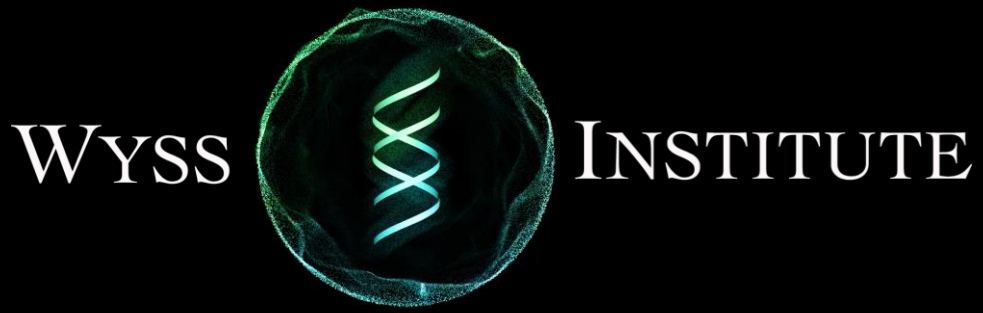
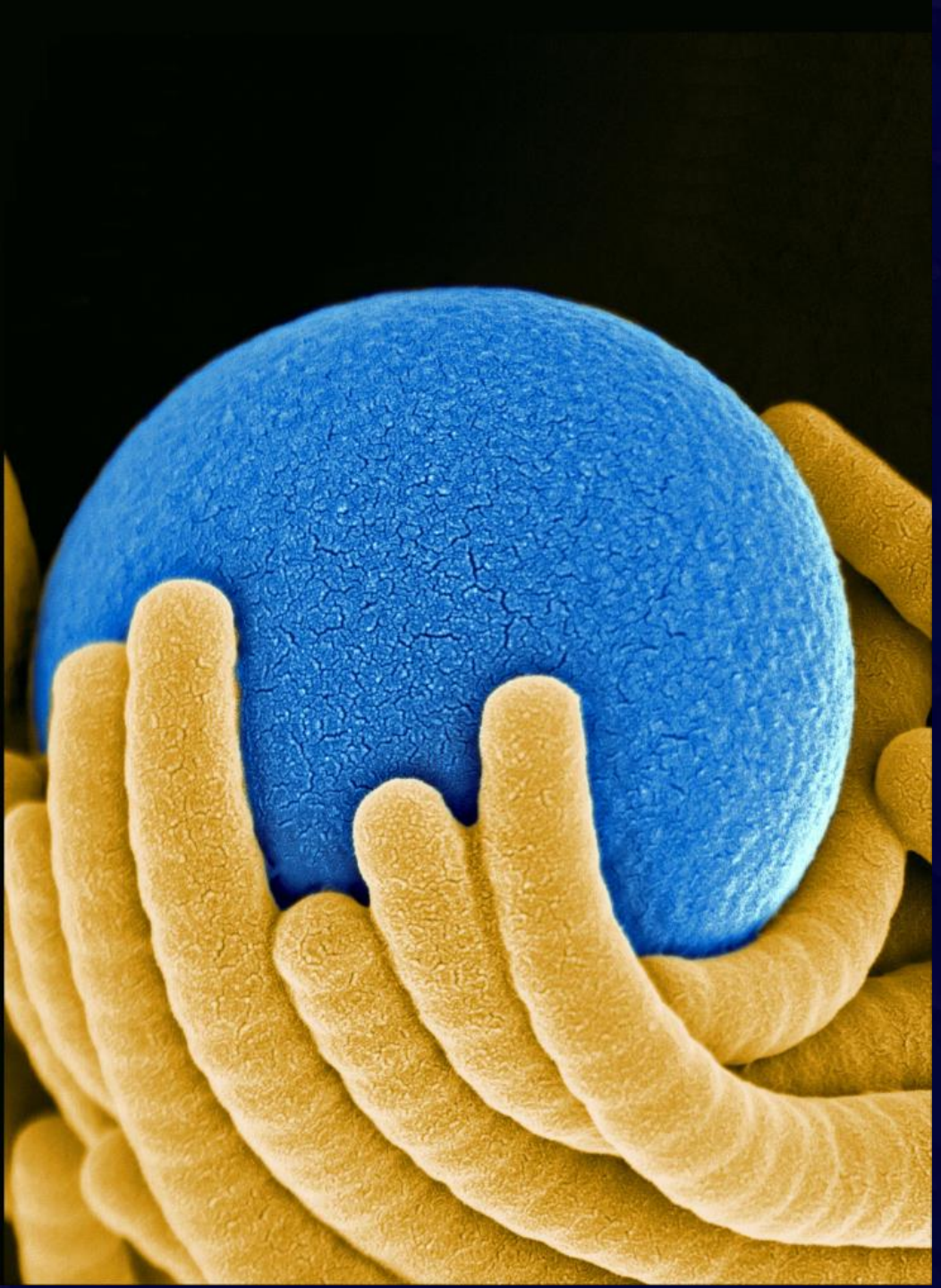


Disruptive Innovation in Drug Development and Personalized Medicine: Human Organ Chips and Beyond

Don Ingber, MD,PhD

Founding Director, Wyss Institute at Harvard University
Judah Folkman Professor of Vascular Biology, Harvard Medical School
& Vascular Biology Program, Boston Children's Hospital
Hansjörg Wyss Professor of Bioinspired Engineering, Harvard School of Engineering and Applied Sciences



WYSS INSTITUTE
for Biologically Inspired Engineering

Our **Mission**

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

our Vision

Breakthrough discoveries

cannot change the world

if they do not leave the lab

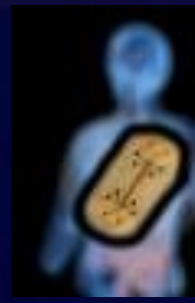
We want to translate disruptive ideas

into impactful products

The Drug Development Model is Challenged

- Cost to develop & approve a new drug > $3 Billion
- Animal studies take years to complete
- Innumerable animal lives are lost
- >70% of results don't predict clinical responses!

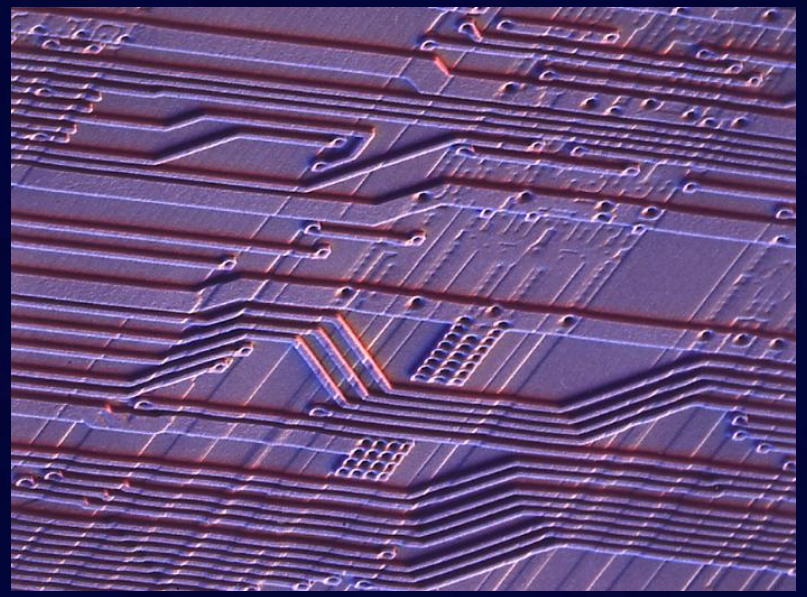
Can we develop safer and more effective drugs faster and at lower cost?

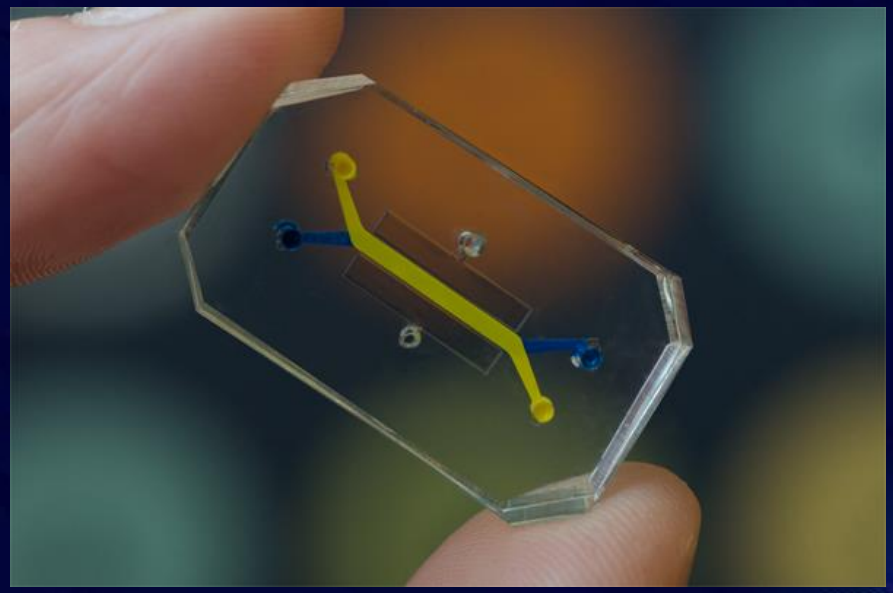


Human Organs-on-Chips

Engineered microchips containing living human cells that reconstitute *organ-level functions*

- ***Accelerate drug development, replace animal testing, and advance personalized medicine***

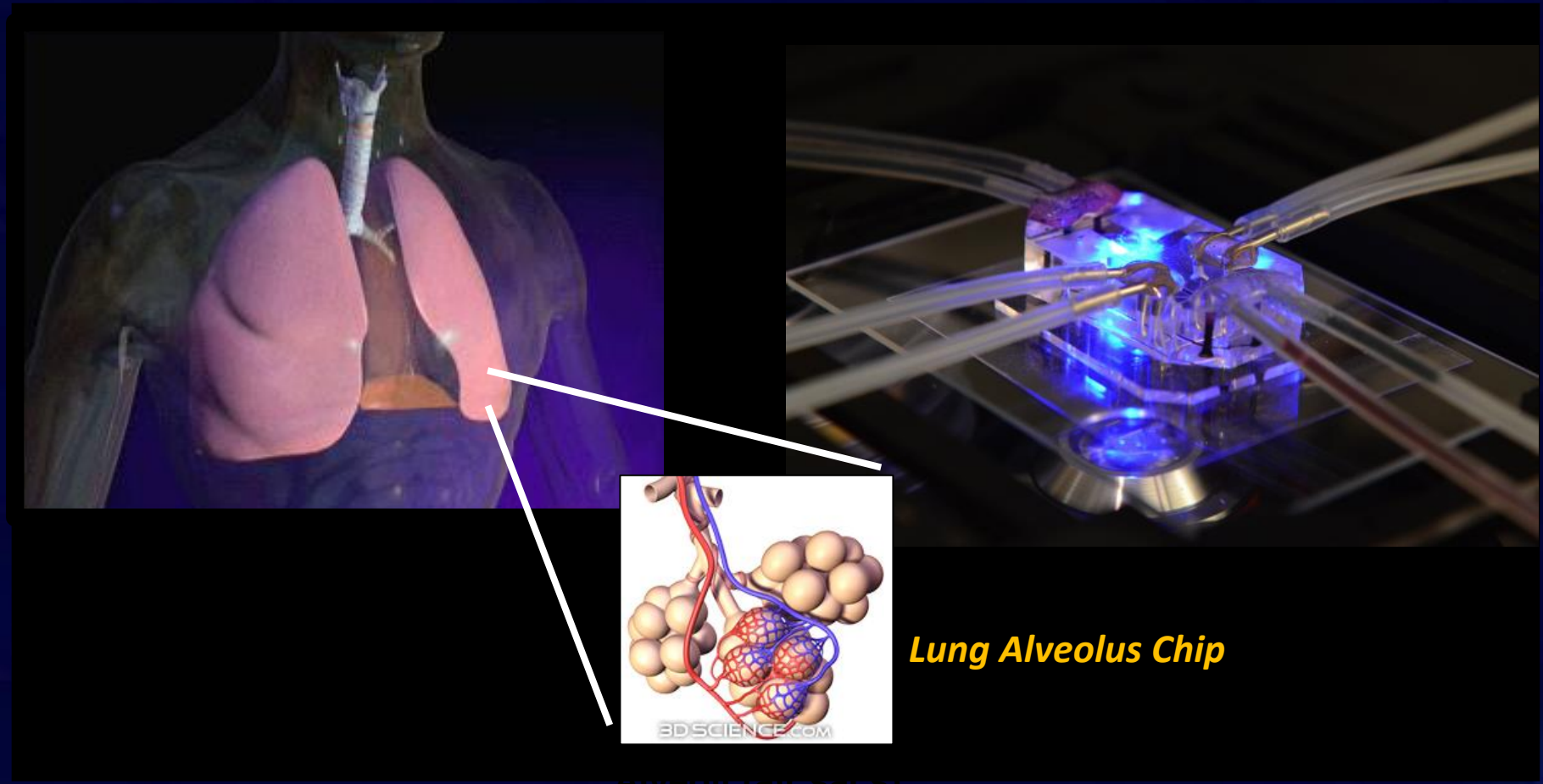


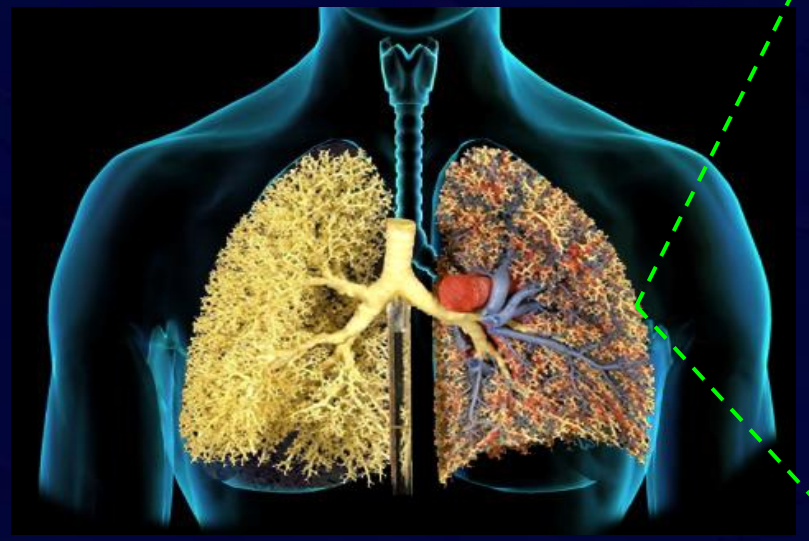


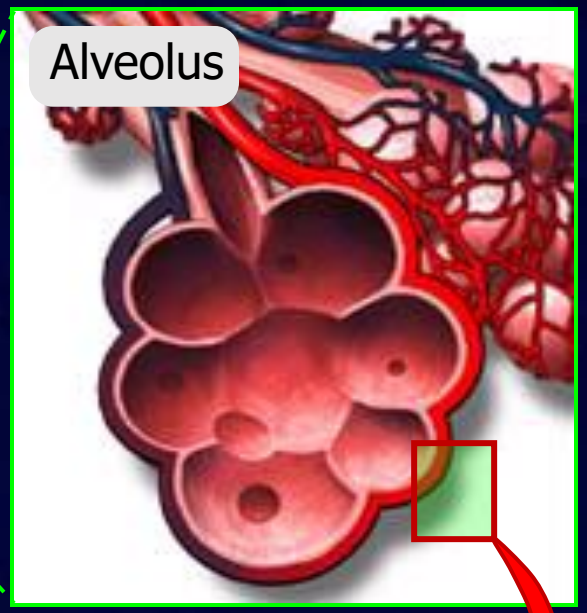
Wyss Institute

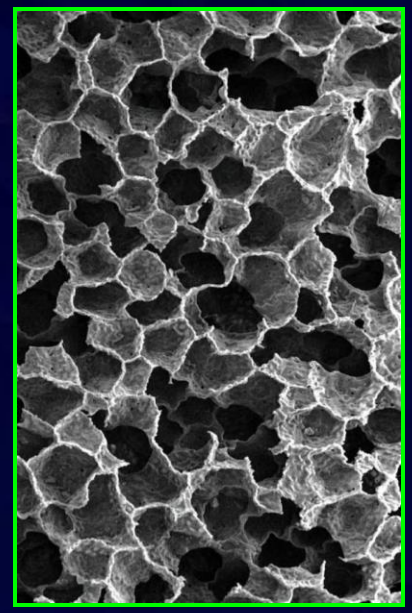
A Human Breathing Lung-on-a-Chip

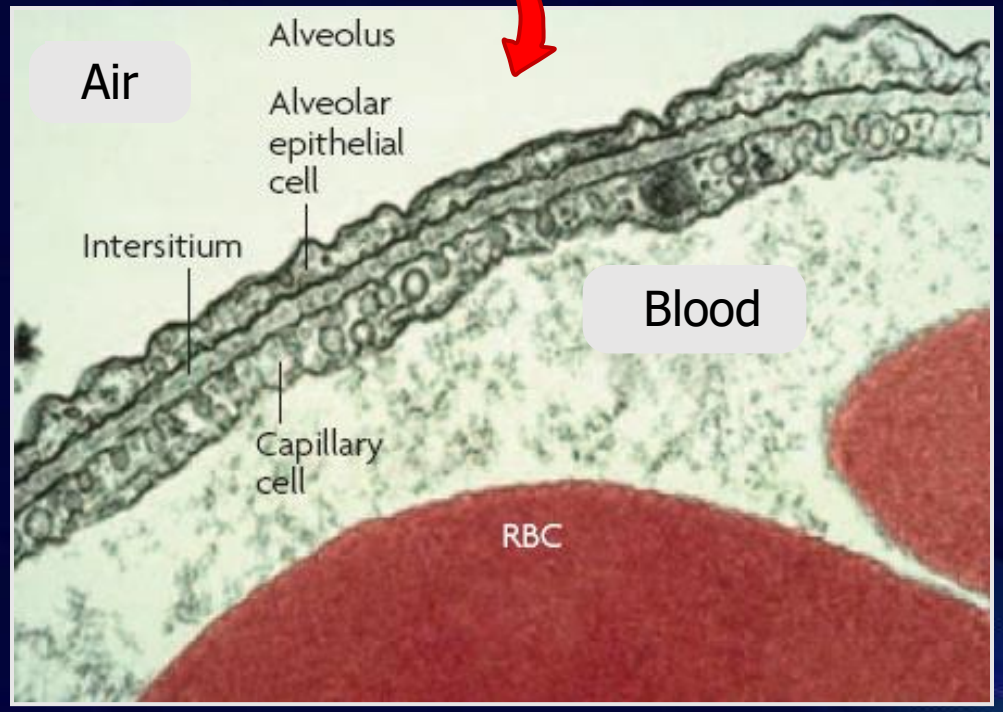
(DAN HUH et al., *Science* 2010)







