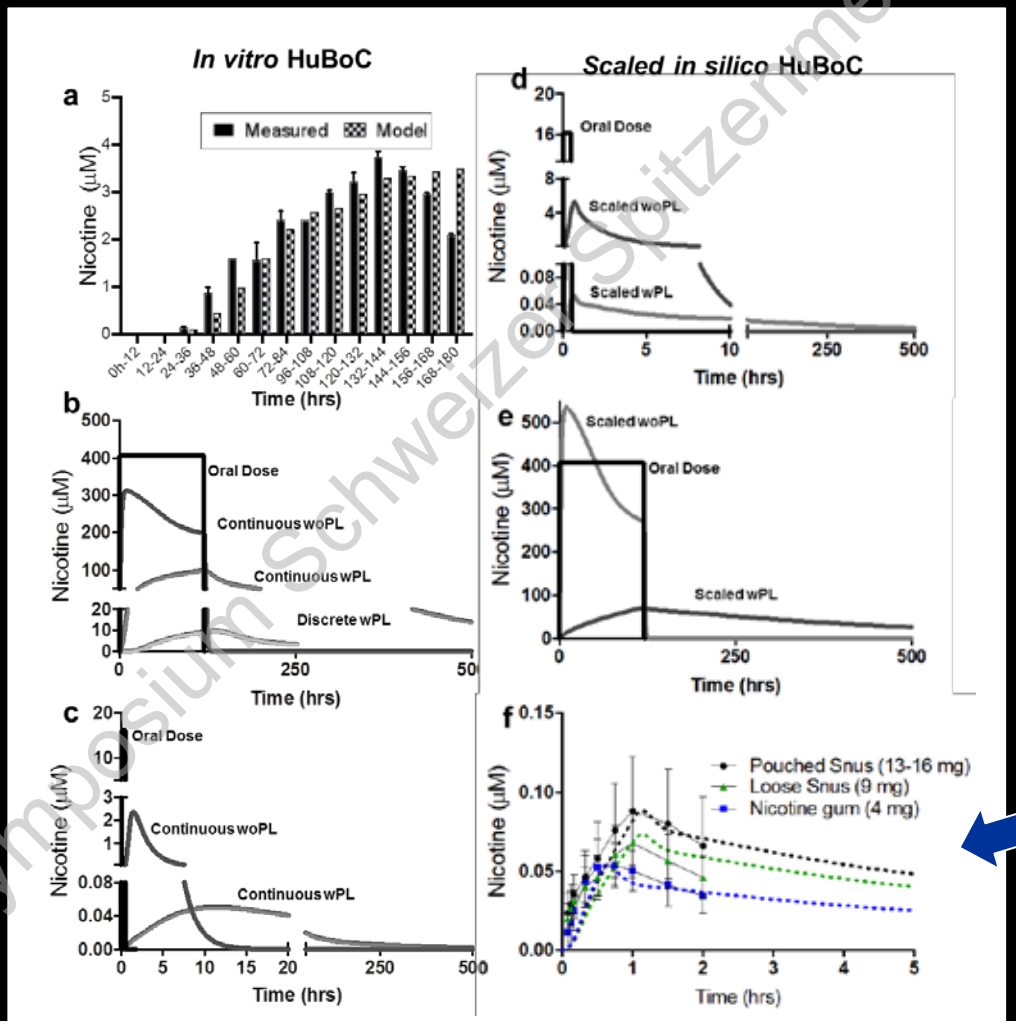
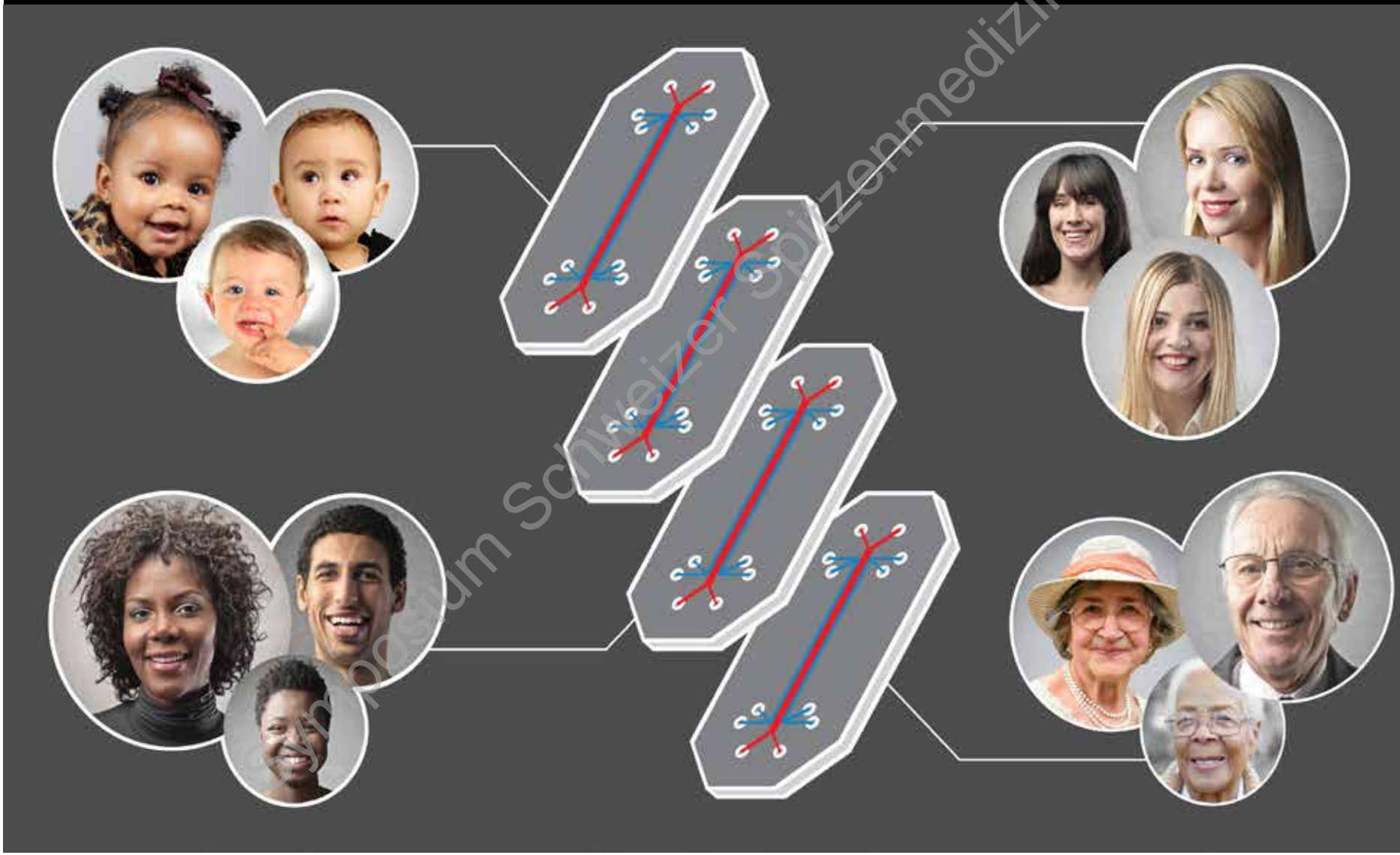
# *In Vitro-to-In Vivo Extrapolation* (IVIVE) using the Human Body-on-Chips

(Herland et al., - in review)




***Predictions of Human Body Chip Model vs. Clinical Data***

# Personalized Organs on Chips
## *(from individuals to populations)*



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# 'Organs-on-Chips' Technology: FDA Testing Groundbreaking Science

Posted on **April 11, 2017** by **FDA Voice**

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*Evaluating Organ Chips for testing of cosmetics, dietary supplements and food*

# Bioinspired Technologies for Clinical Medicine

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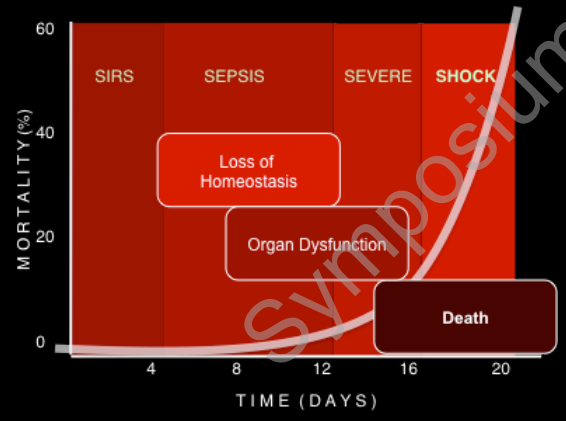
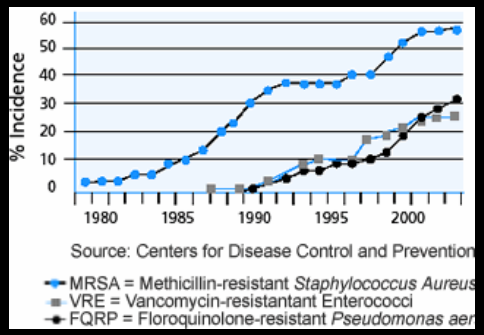
# SEPSIS CHALLENGE

- A major killer worldwide with few treatment options
- >30% mortality even with best antibiotic therapy and ICU care
- Bloodstream infections occur in ~10 % percent of hospital patients, but *cause of ~50% of all U.S. hospital deaths* (May 18, 2014/Drugs.com)
- More than $19B spent in U.S. on treatment

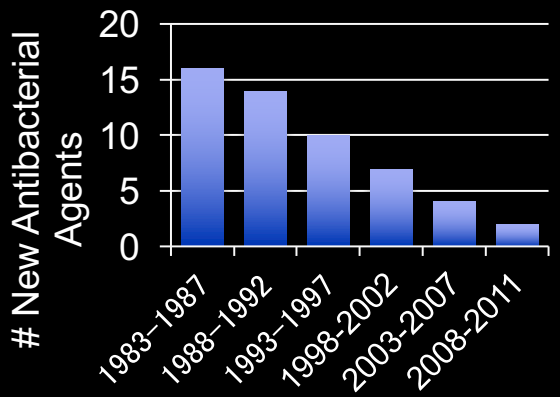
**Rapid Disease Progression**




**Increasing Resistant Microbes**




**New Antibiotic Approvals**



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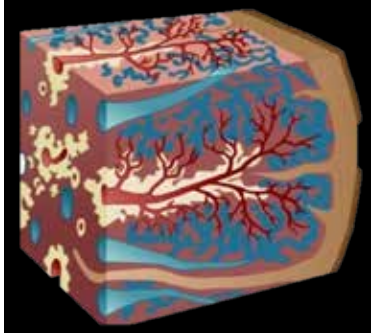
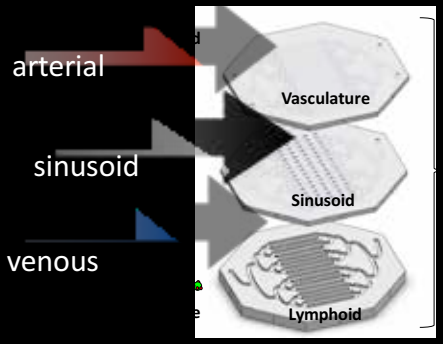
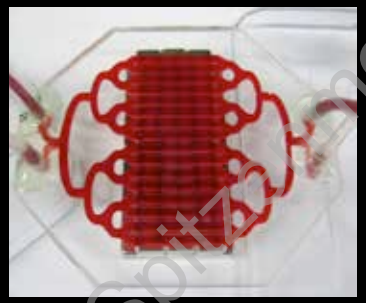
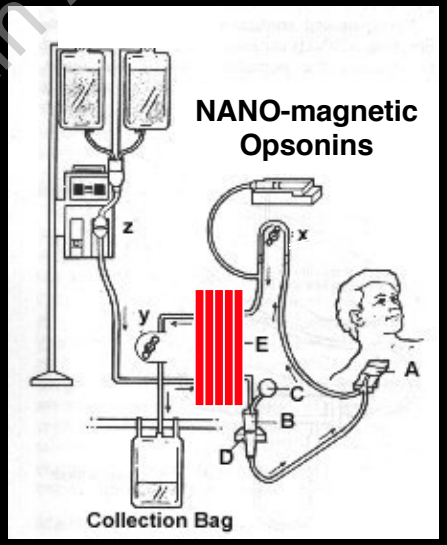
# ‘Biospleen’
# Dialysis-Like Sepsis Therapeutic Device

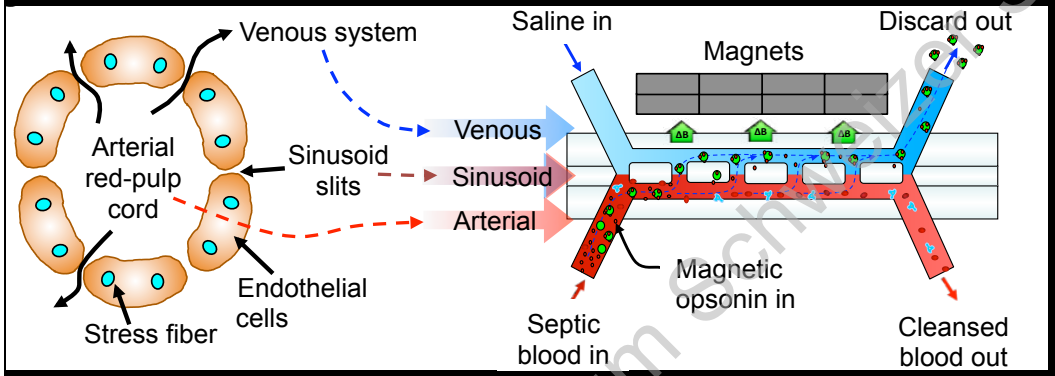
(Kang et al. *Nature Medicine* 2014)

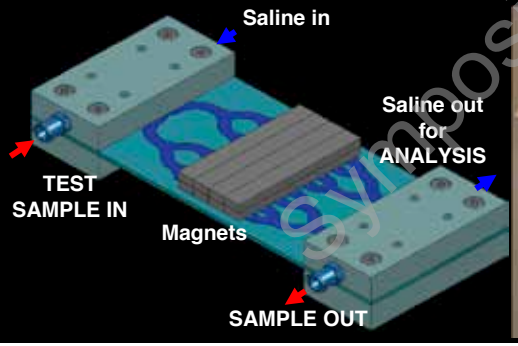


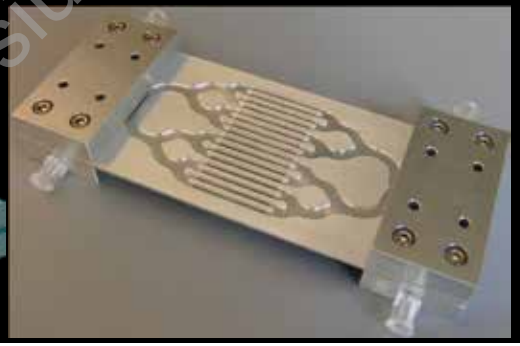




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# ‘Biospleen’
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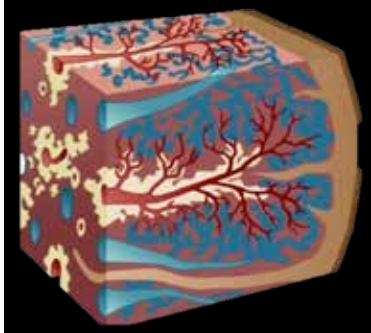
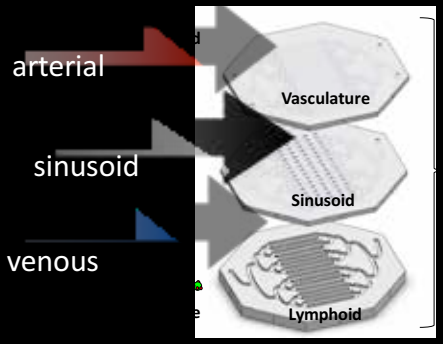
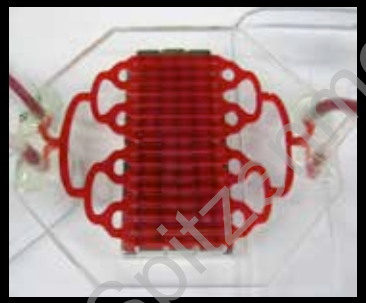
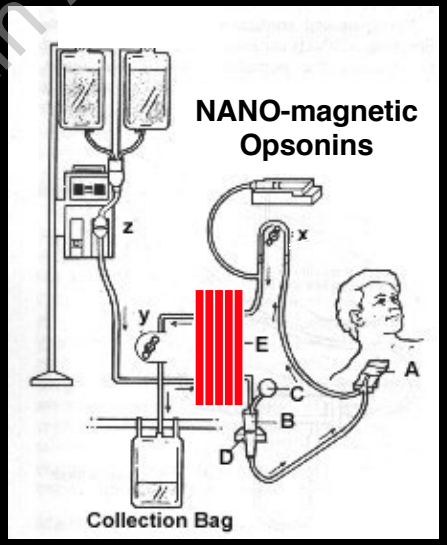
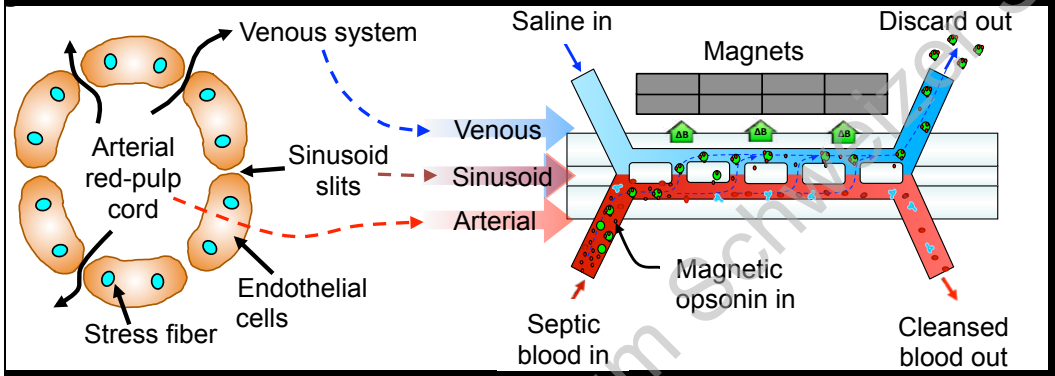
(Kang et al. *Nature Medicine* 2014)