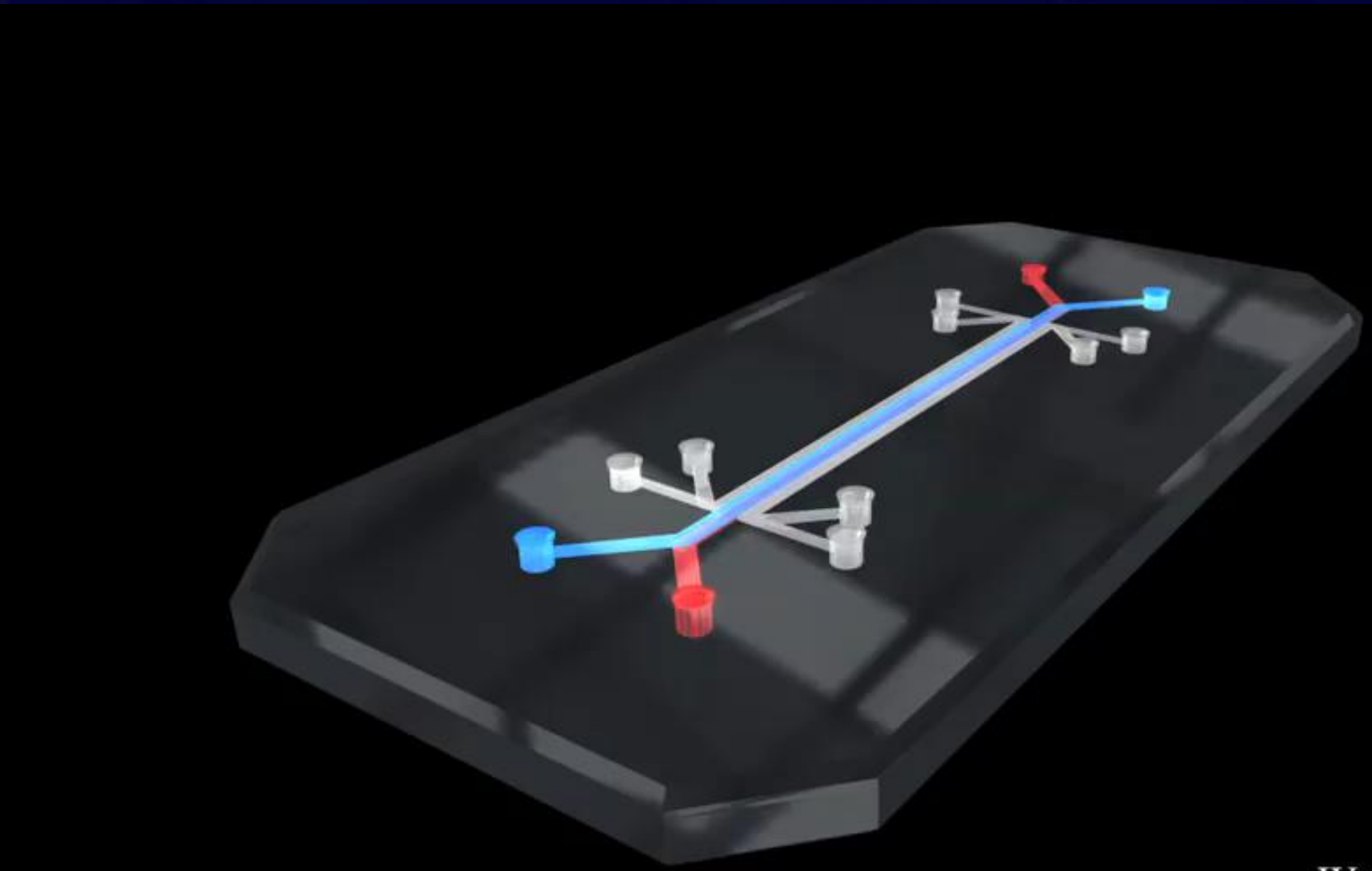




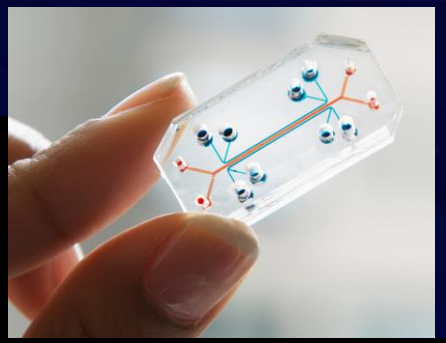
BIODESIGN PRINCIPLES:

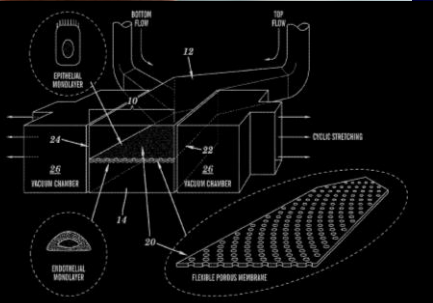
- **Tissue-Tissue Interface**
- **Dynamic Flow**
- **Cyclic Breathing Movements**

WYSS INSTITUTE



WYSS INSTITUTE



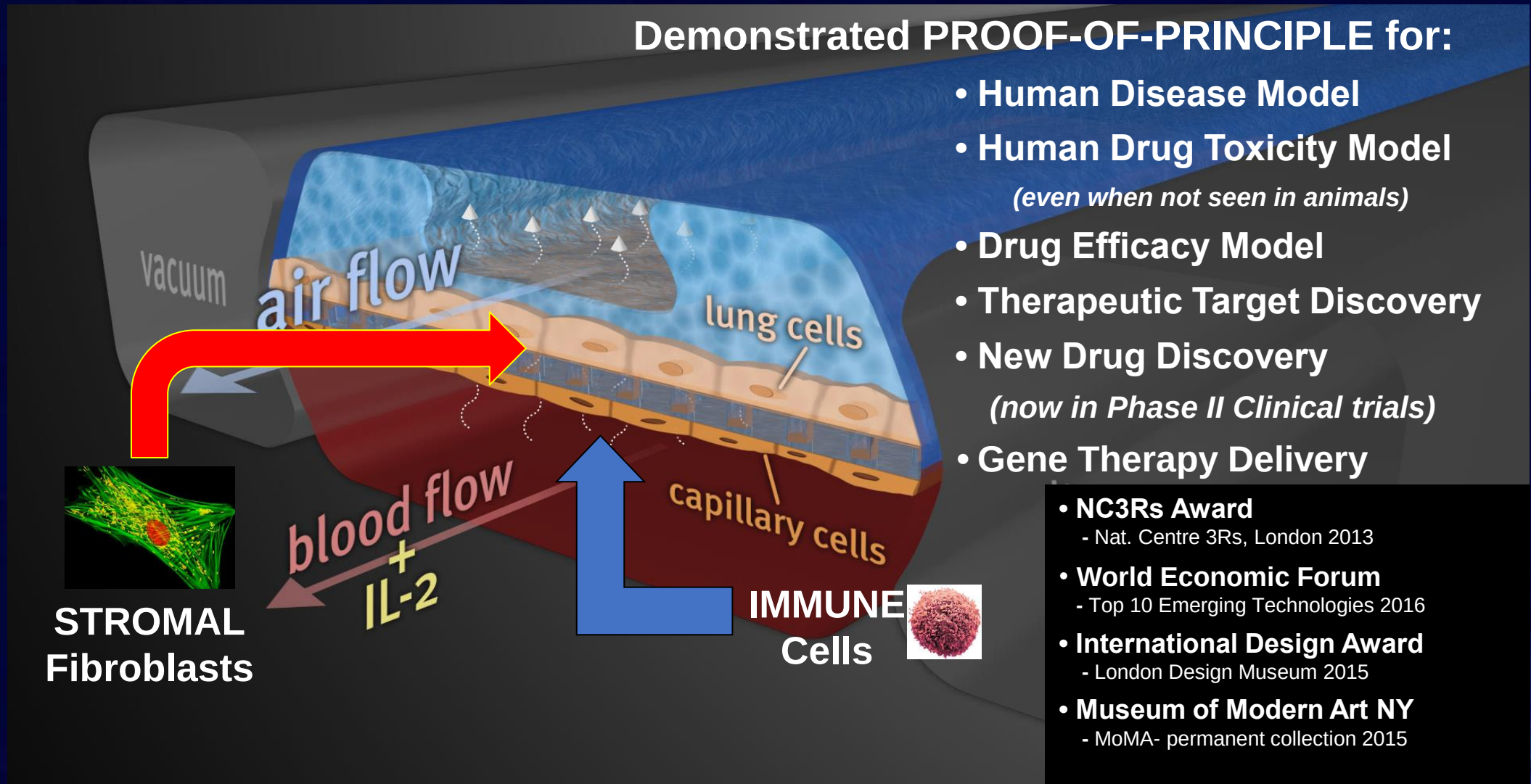


WYSS INSTITUTE

Technology Validation

Human Lung Alveolus Chip

(Huh et al., *Science* 2010 & *Sci. Trans. Med.* 2012; Jain et al., *Clin. Pharm. Ther.* 2018; Barrile et al., *Clin. Pharm. Ther.* 2018)



Demonstrated PROOF-OF-PRINCIPLE for:

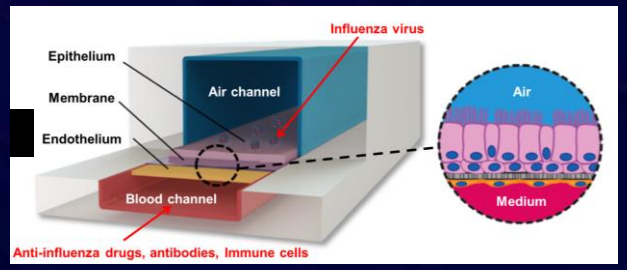
- **Human Disease Model**
- **Human Drug Toxicity Model**
  (even when not seen in animals)
- **Drug Efficacy Model**
- **Therapeutic Target Discovery**
- **New Drug Discovery**
  (now in Phase II Clinical trials)
- **Gene Therapy Delivery**

- **NC3Rs Award**
  - Nat. Centre 3Rs, London 2013
- **World Economic Forum**
  - Top 10 Emerging Technologies 2016
- **International Design Award**
  - London Design Museum 2015
- **Museum of Modern Art NY**
  - MoMA- permanent collection 2015

WYSS INSTITUTE

Human Lung Airway Chip

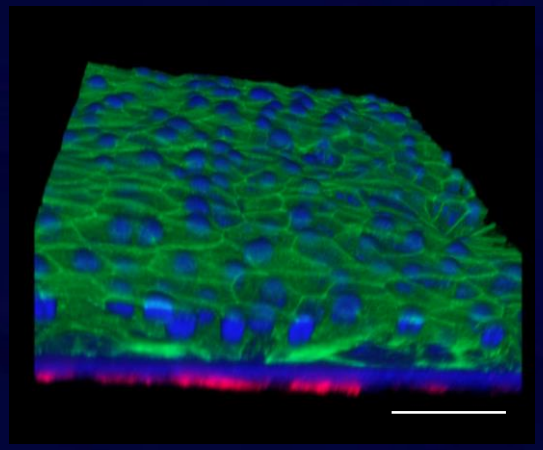
(KAMBEZ BENAM et al., *Nature Meth.* 2016)

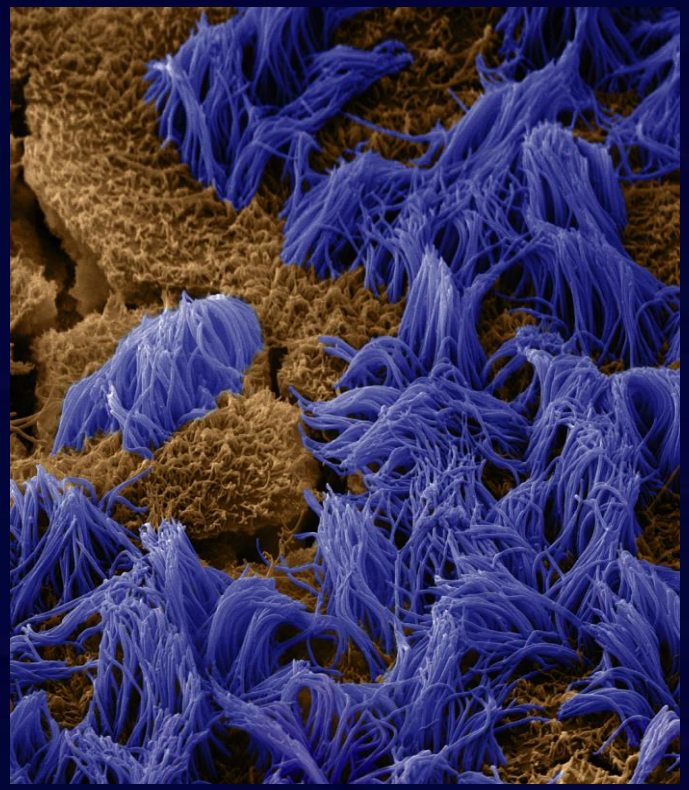


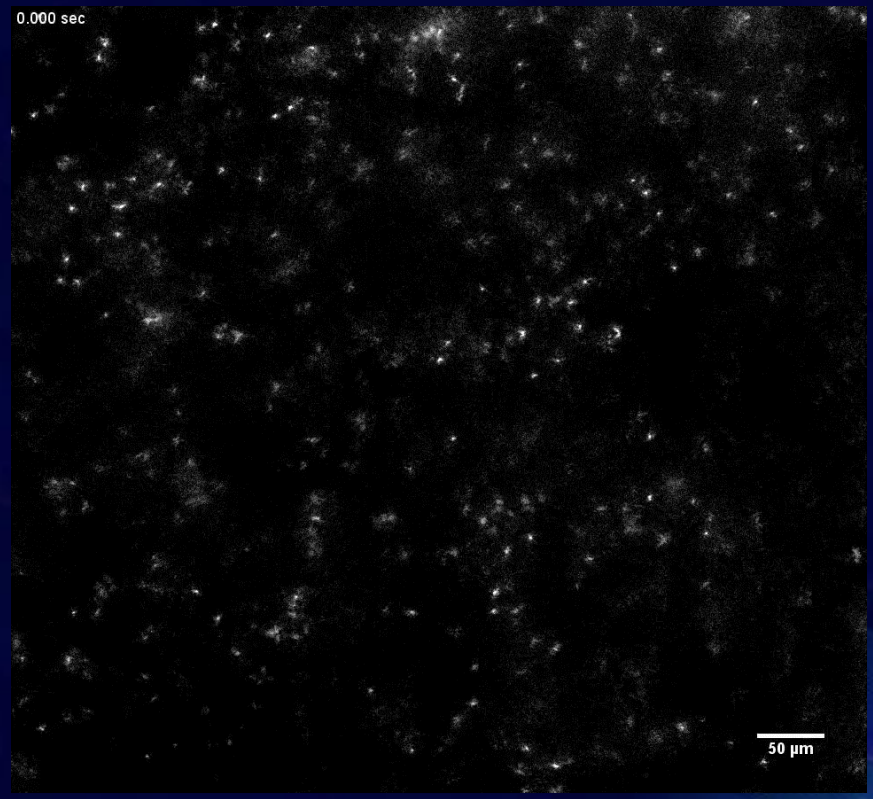
Mucociliary Transport On-Chip

(*Real-Time Imaging*)