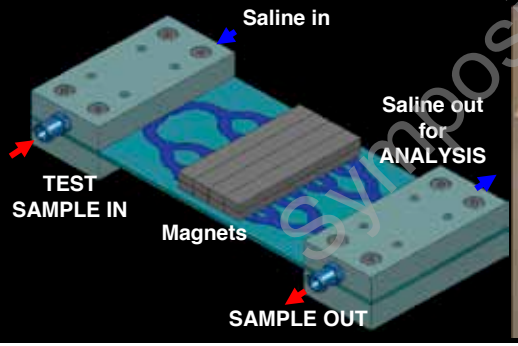


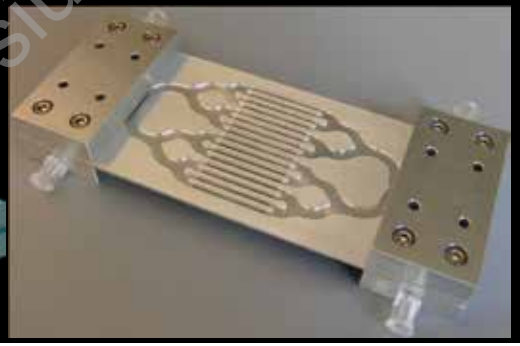




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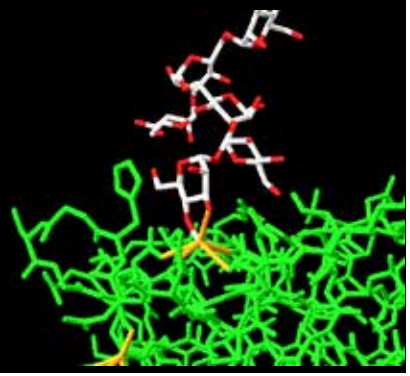
# Generic Pathogen Capture Technology

## *Biological Inspiration:* HUMAN OPSONINS

- Natural blood proteins
- Molecular components of the Innate Immune system
- Many are LECTINS that bind to surface carbohydrates on pathogens that are not commonly found on human cells

## Mannose Binding Lectin (MBL)

- Binds to mannans on bacteria, fungi, viruses, parasites and toxins and thereby targets pathogens for phagocytosis & killing
- Activates complement via the lectin pathway
- Activates coagulation via a thrombin-like activity
- Acts as a multimer



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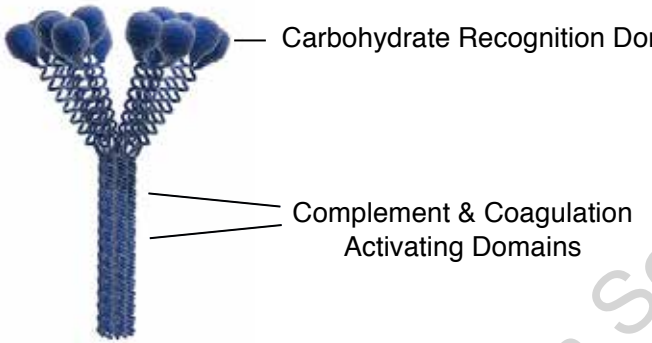
# Genetically Engineered *Generic* Pathogen-Capture Protein

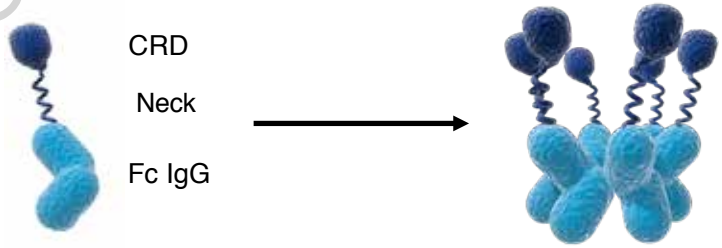
**Human Mannose Binding Lectin (MBL):**

*Binds diverse pathogens, targets them for phagocytosis, stimulates immune response*




**FcMBL:**

*Retains pathogen binding capability while eliminating immune-stimulating activities*




*Recombinant Monomer*

*Spontaneously forms Hexamers*

1. ***REMOVE BAD PARTS***
   (complement and coagulation activities)

2. ***ADD Fc ANTIBODY DOMAIN***
   (rapid, low cost purification)

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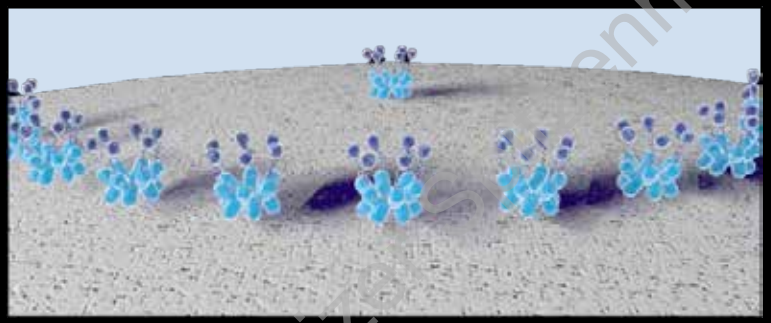
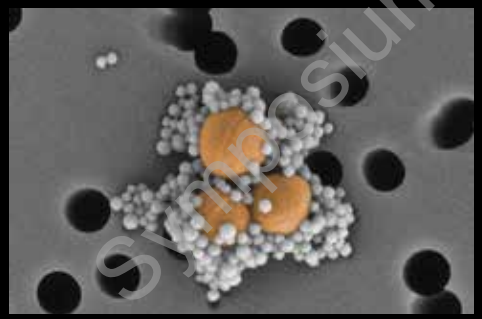
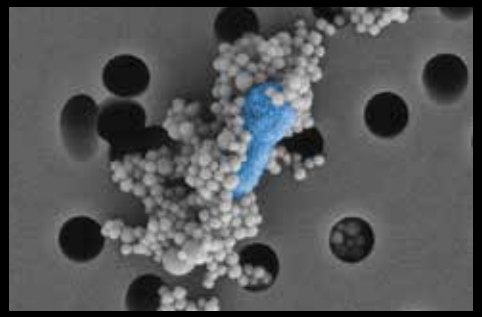
# FcMBL Binds Many Different Pathogens

FcMBL coupled to a
magnetic nanobead



Binds a broad spectrum of pathogens and toxins

| ***S. aureus*** | ***E. coli*** | ***C. albicans*** |
|---|---|---|
|  |  |  |
| *Gram Positive Bacteria* | *Gram Negative Bacteria* | *Fungi* |