Primary Human
Lung Bronchial Epithelium
+ Human Lung Endothelium





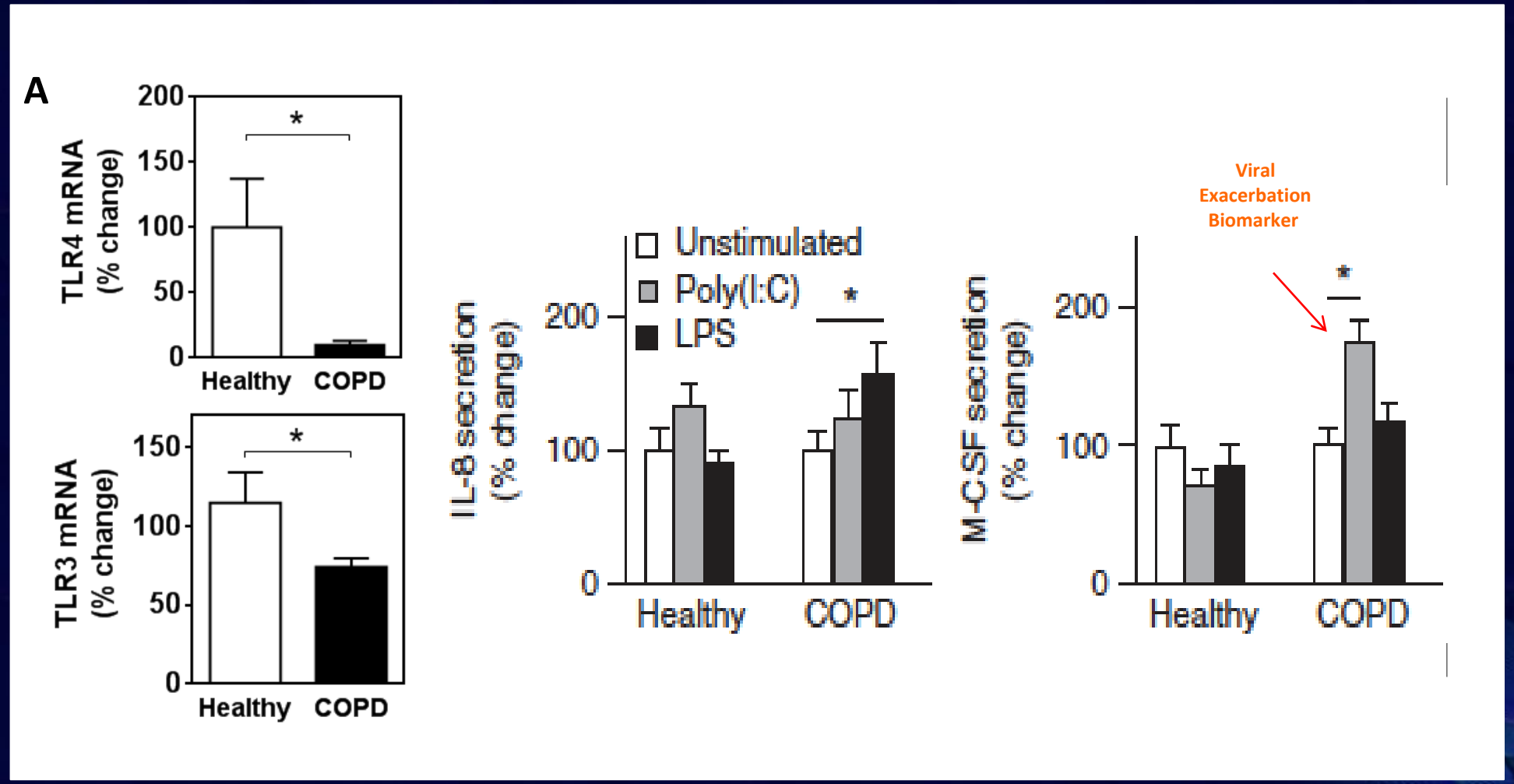


WYSS INSTITUTE

Chips Lined by Cells from COPD Patients

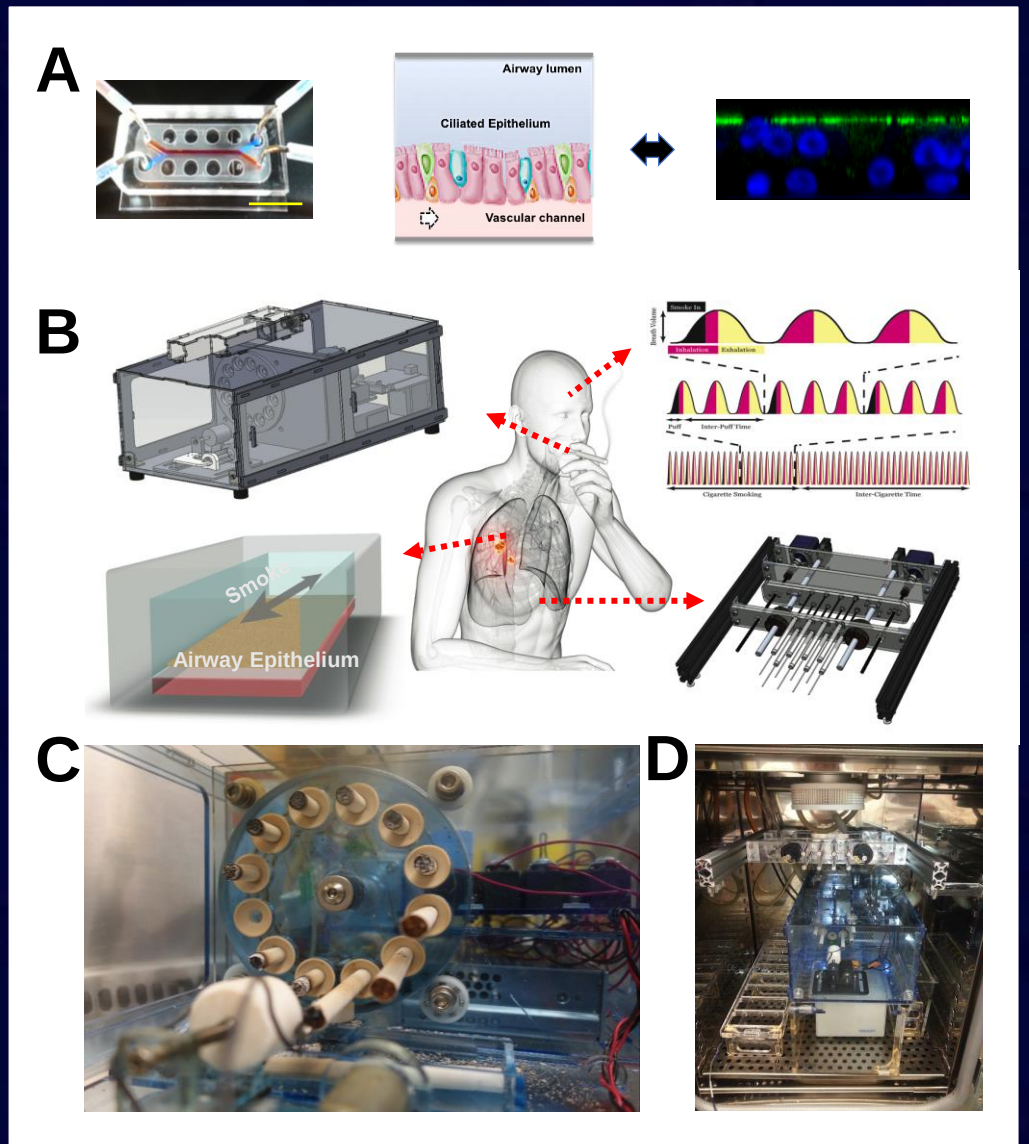
(COPD = Chronic Obstructive Pulmonary Disease)

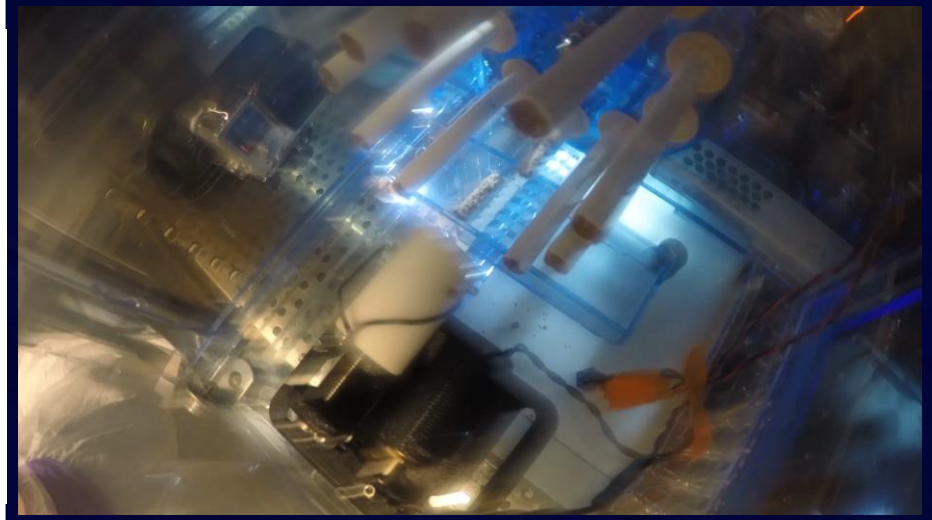
Human COPD Exacerbations Recapitulated On-Chip



Cigarette Smoke Exposure in Airway Chips

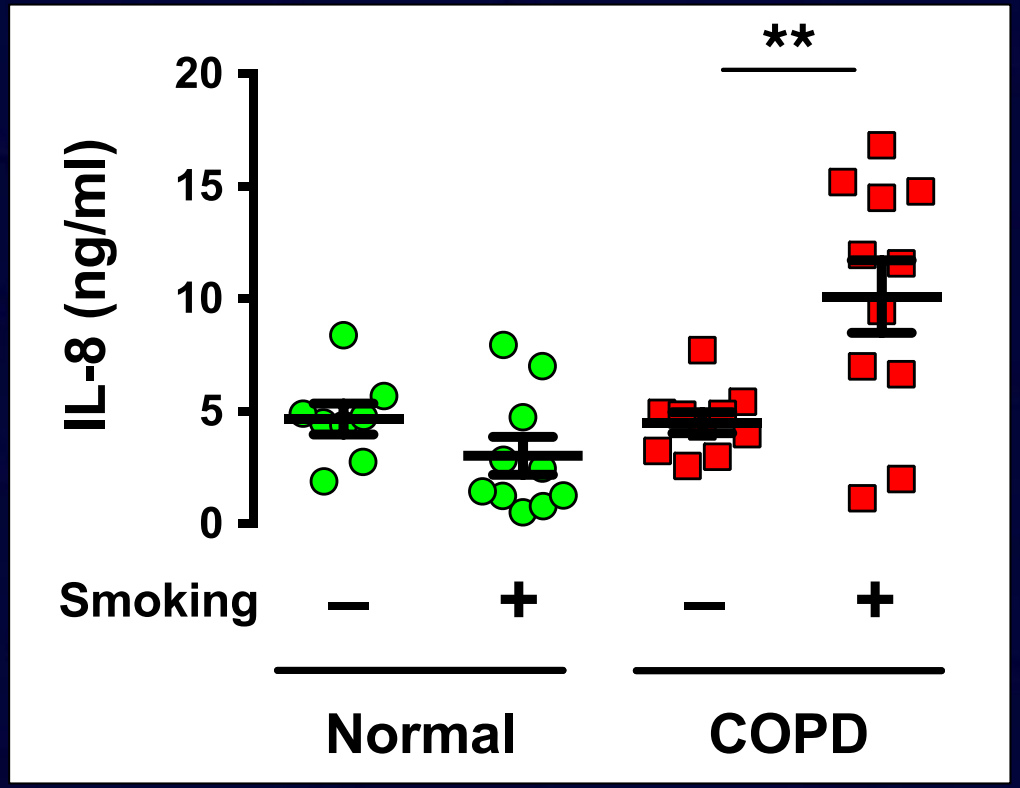
(KAMBEZ BENAM et al. *Cell Syst.* 2016)



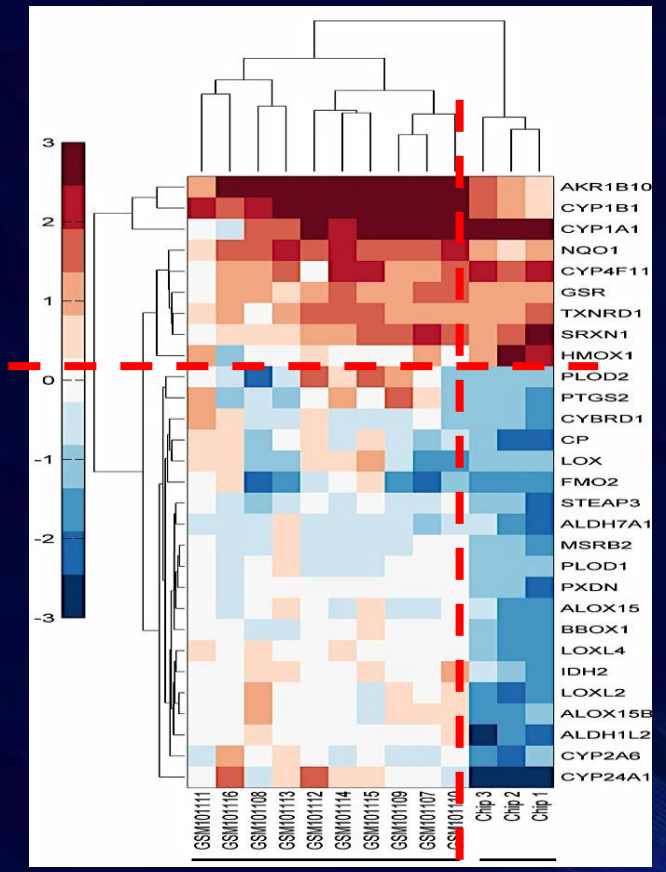


Cigarette Smoke: Matched Comparative Modeling in Lung Chips

Cytokines



Gene Microarrays



Wyss Institute

Funded by CF Foundation

Human Airway Chip Cystic Fibrosis Model

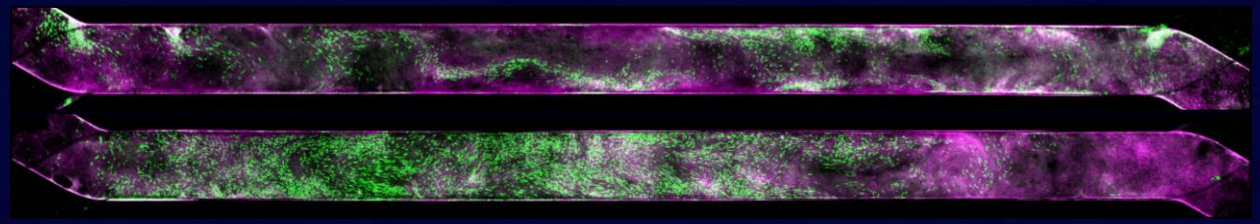
(ROBERTO PLEBANI et al., *J. Cyst. Fibrosis 2021*)

Chips lined with bronchial epithelium from Healthy vs. CF Patients

Ciliated Cells

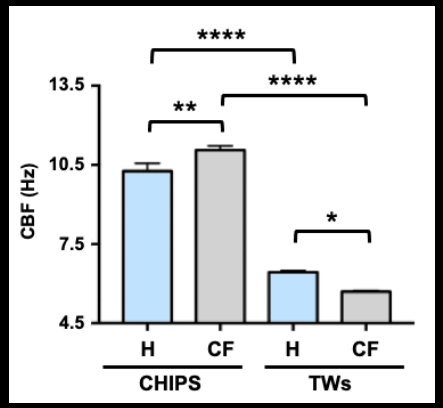
Healthy Chip

CF Chip

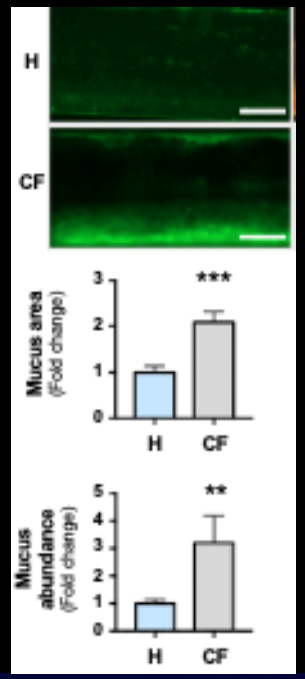


(Top View/Whole Chip)