128 nm
beads

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# FcMBL Opsonin: Bind > 90 Pathogens + Toxins

| Fungi | Gram negative | Gram positive | Viruses | Parasites |
|---|---|---|---|---|
| *Aspergillus spp*<br>*Blastomyces*<br>*Candida albicans, glabrata, guilliermondii, krusei, parapsilosis, tropicalis*<br>*Cryptococcus,*<br>*Fusarium spp.*<br>*Mucor spp.*<br>*Saccharomyces*<br>*Pneumocystis jirovecii (carinii)* | *Acinetobacter baumanii*<br>*Burkholderia cepacia,*<br>*Bacterioides fragilis,*<br>*Chlamydia trachomatis,*<br>*Citrobacter freundii*<br>*Escherichia coli*<br>*Enterobacter aerogenes*<br>*Enterobacter cloacae*<br>*Haemophilus inf b,*<br>*Helicobacter pylori,*<br>*Klebsiella oxytoca,*<br>*K. pneumonia (MDR/CRE),*<br>*Legionella pneumophila,*<br>*Neisseria meningitidis*<br>*Neisseria gonorrhoeae,*<br>*Pseudomonas aeruginosa,*<br>*Salmonella typhi, paratyphi, typhimurium*<br>*Serratia marcescens,*<br>*Shigella flexneri,*<br>*Stenotrophomonas maltophilia,*<br>*Yersinia pseudotuberculosis* | *Bacillus subtilis, Clostridium neoformans, C. difficile, C. perfringens, Corynebacterium spp, Enterococcus faecalis, Enterococcus faecium, VRE*<br>*Listeria monocytogenes,*<br>*Mycobactrium avium ,*<br>*M. tuberculosis, M. leprae,*<br>*Nocardia farcinica,*<br>*P. acnes,*<br>*Staphylococcus aureus MSSA, MRSA*<br>*S. epidermidis, Streptococcus pyogenes*<br>*Strep Group A, Group B (agalactiae), Group C* | *"Dengue", "Ebola", EBV, Hep B, C, HIV, HSV 1, 2, CMV, "Influenza A", Marburg, RSV, SARS-CoV, West Nile* | *Cryptosporidium, Leishmania, Malaria, Schistosoma, Trypanosoma* |
| Mycoplasma | Toxins | | | |
| *M. pneumoniae, M. hominis, M. orale* | *LPS, LTA, WTA, Ricin* | | | |

Code:

- MBL capture reported for ALL
- FcMBL capture confirmed
- "." Pseudovirus (FcMBL)
- **Multi-drug Resistant (FcMBL)**

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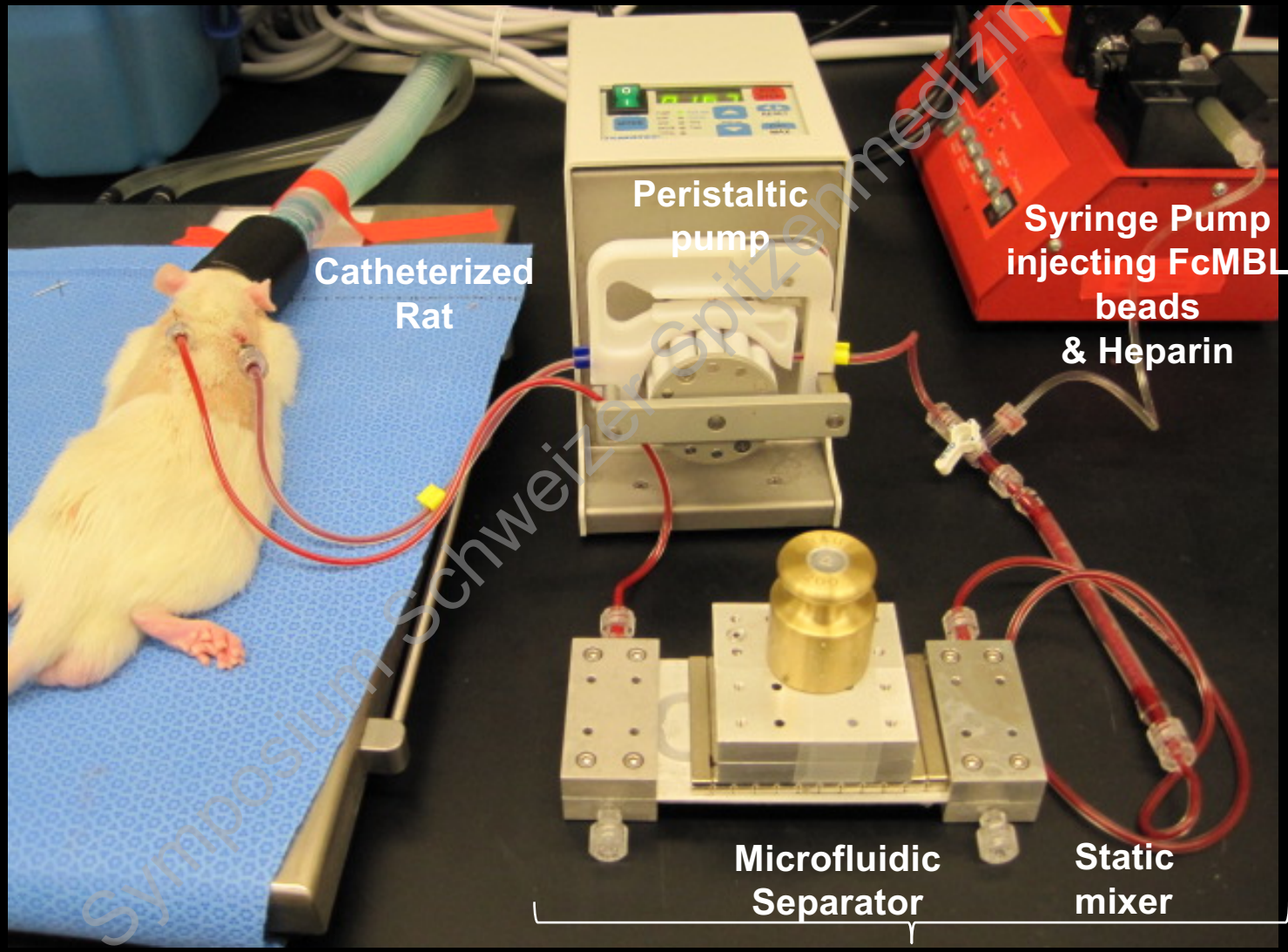
# Rat Sepsis Model



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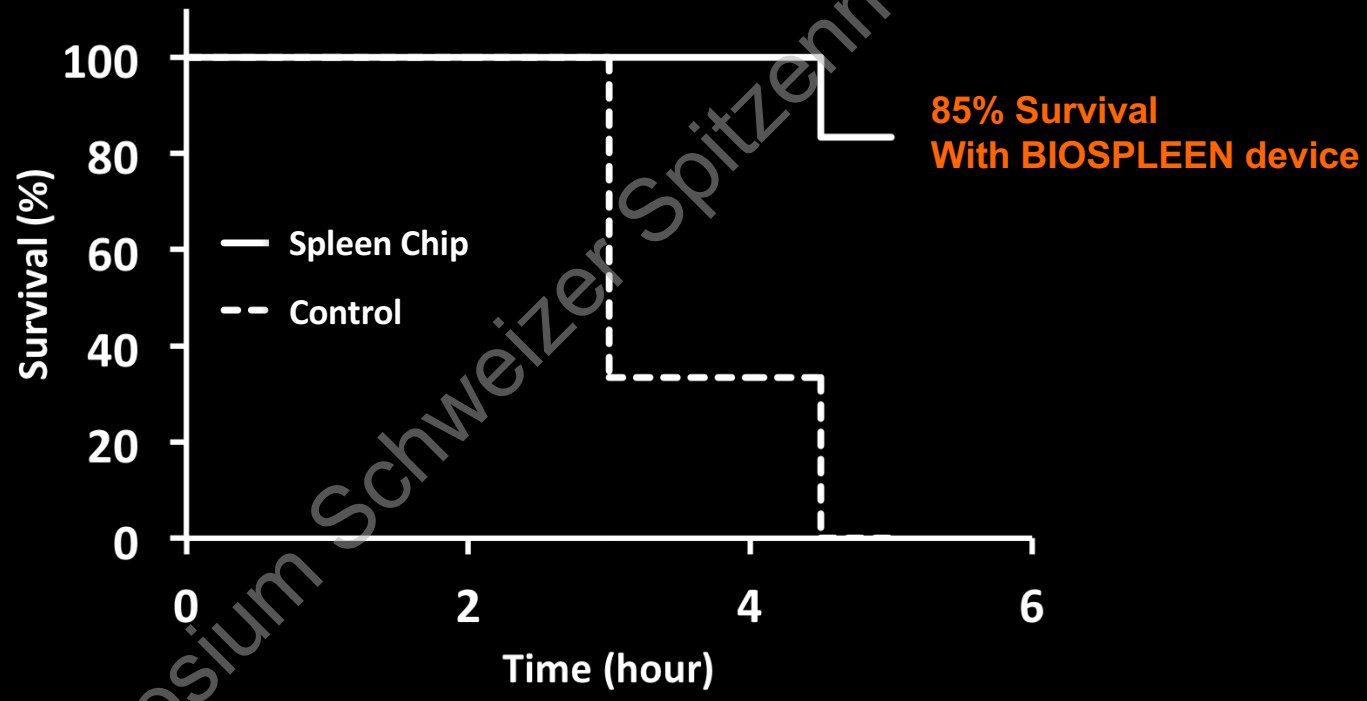
# Blood Cleansing Increases Survival in Rats with Endotoxemia