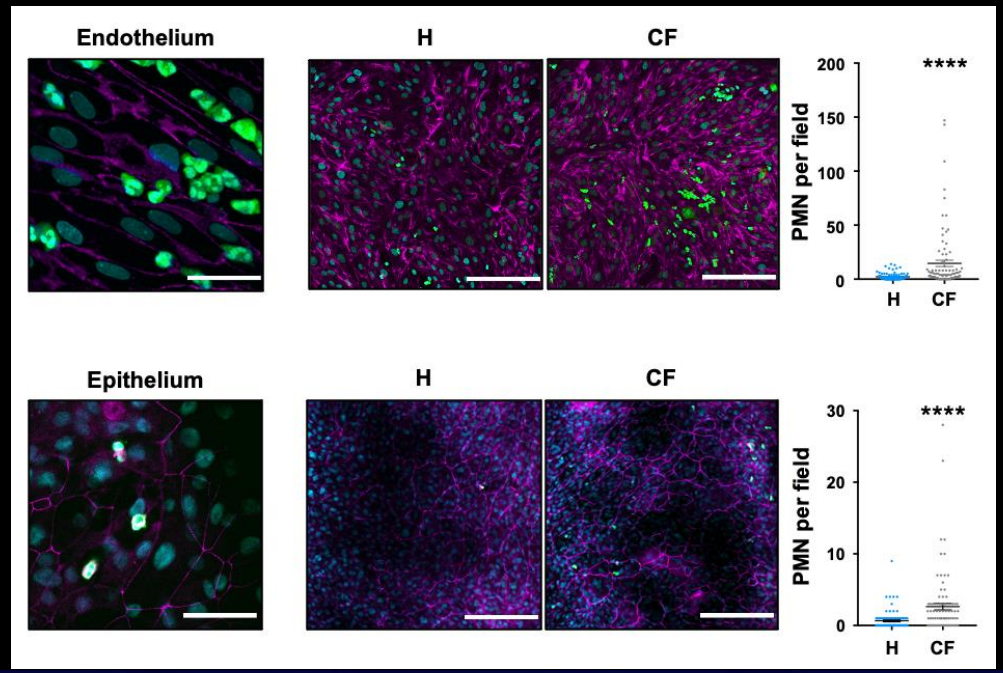
Cilia Beating Frequency



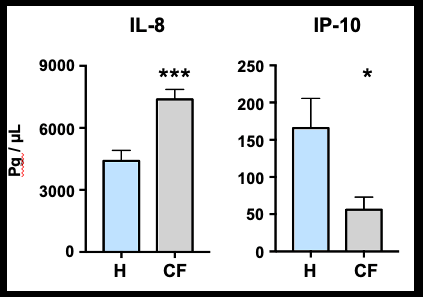
Mucus Production



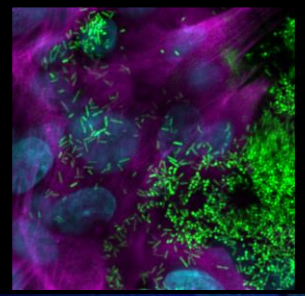
Immune Cell Recruitment

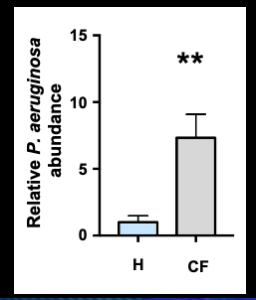


Cytokine Release



P. Aeroginosa Growth





Organ Chips

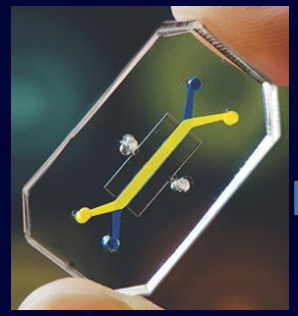
provide a Window

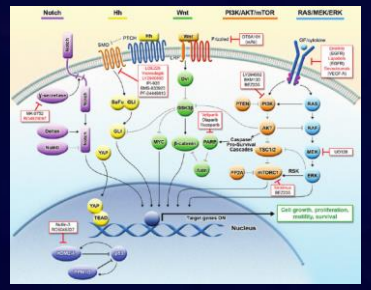
on Molecular Scale Activities

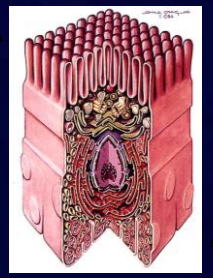
inside Living Human Cells

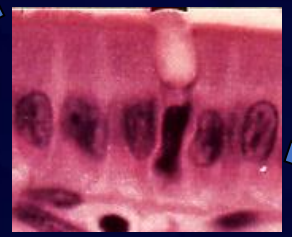
within a relevant Tissue

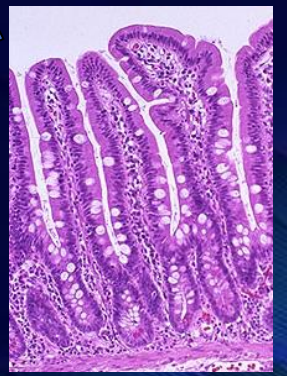
and Organ Context











Could enable new Mechanistic Insights & Drug Discovery

+ Provide a way to Experimentally Test Predictions

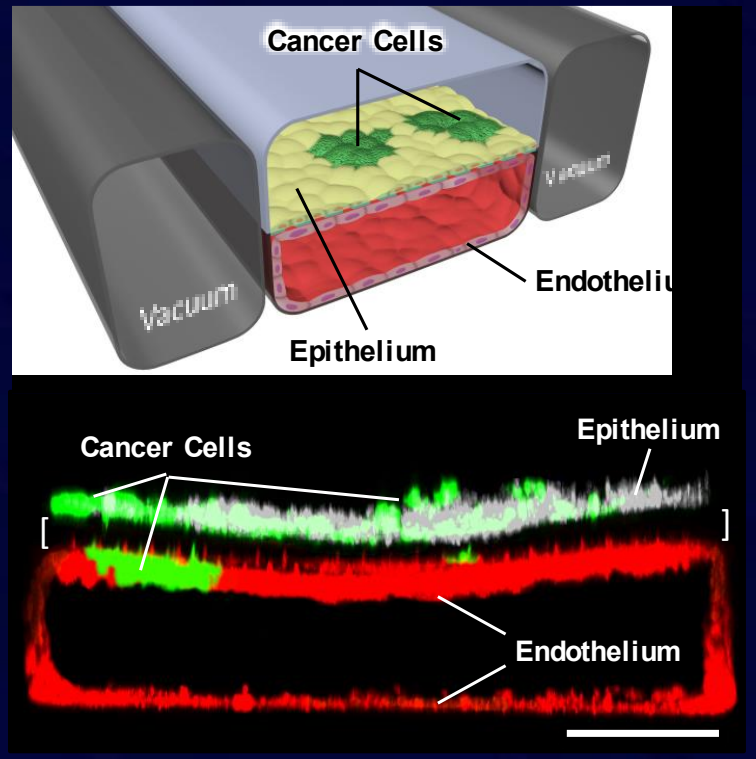
Wyss Institute

Human Orthotopic Lung Cancer Chips

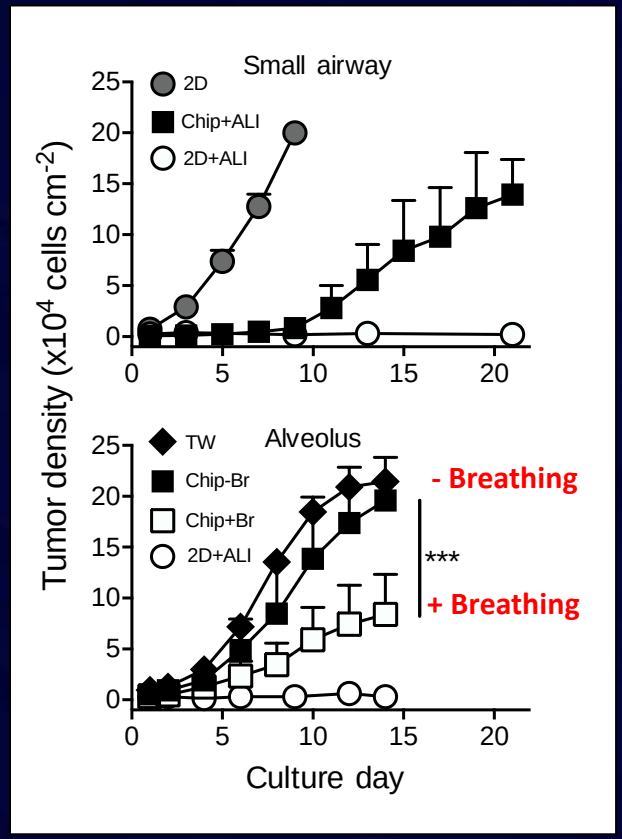
(BRYAN HASSELL et al., *Cell Reports* 2017)

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

Emerges in distant bronchiole but preferentially grows in alveoli in vivo



GFP-H1975 NSCLC cells



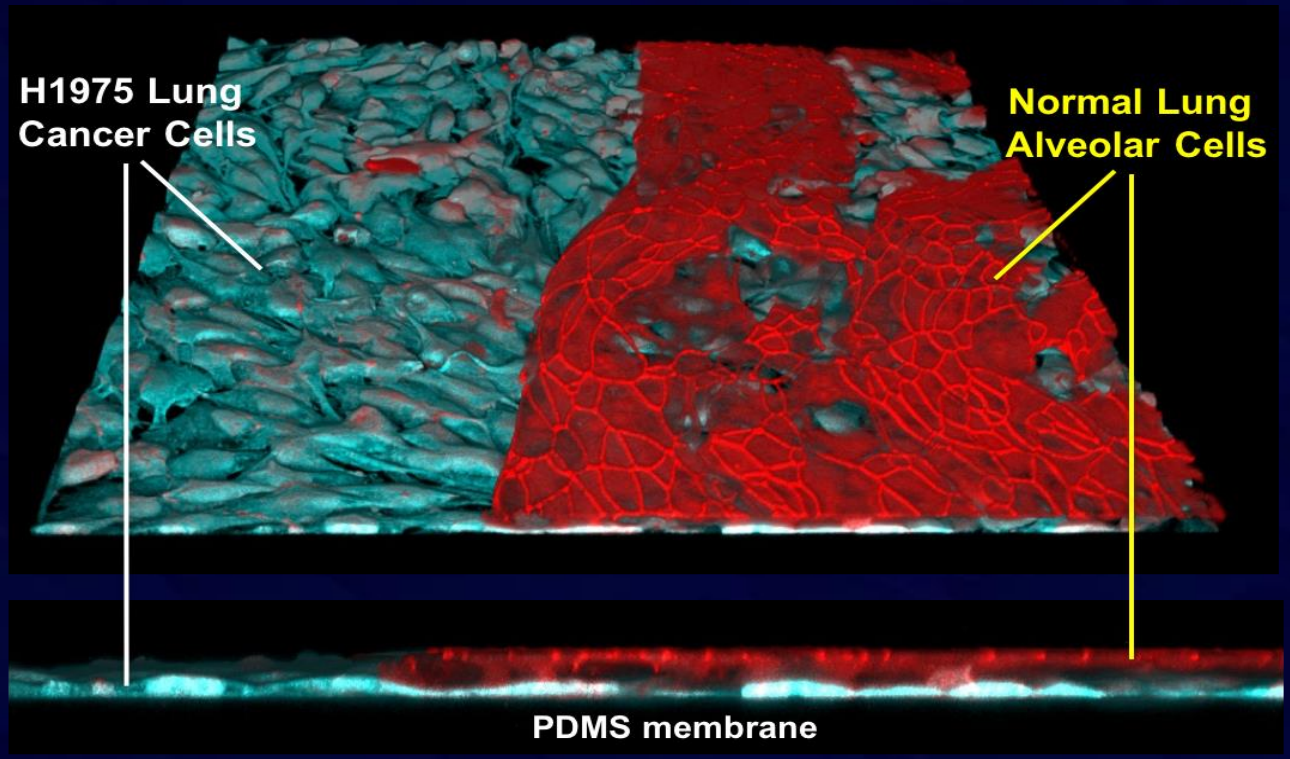
Recapitulates Orthotopic Cancer Growth Patterns in vitro

+

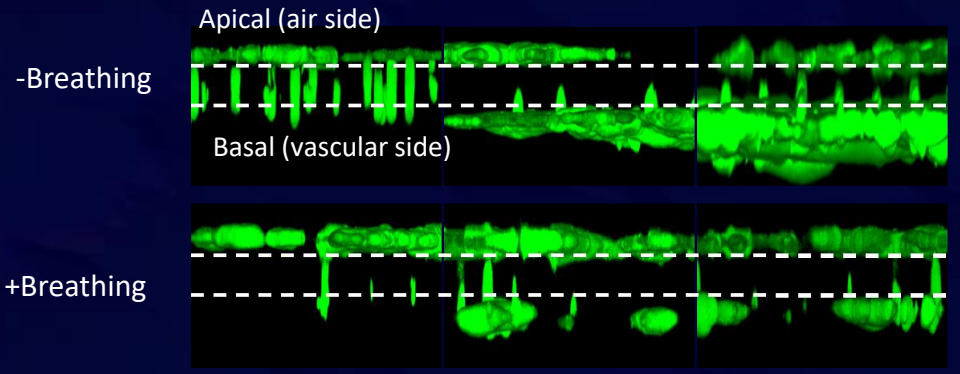
Breathing Motions Suppress Lung Cancer Growth

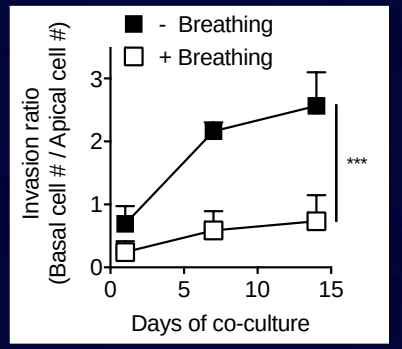
Wyss Institute

NSCLC Adenocarcinoma in Lung ALVEOLUS Chip



Tumor Invasion On-Chip



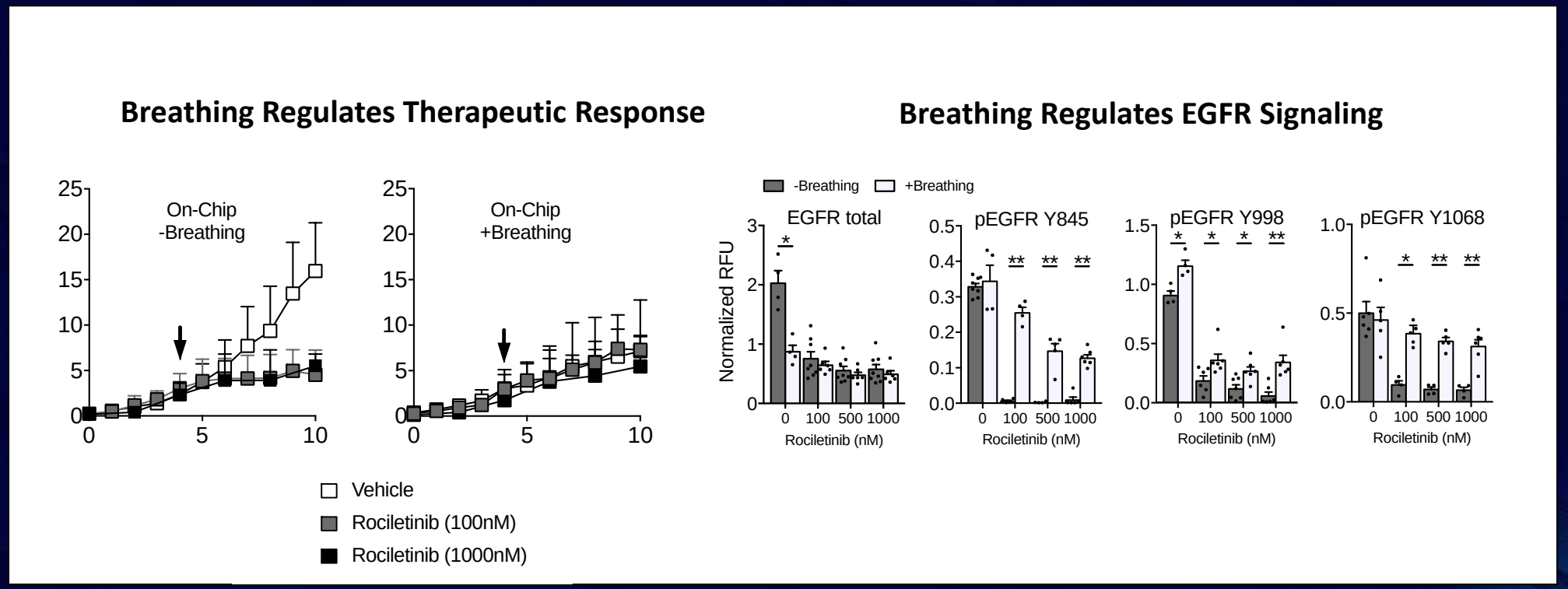


Breathing Inhibits Invasion

Wyss Institute

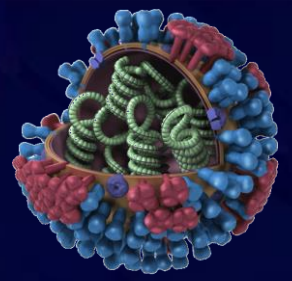
Tumor Cells are LESS Responsive to Therapy with Mechanical Breathing Motions

(mediated by altered EGFR Phosphorylation)



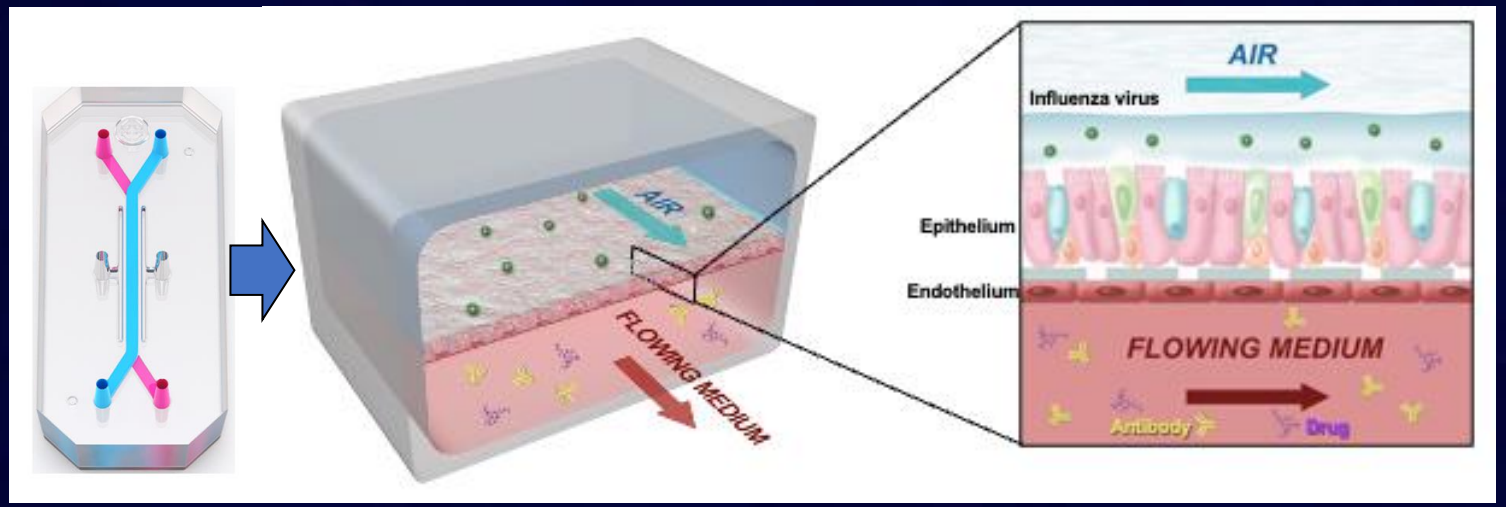
WYSS INSTITUTE

Funded by DARPA & NIH in 2017

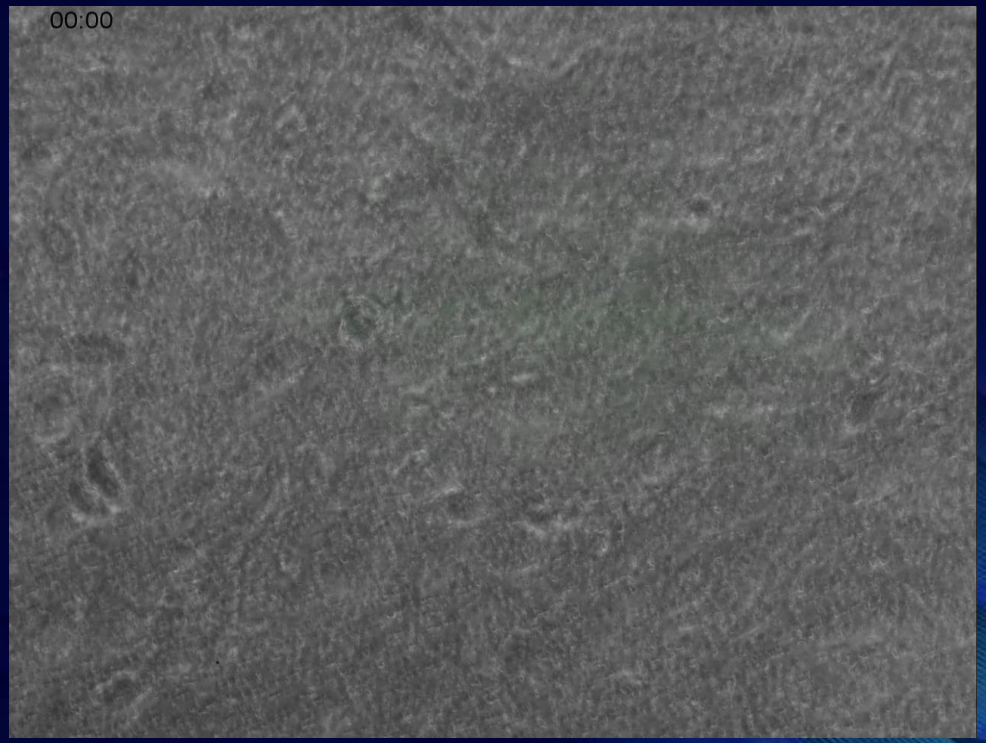


Large Airway Chip Viral Infection Model

(Si et al., *Nature Biomed. Engin*. 2021 & *Microbio. Spectrum* 2021)



Live Infection
(GFP-Influenza H1N1)



Funded by DARPA & NIH

Human Airway Influenza Infection Chip

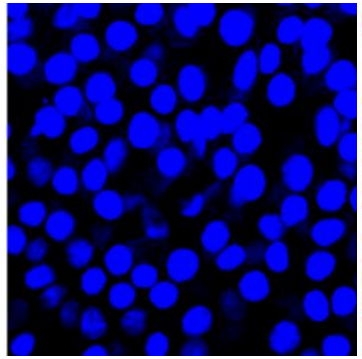
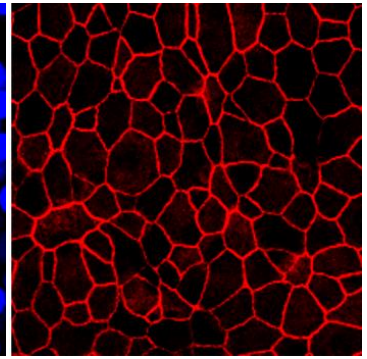
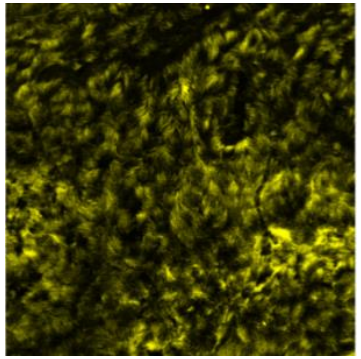
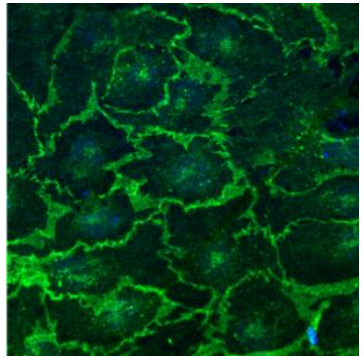
(LONGLONG SI et al., *Nature Biomed. Engin. 2021*)

Epithelium

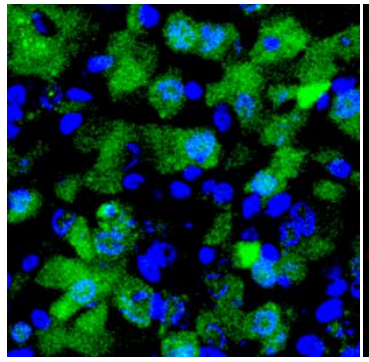
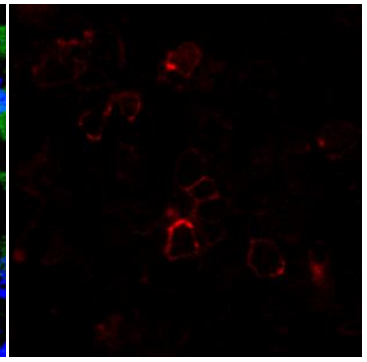
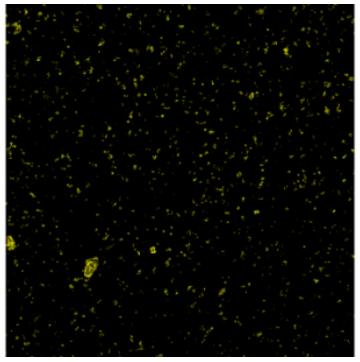
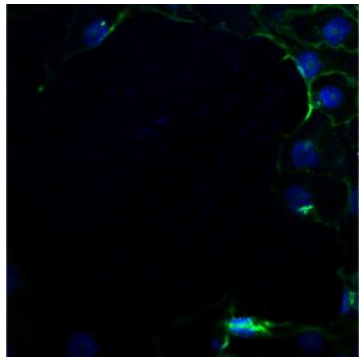
Endothelium

GFP | ZO-1 | Cilia | VE-cadherin

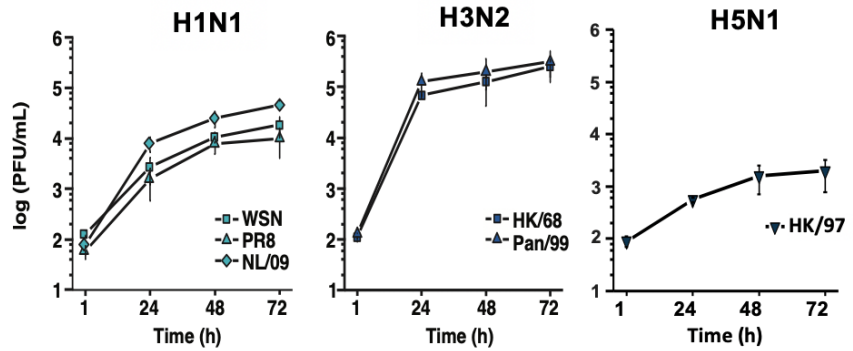
- Virus

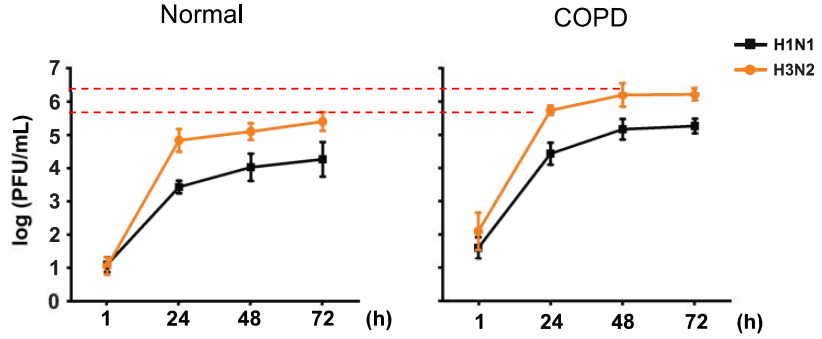
+ Virus

Viral Strain-Dependent Virulence

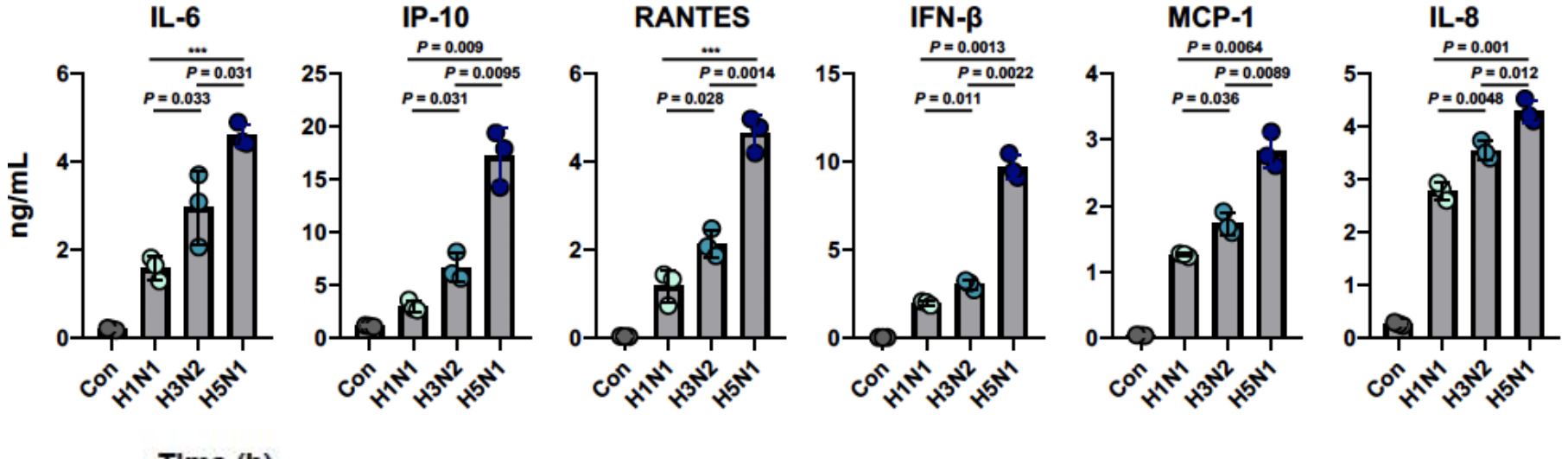


Effects of Comorbidity

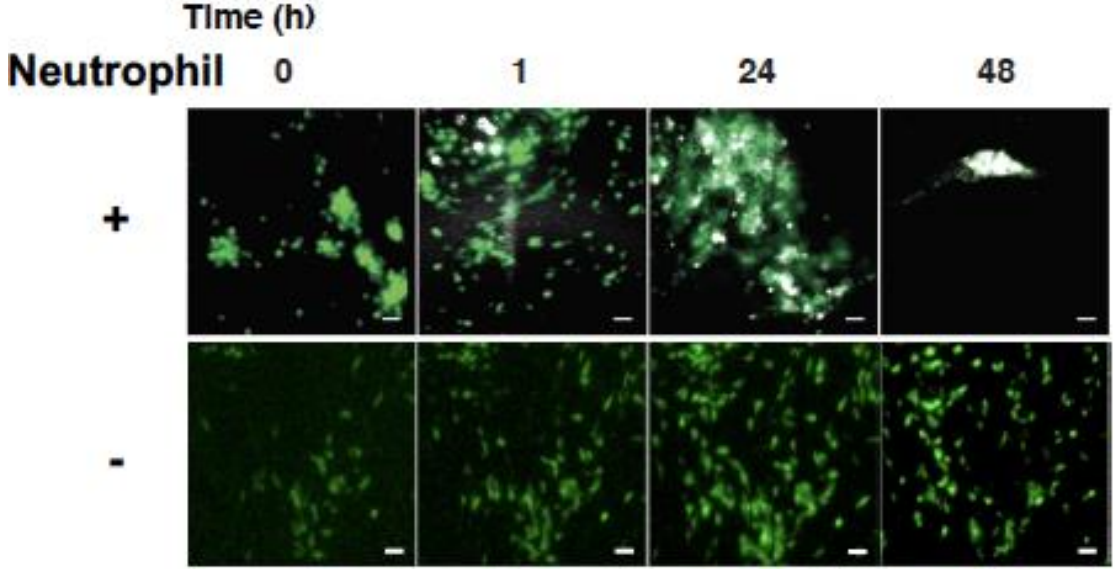


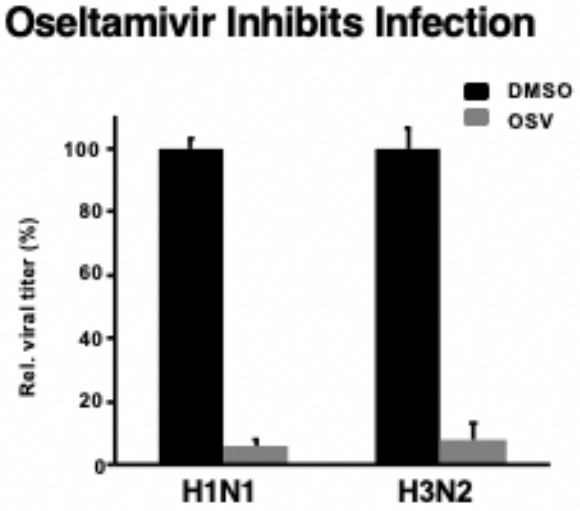
Can Analyze Host Responses to Infection & Drugs

Cytokines



Immune Cell Recruitment



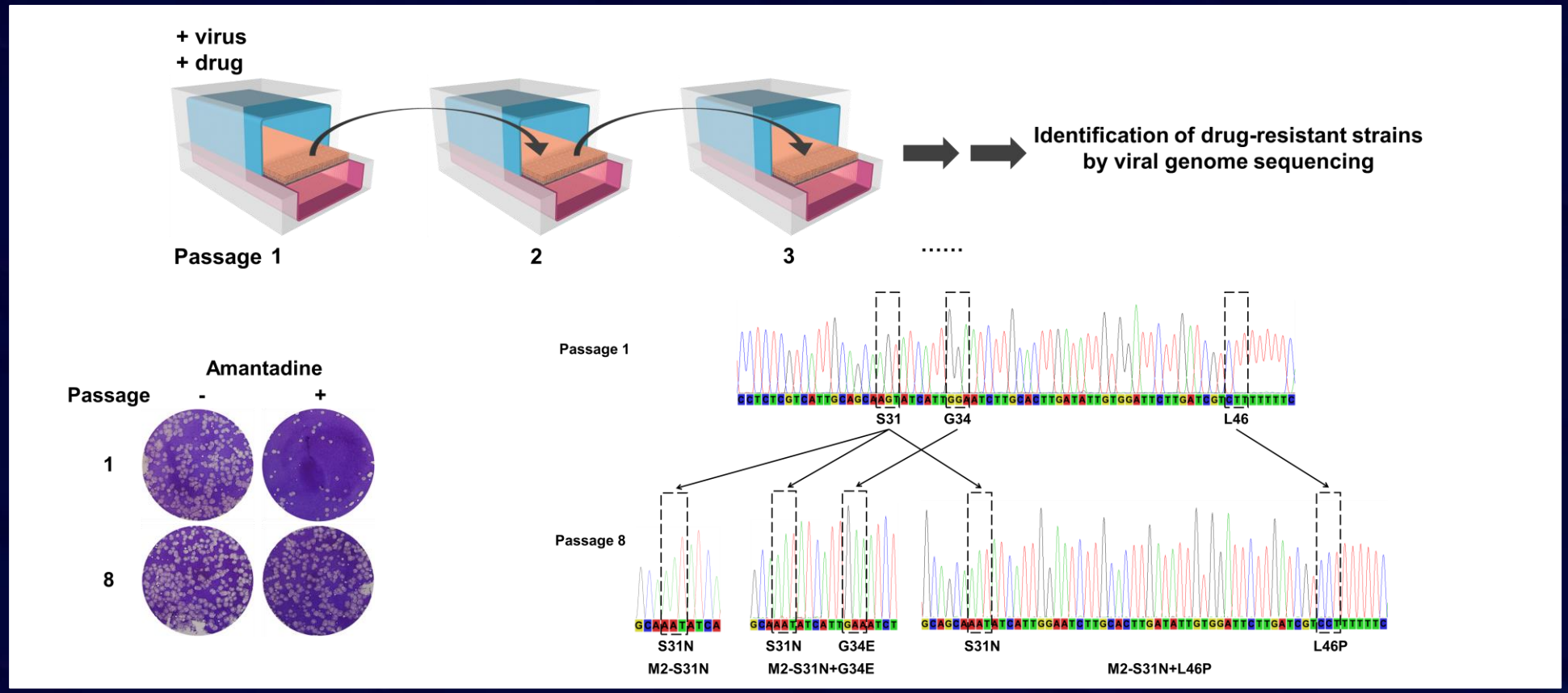


Drug Effects

Wyss Institute

Modeling Viral Evolution of Resistance to Therapy due to Human-to-Human Transmission in vitro

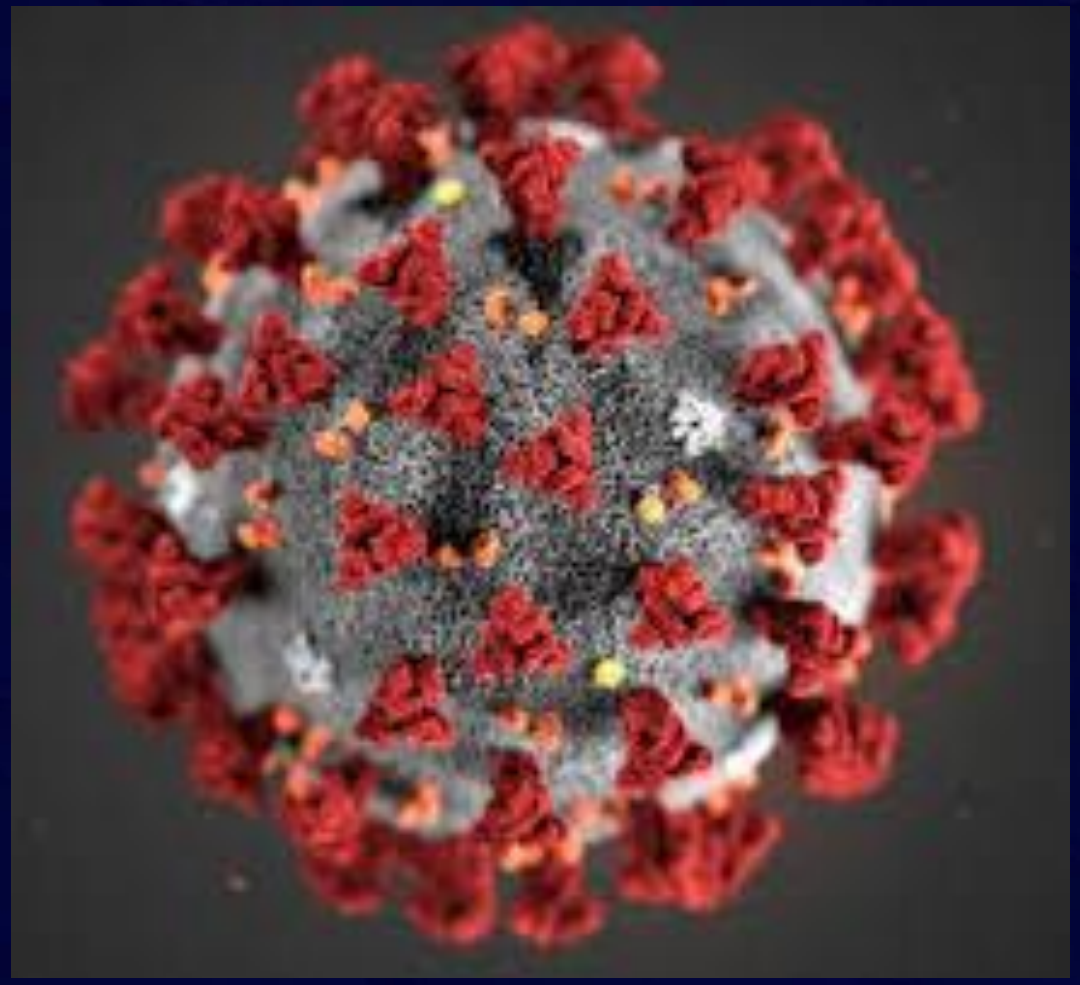
(Longlong Si et al., *Microbiology Spectrum 2021*)