(Kang et al., *Nature Medicine 2014)*




- LPS (1.4 x$10^7$ EU/mL) injected IV into rats (*n=6)*
- ***100% of control animals die by 4.5 hrs vs. 85% survival with DLT Device therapy***

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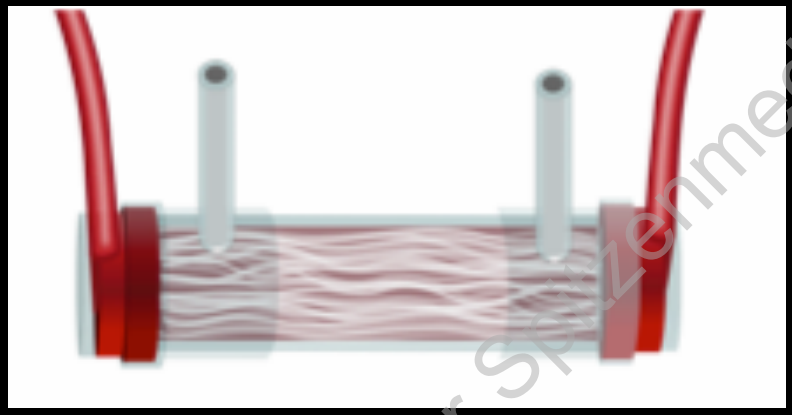
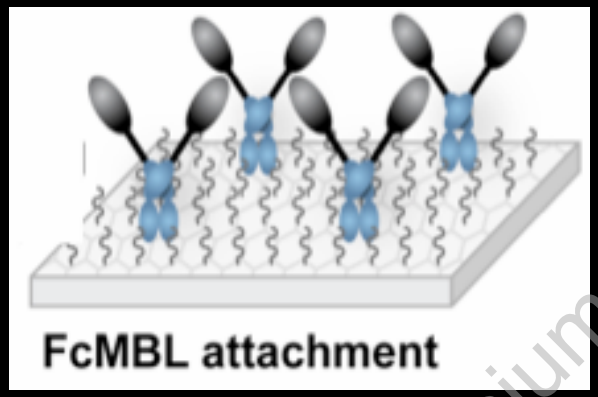
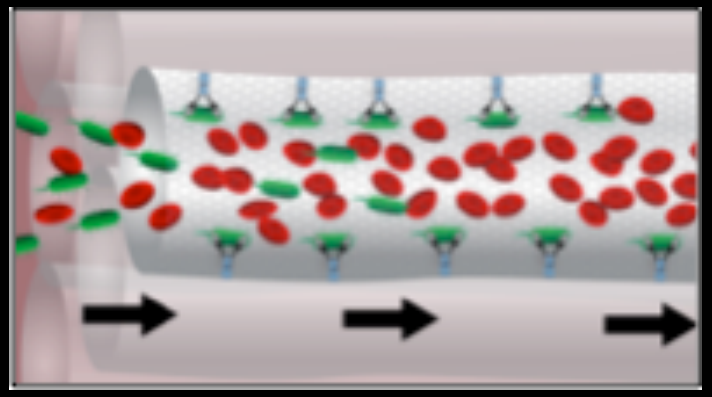
# Simplified Dialysis-Like Configuration

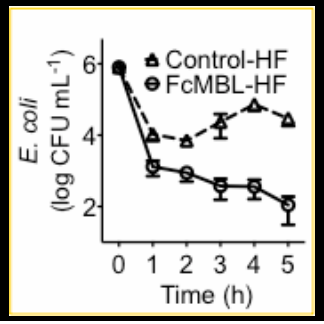
(Didar et al., *Biomaterials* 2015)

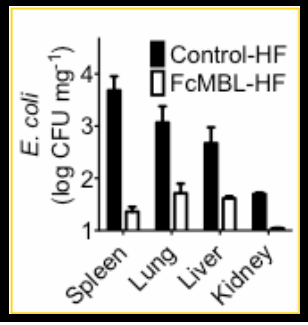











***+ Synergizes with Antibiotic Therapy***

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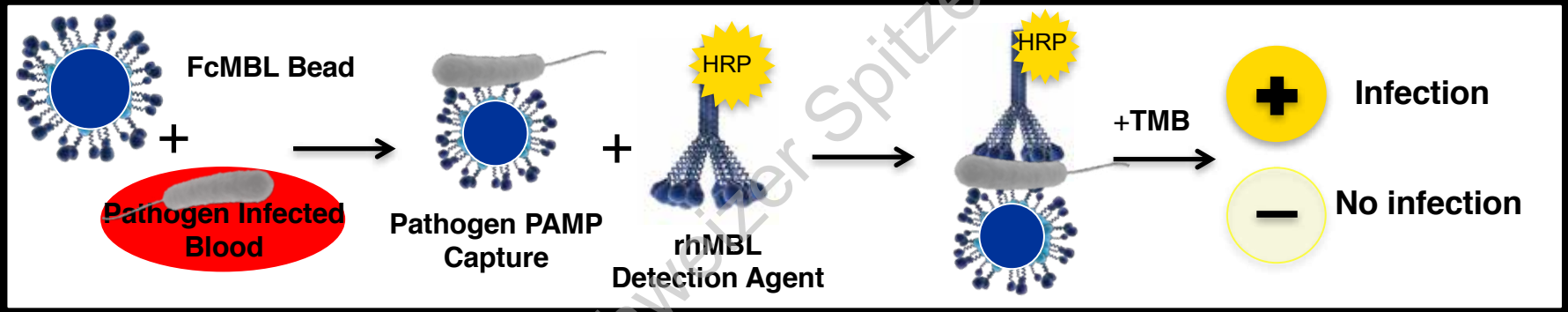
# Rapid Infection Diagnostic

(Cartwright et al., *eBiomedicine* 2016)

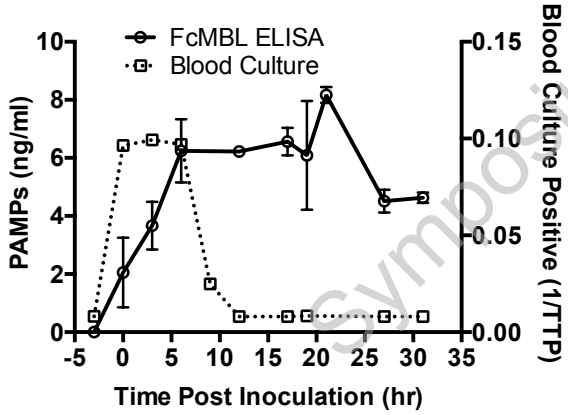


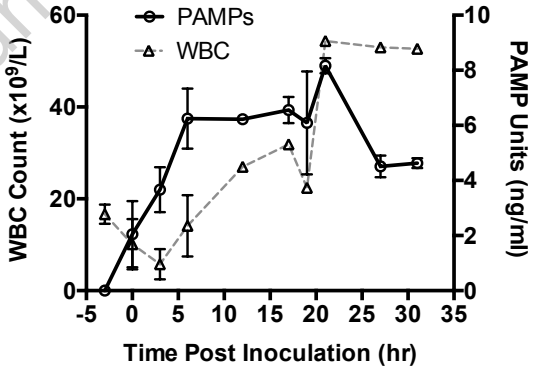
***FcMBL ELISA measures cell wall Pathogen-Associated Molecular Patterns (PAMPs)***

- Measures live pathogens + immunogenic toxins released from dead pathogens




## PAMPs ELISA tracks infection in *E. coli* pig model




## PAMPs Correlate with Sepsis in Humans

| Assay (Draw Time) | Sensitivity (%) | Specificity (%) |
|---|---|---|
| PAMPs ELISA (0) | 81 | 89 |
| PAMPs ELISA (24) | 85 | 89 |
| Blood Culture (0) | 18 | 92 |

*78 Sepsis patients*
*34 Non-Infected Controls*
*52 Non-Infected Trauma patients*