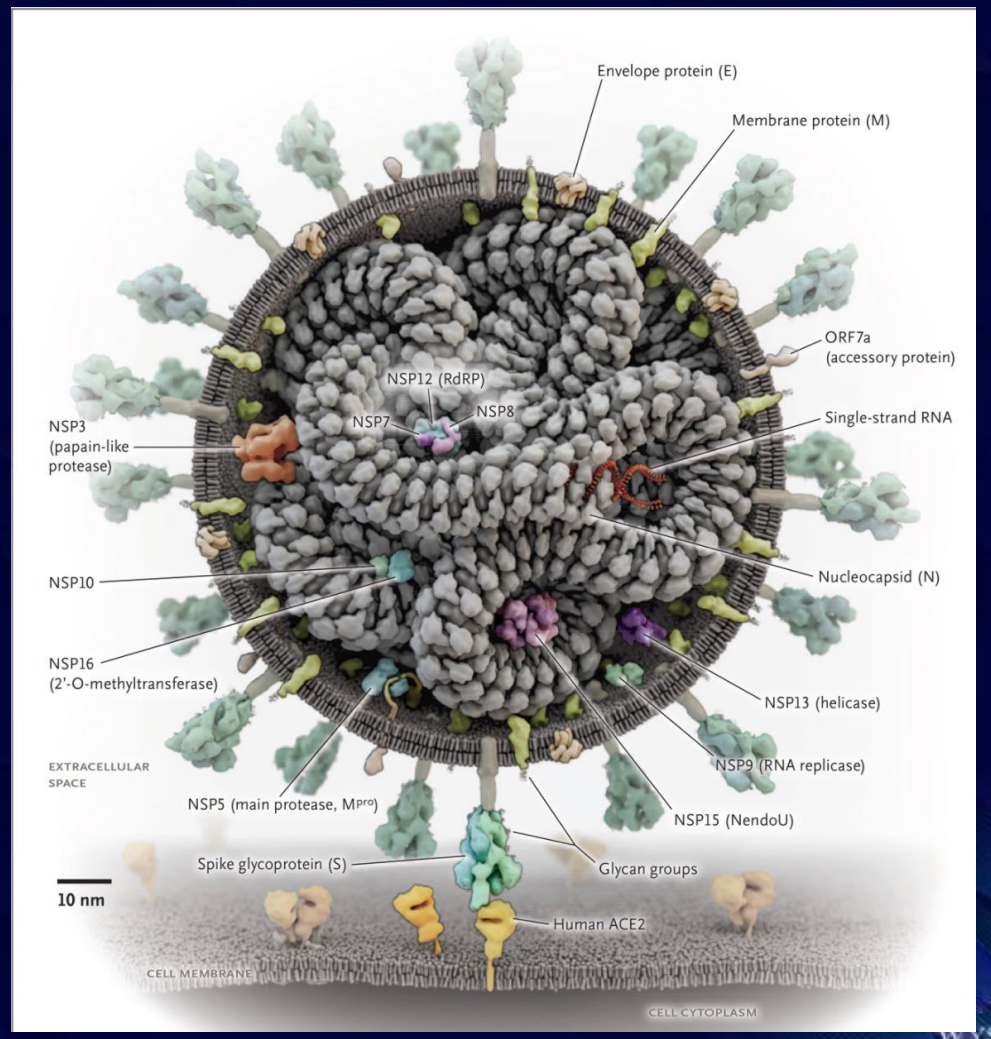


- *Influenza evolution under drug pressure and patient-to-patient transmission can be mimicked on-chip*
- *3 known and 2 unknown mutations were identified that mediate resistance to amantadine & oseltamivir*

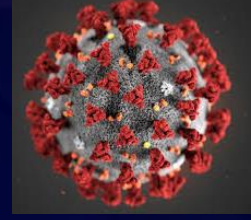
Wyss Institute

Pivot to COVID-19





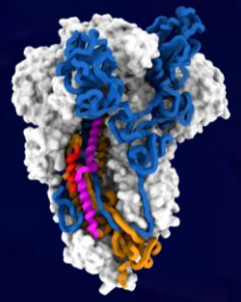
WYSS INSTITUTE



DARPA COVID19 Program

(12 months duration; May 2020 start)

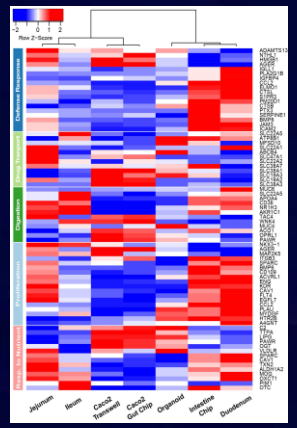
Structural Similarity and SAR



CoV-2 Spike Protein

MDS + AI + Medicinal Chemistry Pipeline

Transcriptomic Data from COVID patients



Computational AI/Network Analysis Pipeline (NemoCAD)

FDA Approved Drugs

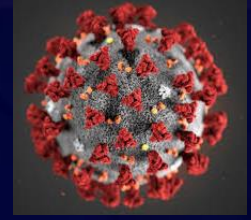
In vitro Assays & Human Organ Chips *[with Matt Frieman, U. Maryland Sch. Med.]*

Hamster/PK

Hamster Native CoV2 Models *[with Ben tenOever, Mt Sinai Sch. Med.i]*

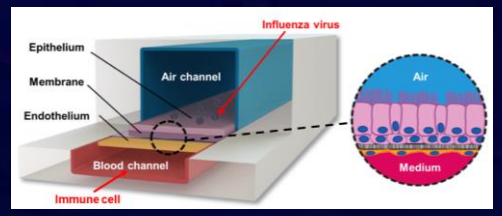
Wyss Institute

Repurposing of Drugs for COVID-19 enabled by Human Lung Chips

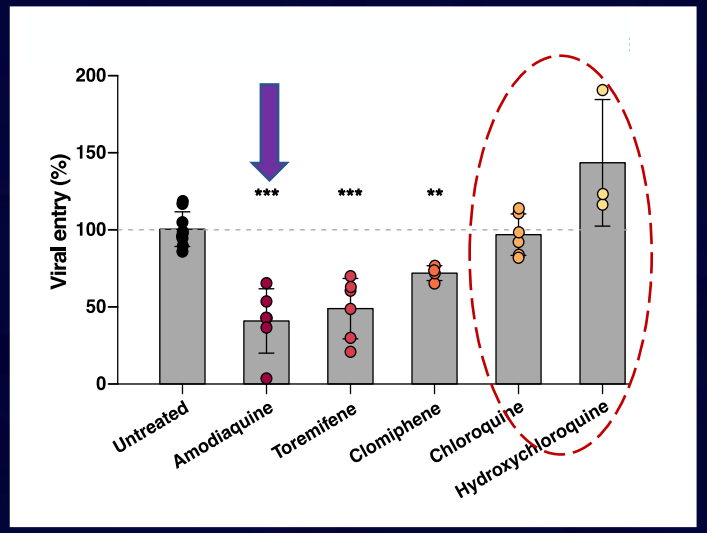


(LONGLONG SI et al., *Nature Biomed. Eng. 2021*)

Lung Airway Chip

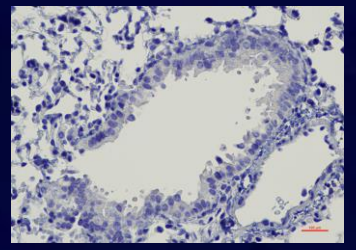


Drugs Flowed through Chip at Clinical Doses (C_{max})

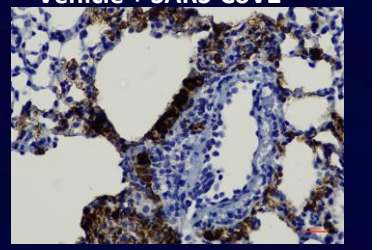


Hamster COVID-19 model with Ben tenOever, Mt. Sinai

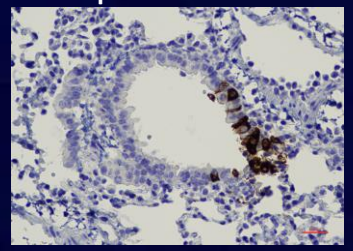
Mock Infected



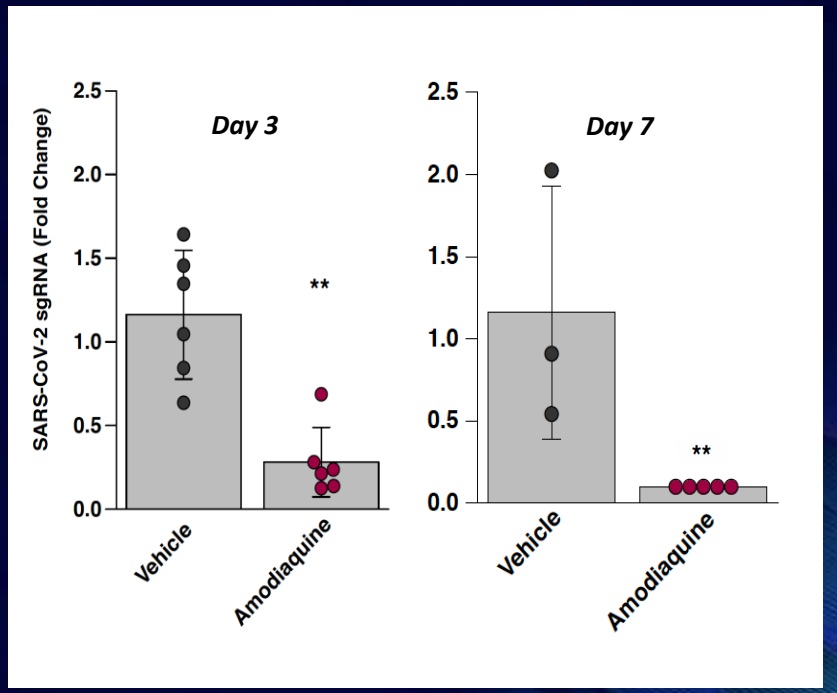
Vehicle + SARS-CoV2



Amodiaquine + SARS-CoV2



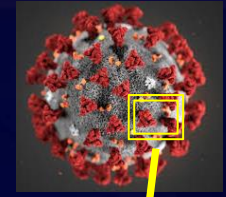
TREATMENT MODE



Drug moved to Clinical Trials across 20 sites in Africa

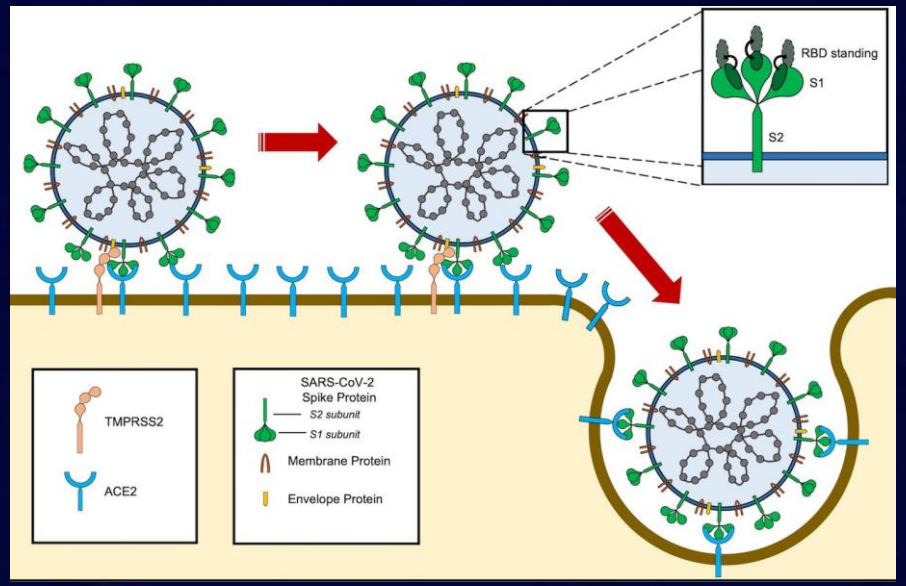
WYSS INSTITUTE

Funded by DARPA Covid-19

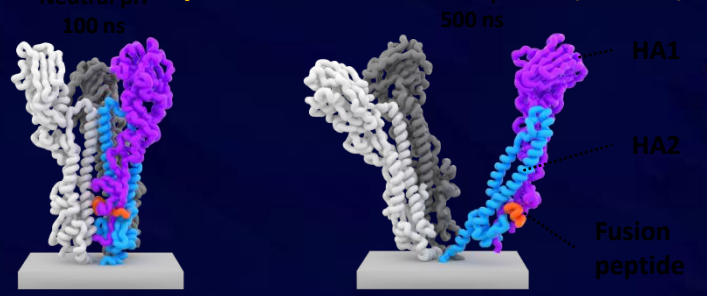


MDS APPROACH:

Targeting Conserved Regions of CoV-2 Spike Protein for Broad-Spectrum Activity

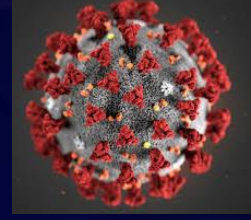


Molecular Dynamics Simulation (MDS)

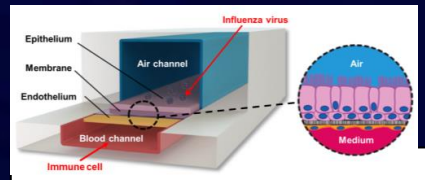


WYSS INSTITUTE

Funded by DARPA Covid-19



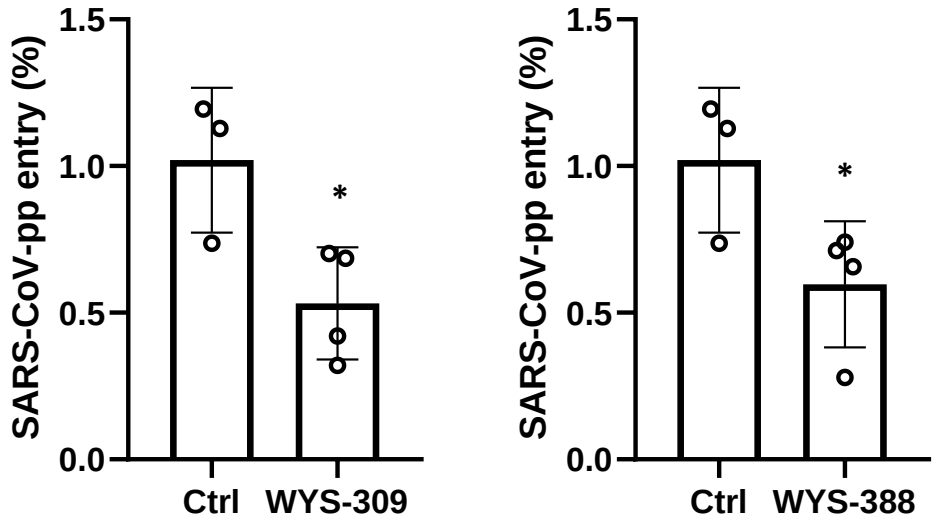
MDS-identified Compounds Inhibit SARS-CoV-2pp Infection in Human Lung Airway Chips



SARS-CoV-2pp

REPURPOSED Approved Drugs

(from computational pipelines)



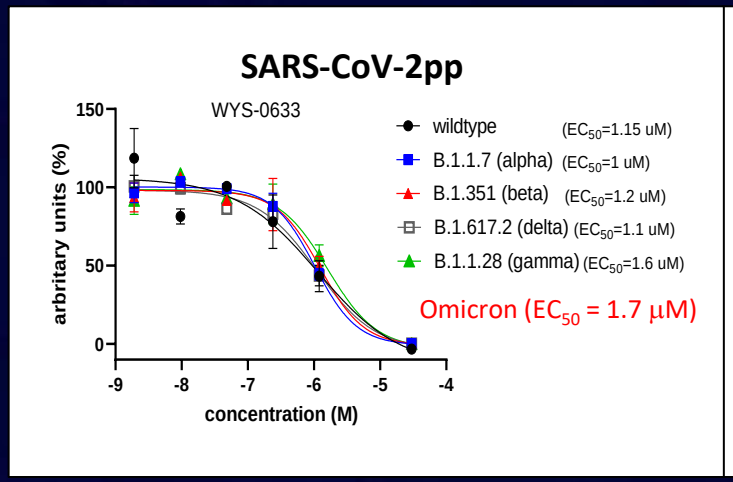
10 μM dose

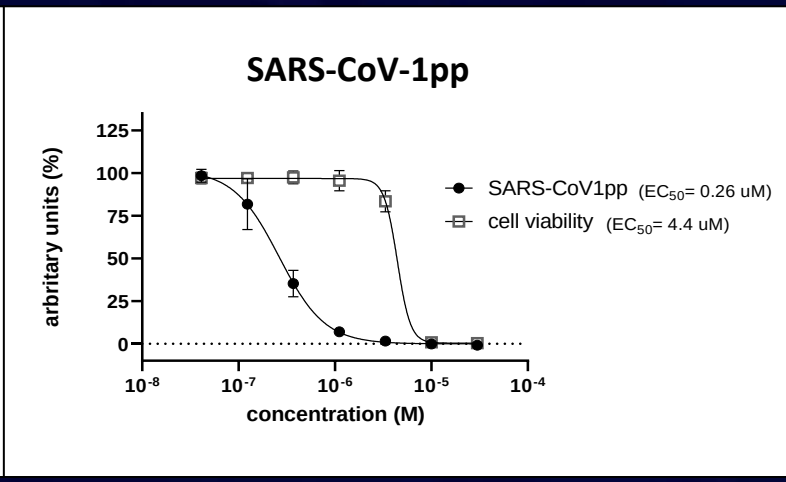
Wyss Institute

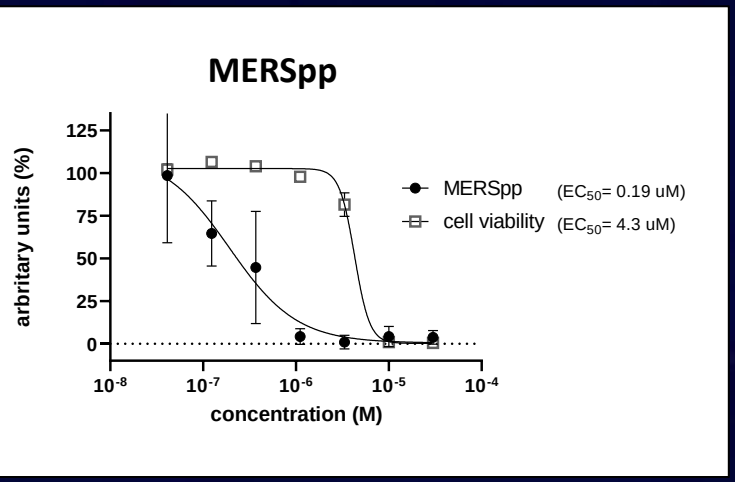
Funded by NIH. DARPA Covid-19, & Open Philanthropy