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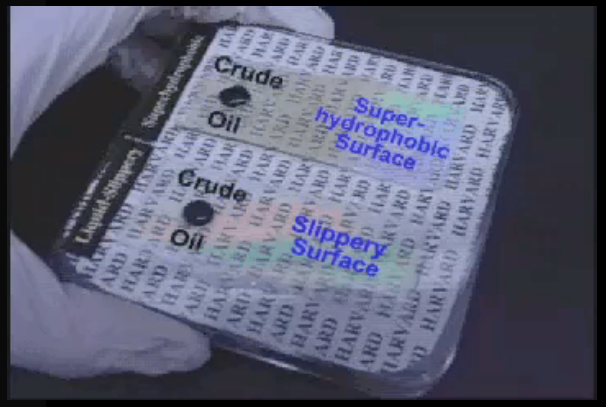
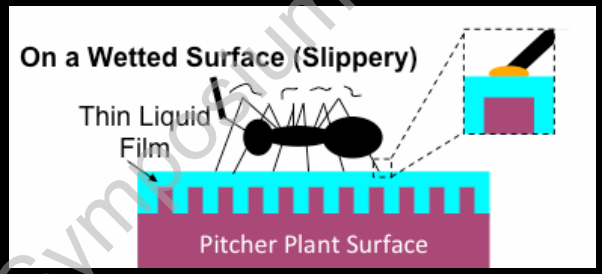
Collaboration with Adaptive Materials Platform

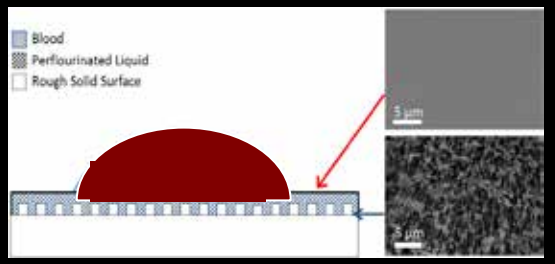
# Inspiration from the Non-Medical World

## Non-Stick
## Slippery Liquid-Infused Porous Surfaces (SLIPS)

*(Joanna Aizenberg Lab)*


***Winner of 2012 R&D Technology Award***

SLIPS TECHNOLOGIES

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Collaboration with Adaptive Materials Platform

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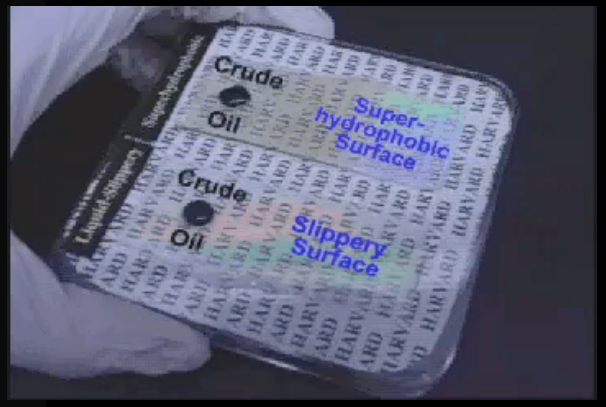


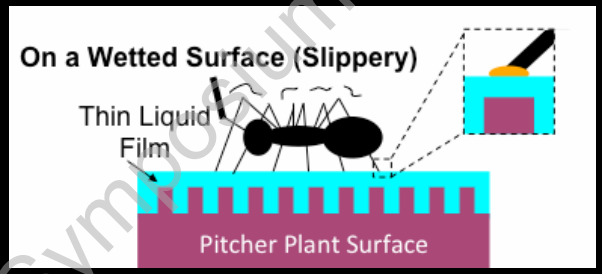


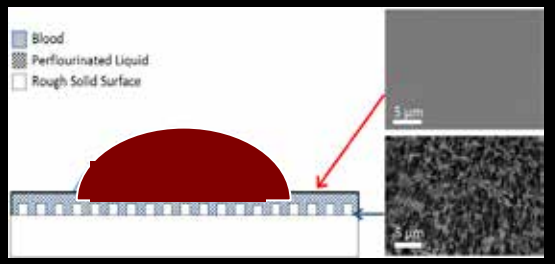


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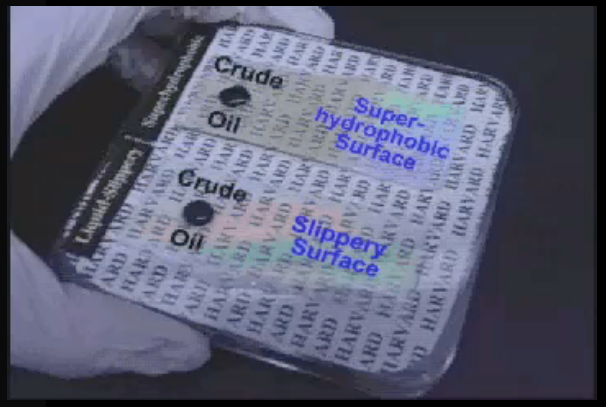


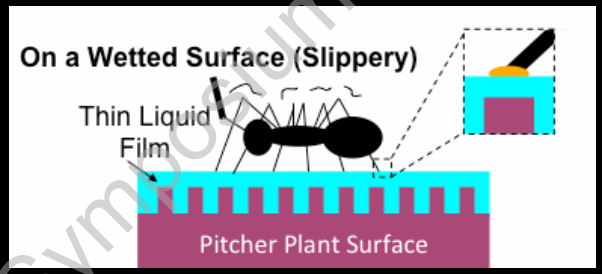


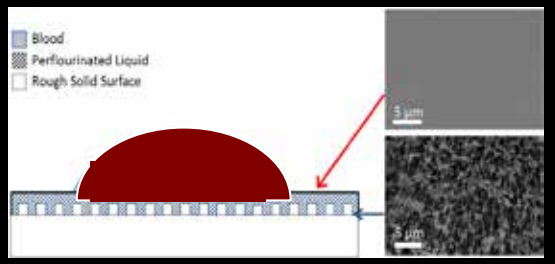


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SLIPS TECHNOLOGIES

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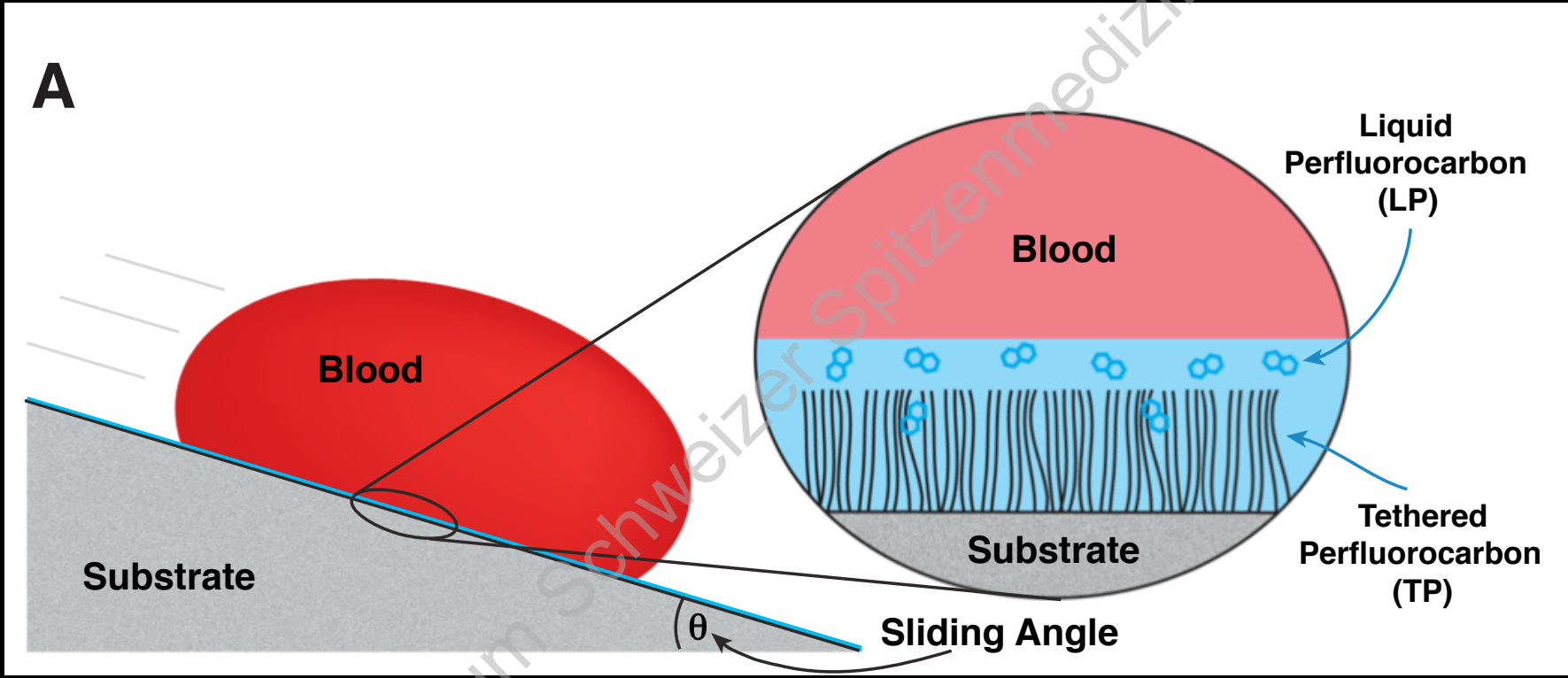
# Medical SLIPS

## *Tethered Liquid Perfluorocarbon (TLP)*




1. FDA approved indwelling devices are silanized with Tethered Perfluorocarbon (TP), then sterilized and stored > 1 year

1. Prior to use, an FDA-approved Liquid Perfluorocarbon (e.g. Perfluorodecalin; PFD) is added

1. The TP retains the LP and repels blood

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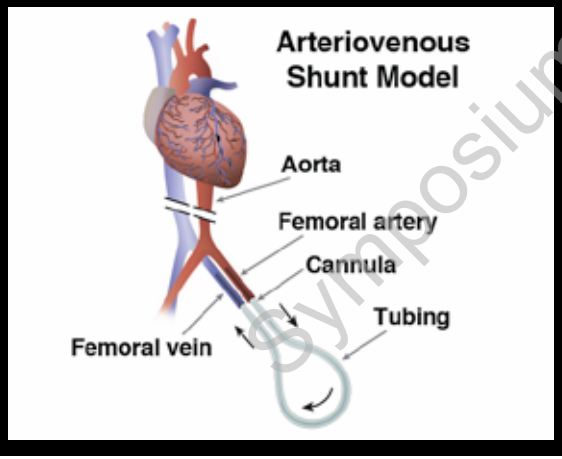
# TLP Coating for Medical Devices

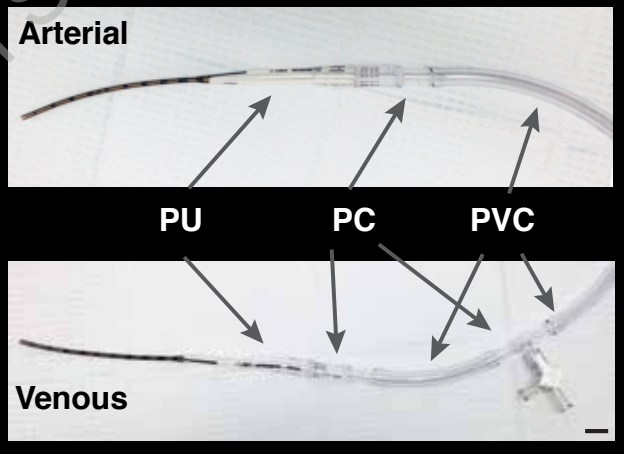
(Leslie et al., ***Nature Biotechnology*** 2014)

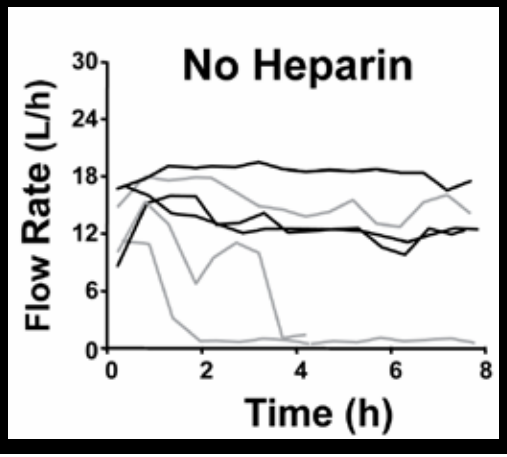


- **TLP works on SMOOTH FDA-approved Medical Materials**


- **TLP-treated arteriovenous (AV) shunt functioned for 8 hrs in a pig without heparin**



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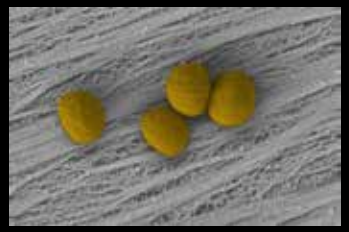
# Disclosure Statement of Financial Interest:

- I hold equity & chair the Scientific Advisory Boards of:

emulate

opsonix



FREEFLOW MEDICAL DEVICES

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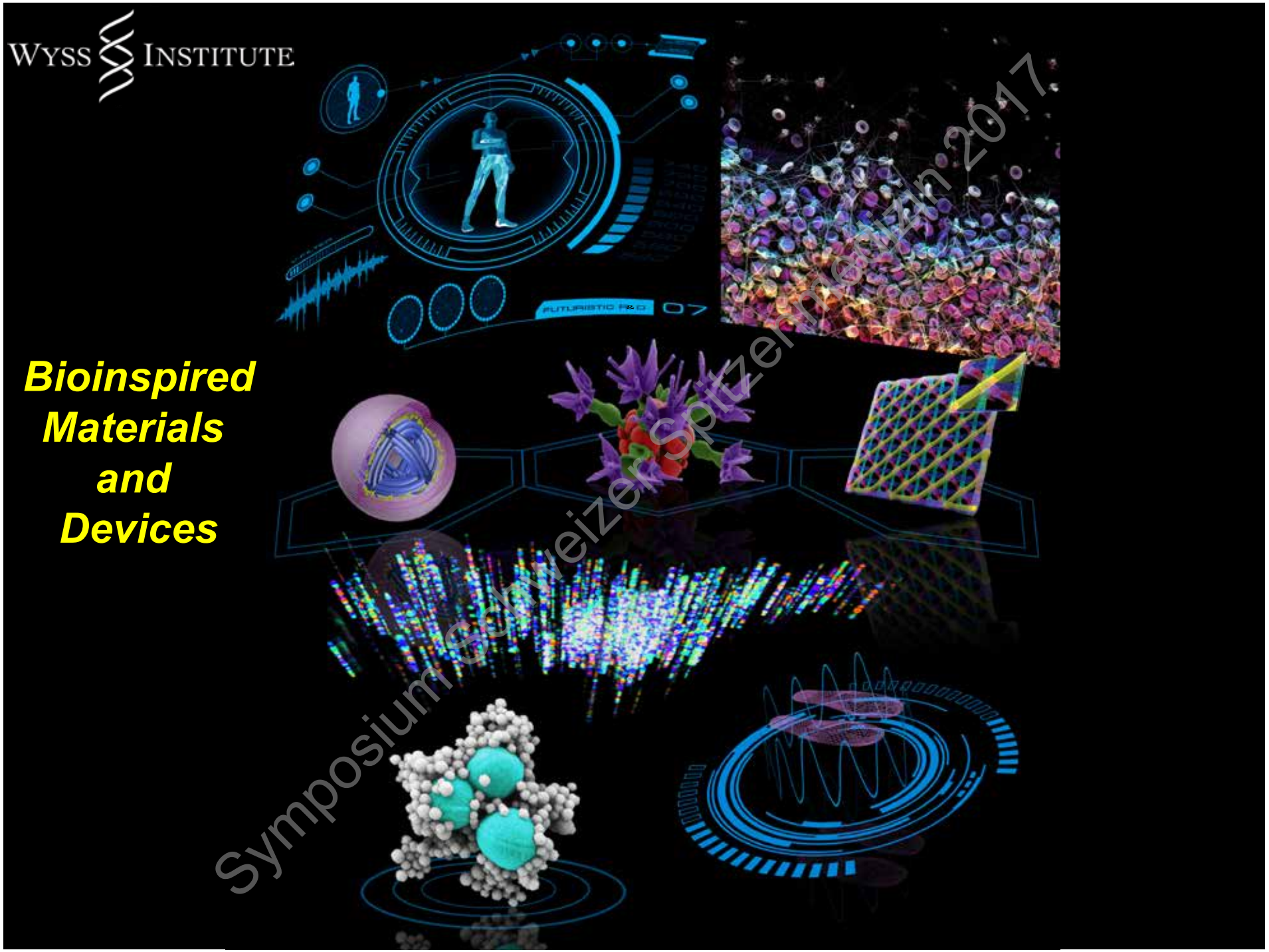


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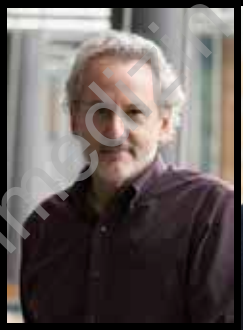
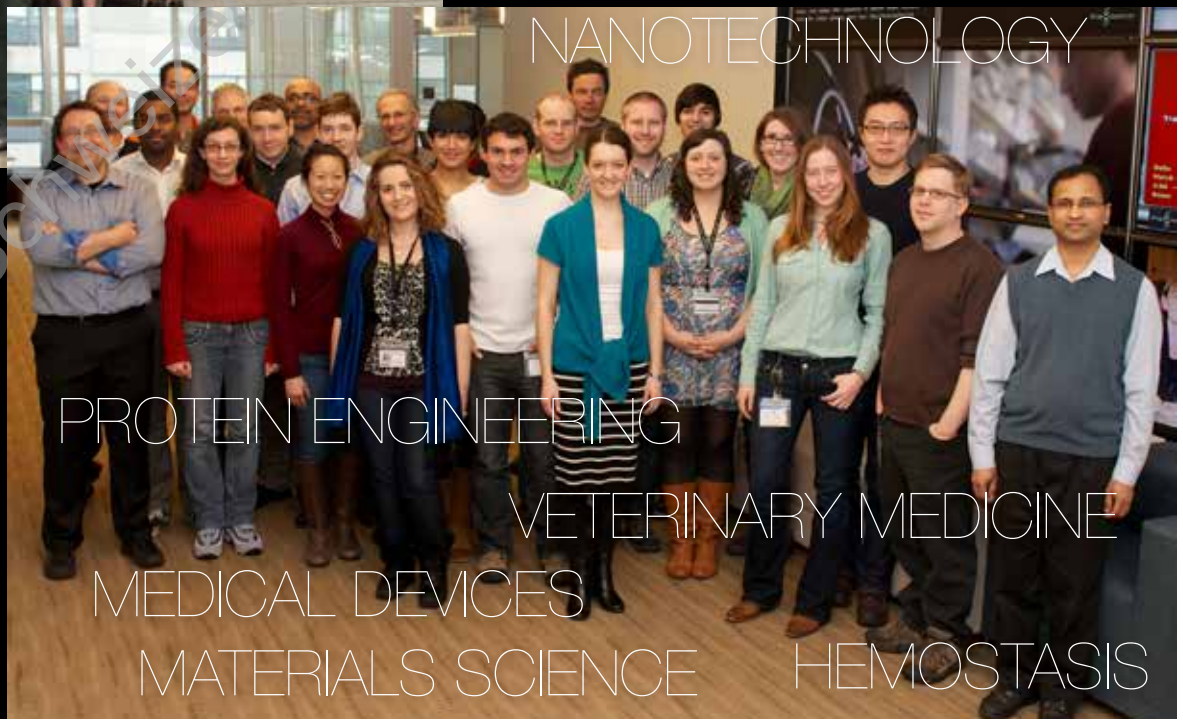
DISRUPTIVE INNOVATION
Symposium Schweizer Spitzenmedizin 2017


**Organs-on-Chips**



Don Ingber

Kit Parker




**Sepsis & TLP Coating**

Don Ingber

Joanna Aizenberg

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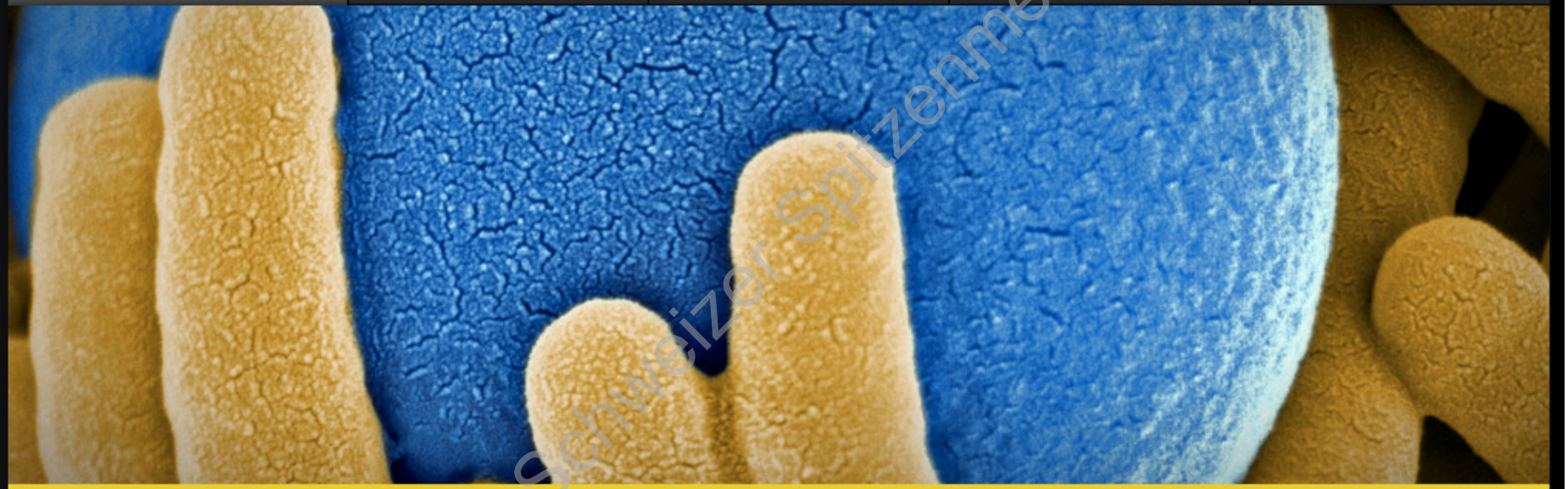
Wyss Institute is proud to announce our win in the 2012 Webby Awards in the Science category.





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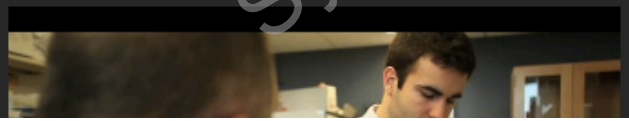

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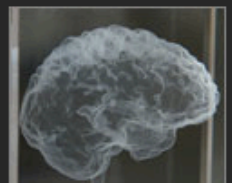

**DON INGBER AND WYSS INSTITUTE WIN WORLD TECHNOLOGY AWARDS**

The World Technology Network

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THE COLBERT REPORT

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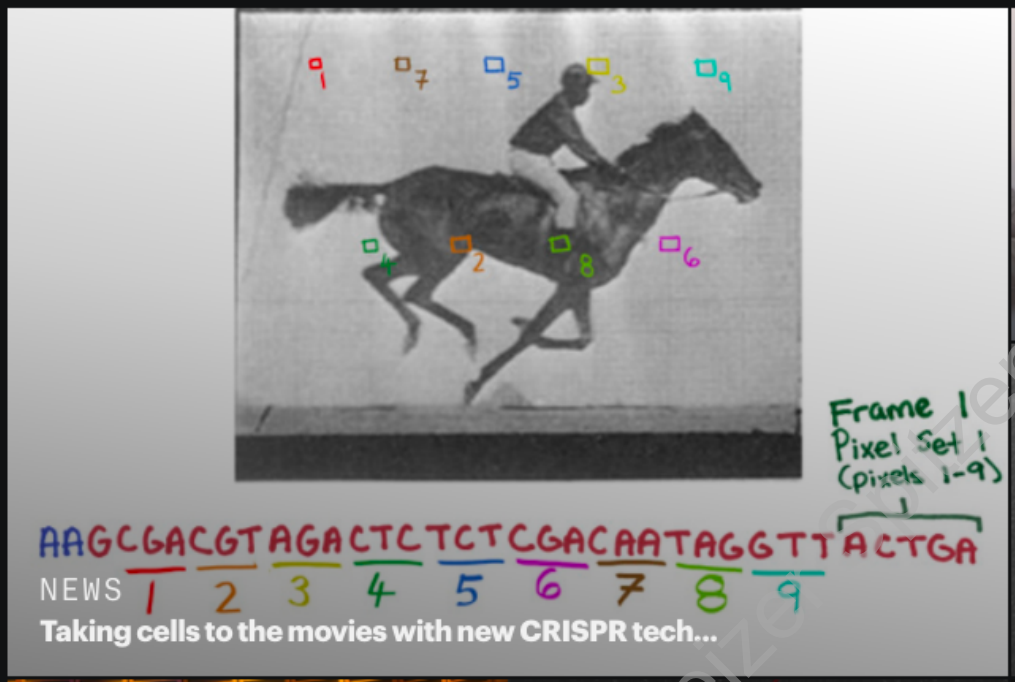


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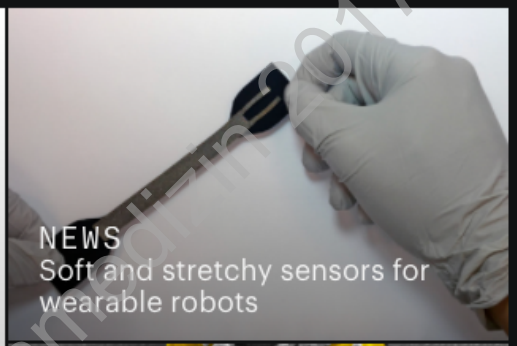
**Taking cells to the movies with new CRISPR tech...**



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**Breakthrough discoveries cannot change the world if they do not leave the lab**

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