Novel Analogue Displays Broad Spectrum Activity

Pseudotyped Virus Assays:

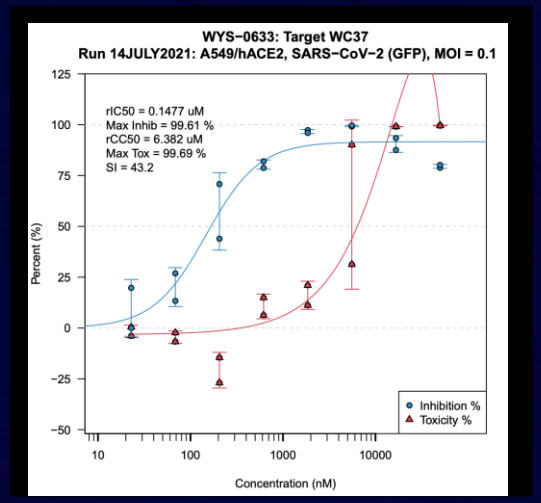






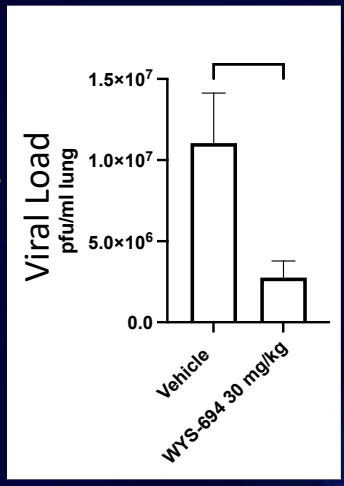
Potent Inhibition of Infectious SARS-CoV2 in Human Lung Cells

(with Matt Frieman, U. Maryland)



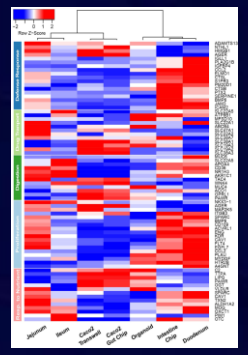
IC_{50} = 150 nM

Inhibition of Infectious SARS-CoV2 *In Vivo* (Mouse) using ORAL ADMINISTRATION



Wyss Institute

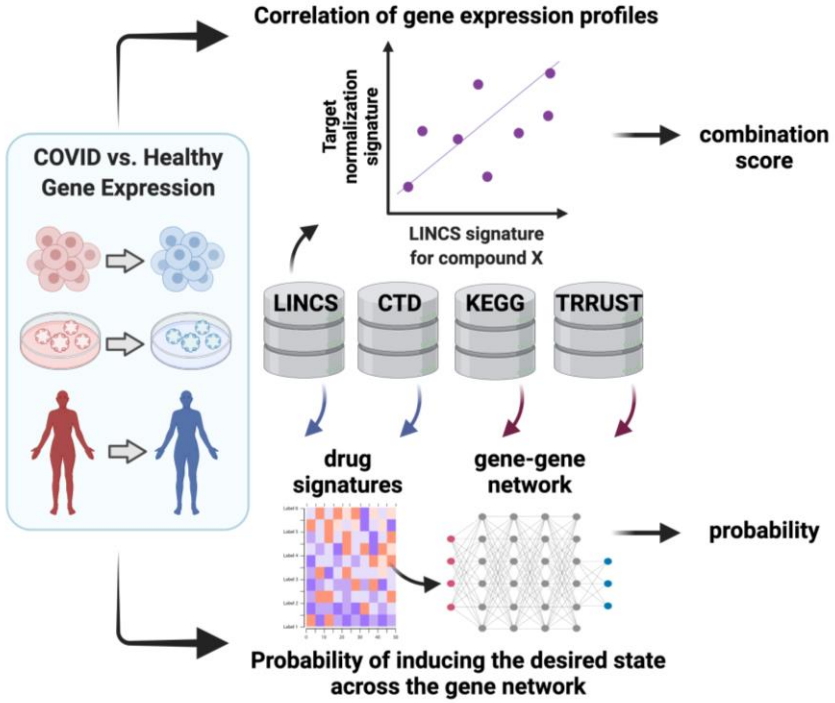
Funded by DARPA Covid-19



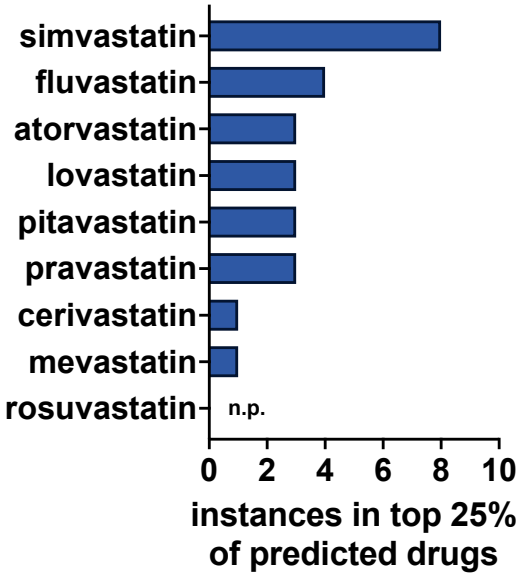
Computational AI Approach Predicts Specific Statins Protect Against COVID-19

(Sperry et al., *PLOS Comp. Biol.* 2023)

NemoCAD



NemoCAD Predictions



In Vitro Measurements

(SARS-CoV-2 infected Vero Cells)

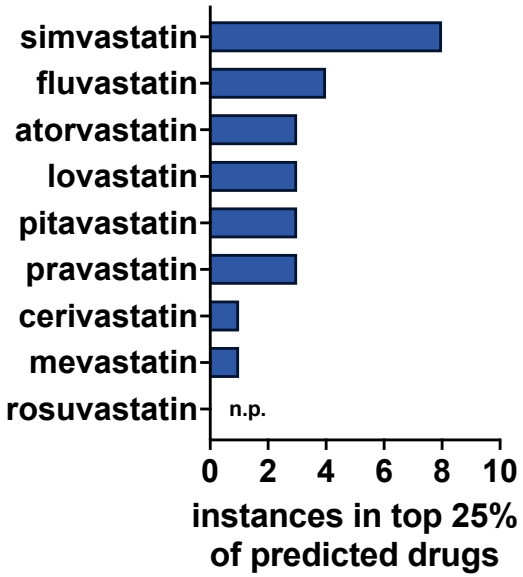
Statin	Max Inhibition (%)	IC50	Max Toxicity (%)	CC50
atorvastatin	24.4	1.9	92	5.4
fluvastatin	19	--	80.4	10.6
lovastatin	55.8	7.8	74.2	16.9
pitavastatin	19.1	1.6	83.6	0.3
pravastatin	21.7	--	4	--
simvastatin	**93.7**	0.8	78.5	6.5
simvastatin hydroxy acid	**57.0**	3.2	79.2	5.7

Funded by DARPA Covid-19

Retrospective Clinical Study Confirms Statin-Specific Increases in COVID-19 Patient Survival

(Sperry et al., *PLOS Comp. Biol.* 2023)

NemoCAD Predictions



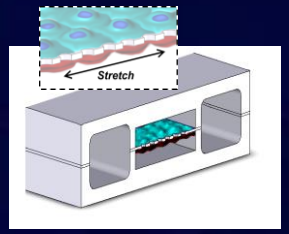
Retrospective Analysis of Clinical Database

(4,000 patients w/ Stanford U.)

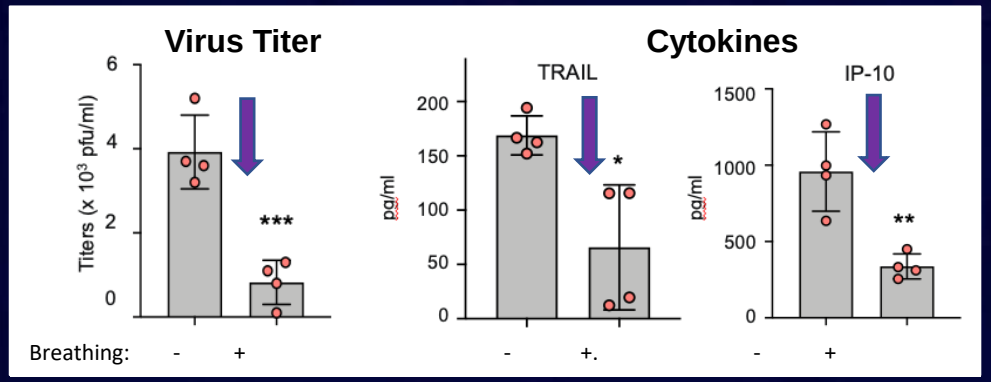
	treated patients		controls			
Statin (moderate dose)	Mortality rate, %	No. died/No. treated	Mortality rate, %	No. died/No. treated	Relative risk (95% CI)	Adjusted P-value*
Atorvastatin	16.1	431/2676	20.4	545/2676	**0.86 (0.80-0.93)**	6.24E-05
Lovastatin	21.4	15/70	19.1	134/700	1.14 (0.66-1.96)	0.76
Pravastatin	18.5	71/383	23.1	883/3830	0.78 (0.61-1.00)	0.05
Rosuvastatin	13.1	53/404	21.0	850/4040	**0.59 (0.45-0.78)**	9.61E-05
Simvastatin	19.5	153/784	23.3	914/3920	**0.83 (0.70-0.97)**	0.02

COVID-19 Drug Repurposing Enabled by Mechanistic Studies in Human Lung Chips

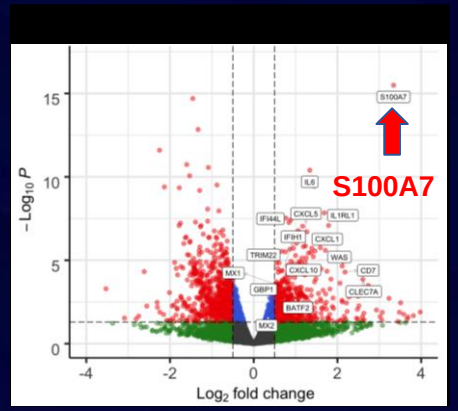
(**HAIQING BAI** et al., *Nature Commun. 2022*)



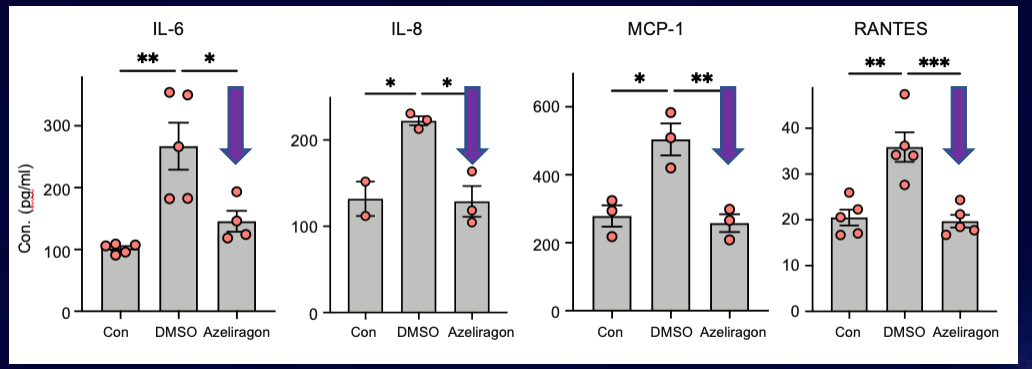
Breathing Motions Suppress Viral Infection & Inflammation



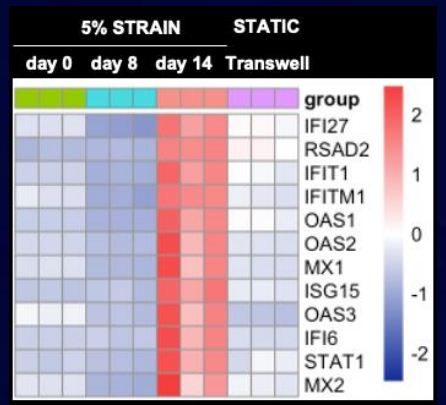
Gene Expression + vs - Breathing



AZELIRAGON Drug Prevents Viral Infection-Induced Inflammation



Breathing Activates Innate Immunity



Interferon-Stimulated Genes

- ***S100A7 Binds RAGE***
- **AZELIRAGON *is a RAGE Inhibitor Drug***

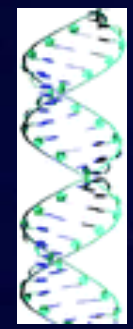
Data included in IND application to FDA by Cantex Pharma to start COVID-19 Trials

WYSS INSTITUTE

Discovery of Broad Spectrum Antivirals

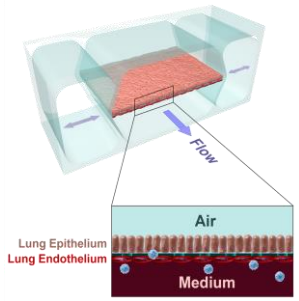
Type I/III Interferon-Inducing Short Duplex RNAs

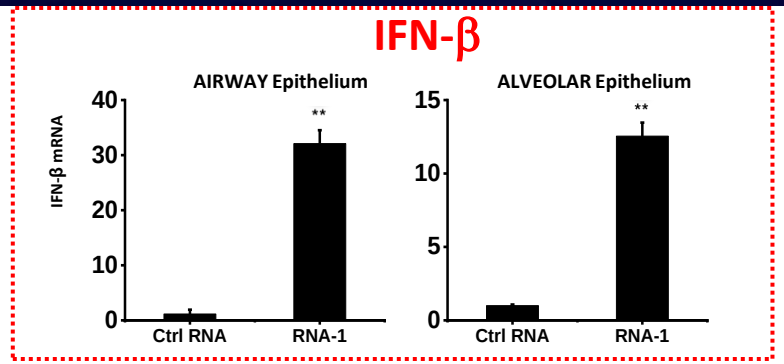
(Si et al., *Mol. Ther. Nucl. Acid* 2022)



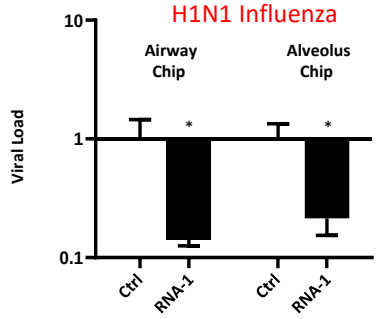
In Vitro:

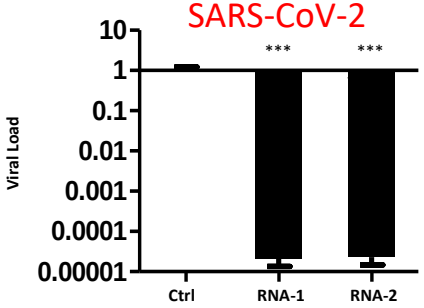
Potent Induction of IFN- α, β, and λ

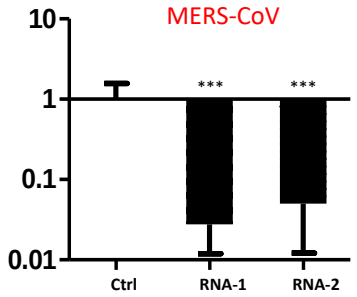


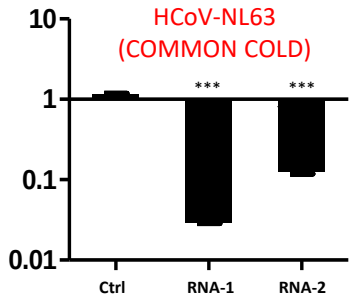


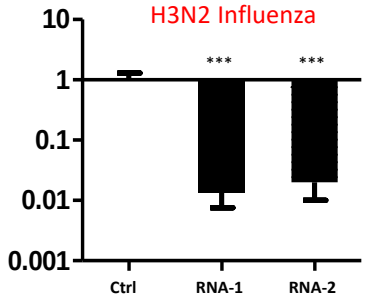
Viral Load







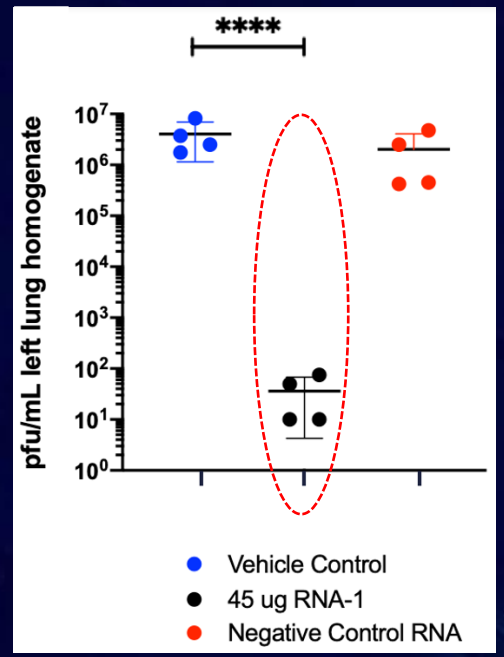




Viral Load

In Vivo:

SARS-CoV-2 Infection in Mice



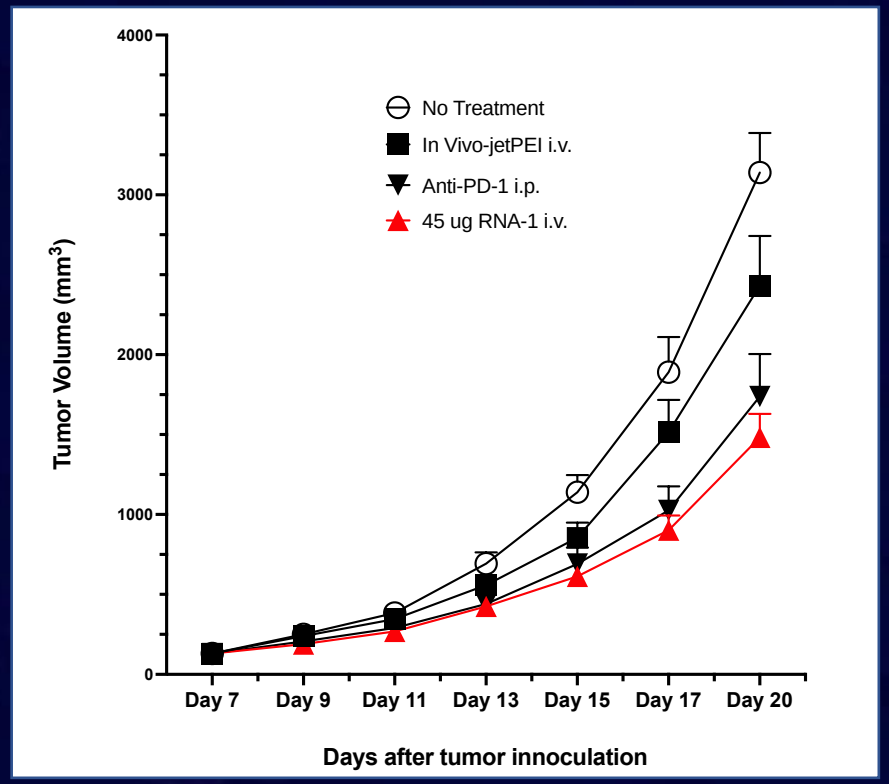
10,000 to 100,000-fold REDUCTION in Virus #

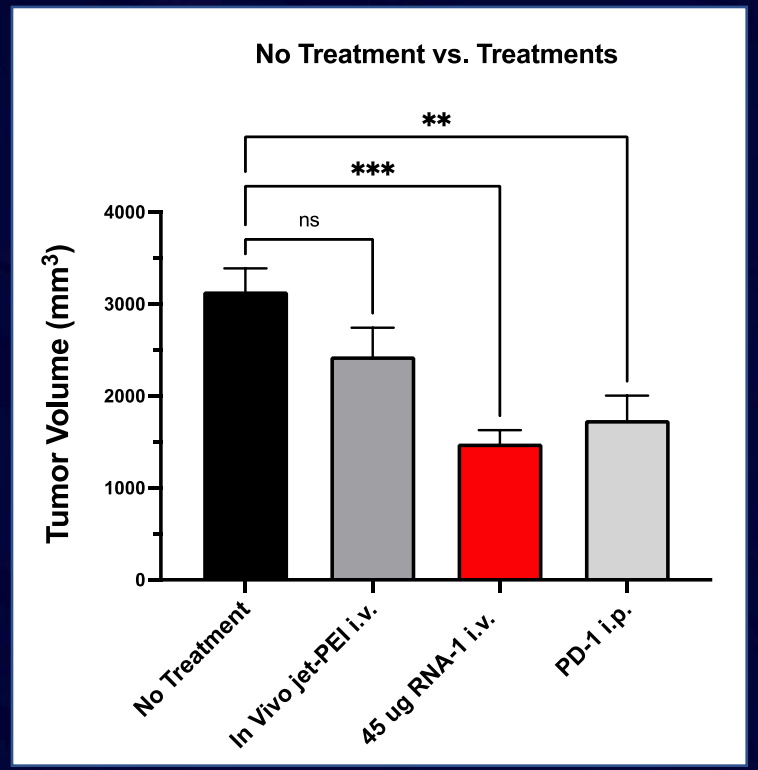
Wyss Institute

dsRNA Innate Immunotherapeutics are Disease Agnostic

Short Duplex RNAs also Inhibit Cancer Growth

Daily I.V. administration in B16-ova Melanoma Model





Daily treatment was well tolerated

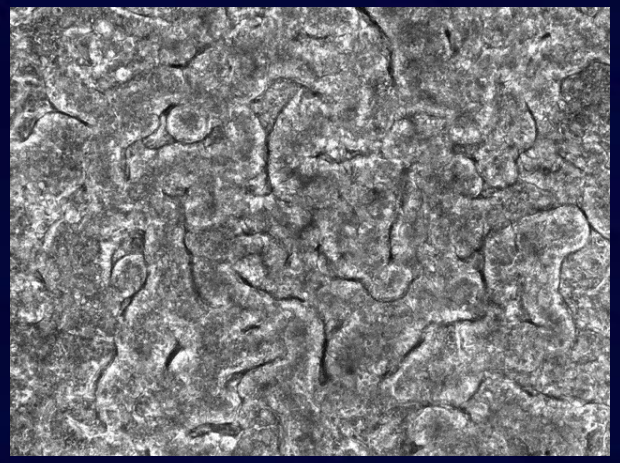
(no effect on body weight or clinical signs)

Wyss Institute

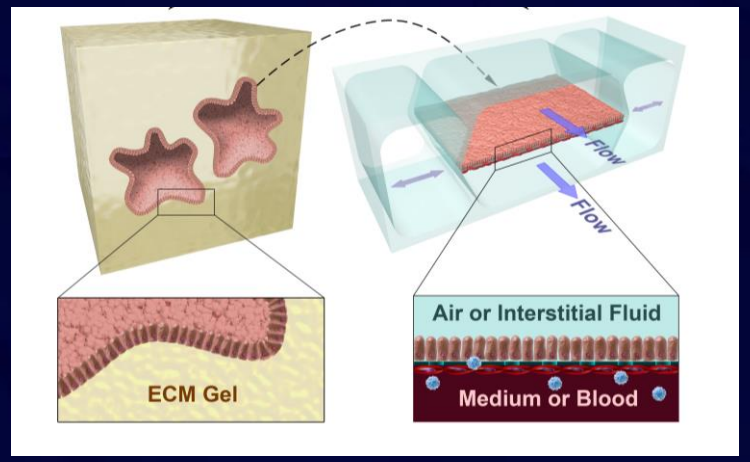
Human Intestine Chip

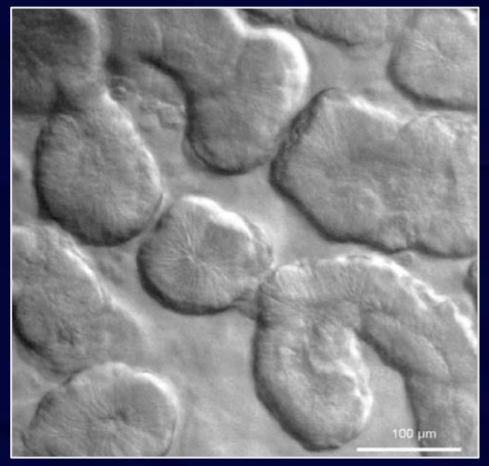
(HYUN JUNG KIM et al., *Lab Chip* 2012, *Integ. Biol*. 2013 &*PNAS* 17; MAGDA KASENDRA et al., *Sci. Rep*. 2018; ALEXANDRA SONTHEIMER-PHELPS et al., *Cell Mol. Gastro. Hep. 2019*)

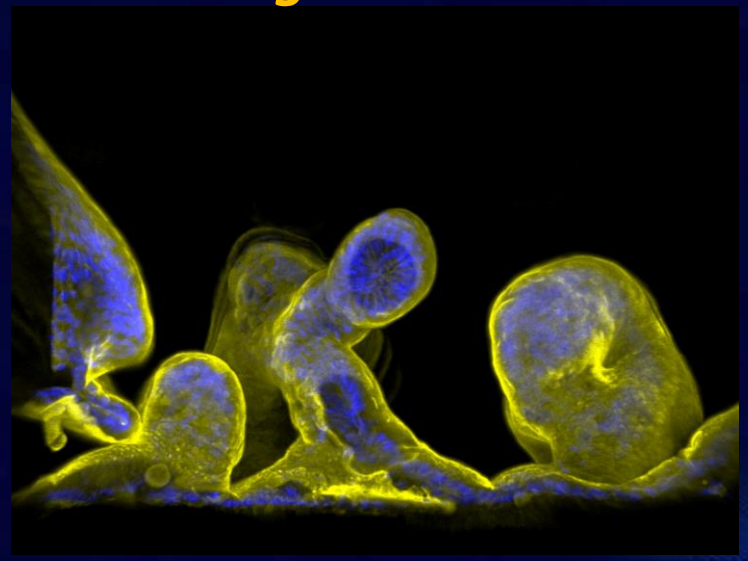
INTESTINAL VILLI FORMATION on-chip



PRIMARY Intestine Chips using cells from Patient-Derived Organoids:







DUODENUM Chip

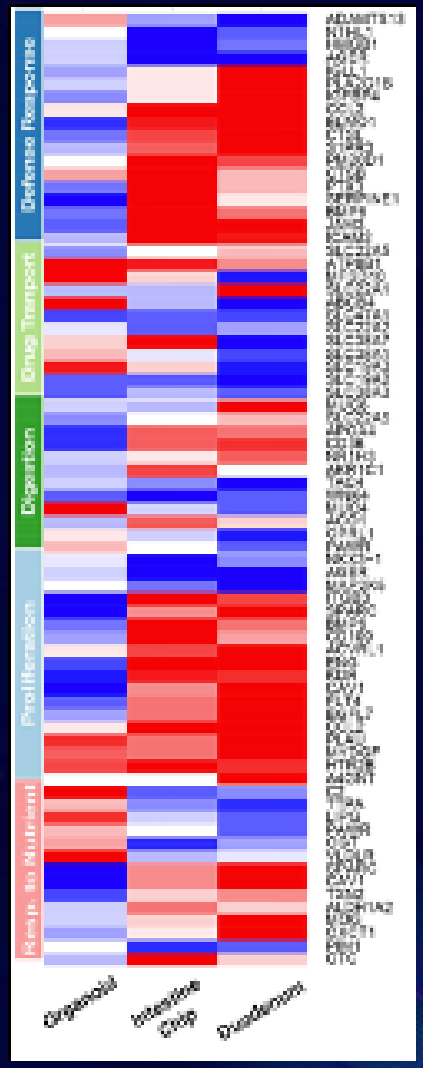
WYSS INSTITUTE

Intestine Chip More Closely Mimics Duodenum than Duodenal Organoids

(MAGDA KASENDRA et al. *Sci. Rep.* 2018)

Human Intestine Chip
(lined by cells from DUODENAL Organoids)

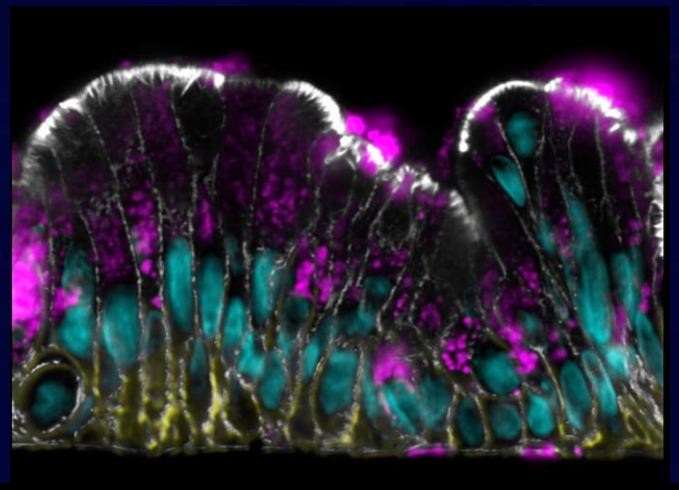
Transcriptomic Analysis:



Wyss Institute

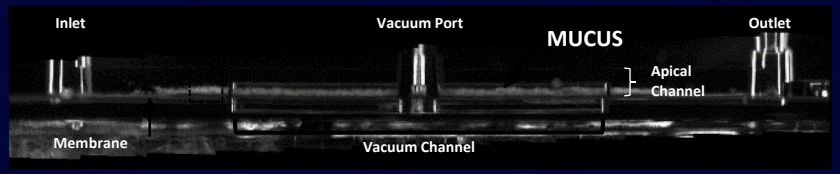
Human Colon Chip Forms a Mucus Bilayer

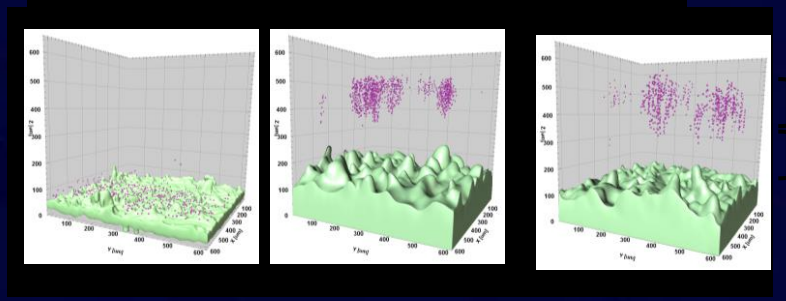
(Sontheimer-Phelps et al., *Cell Mol. Gastro. Hepatol.* 2019)



Chip
Cross-Section

SIDE VIEW of Whole Chip

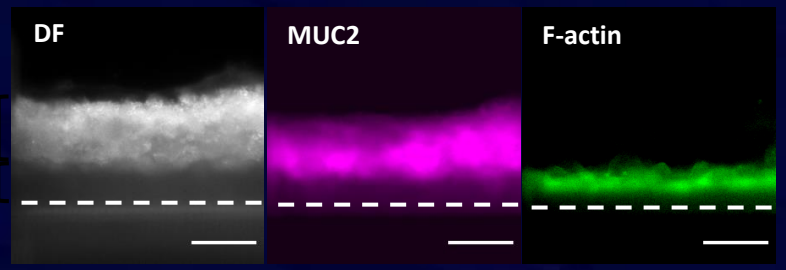




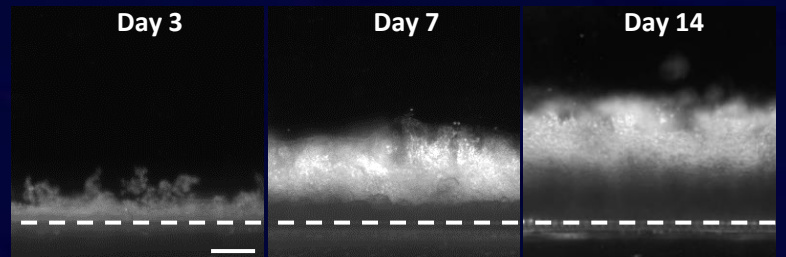
Penetrable MUCUS Layer

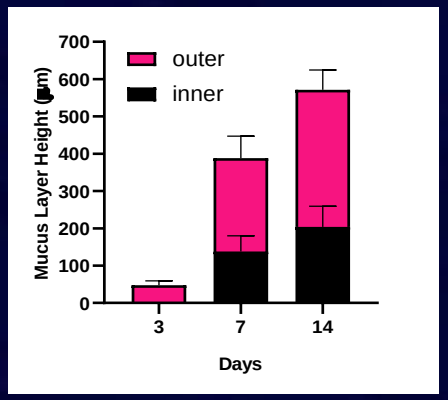
NON-Penetrable MUCUS Layer

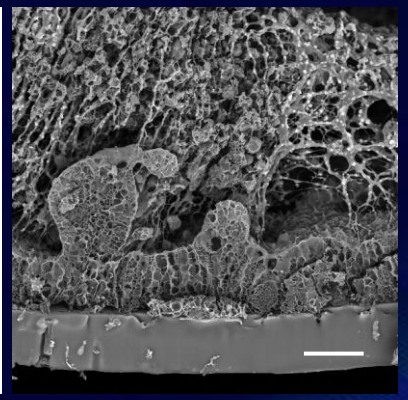
Mucus
Cells



Live
Imaging





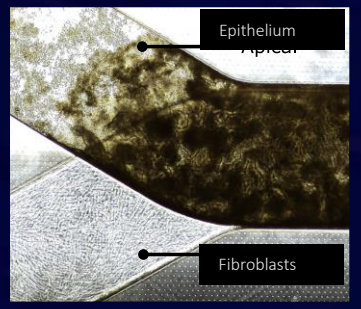


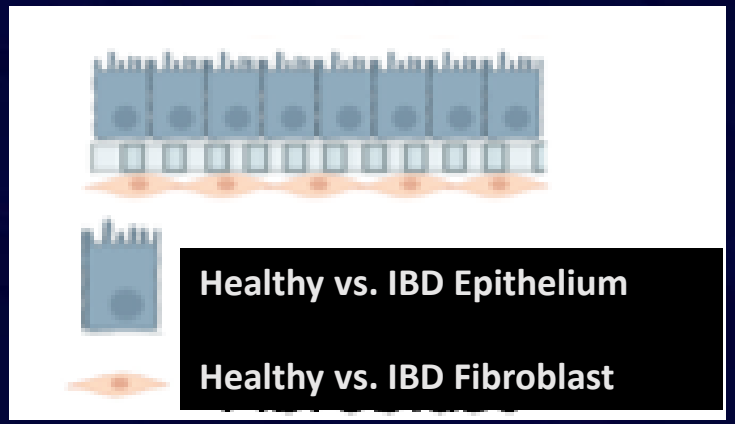
WYSS INSTITUTE

Effect of Stromal Microenvironment in Inflammatory Bowel Disease (IBD) Colon Chips

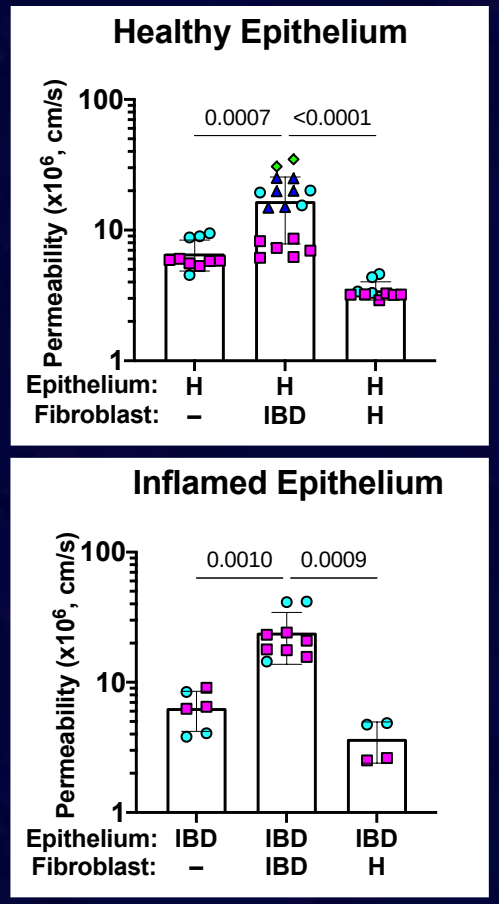
(Ozkan et al., - in preparation)

Epithelium-Stromal Tissue Recombinants On-Chip

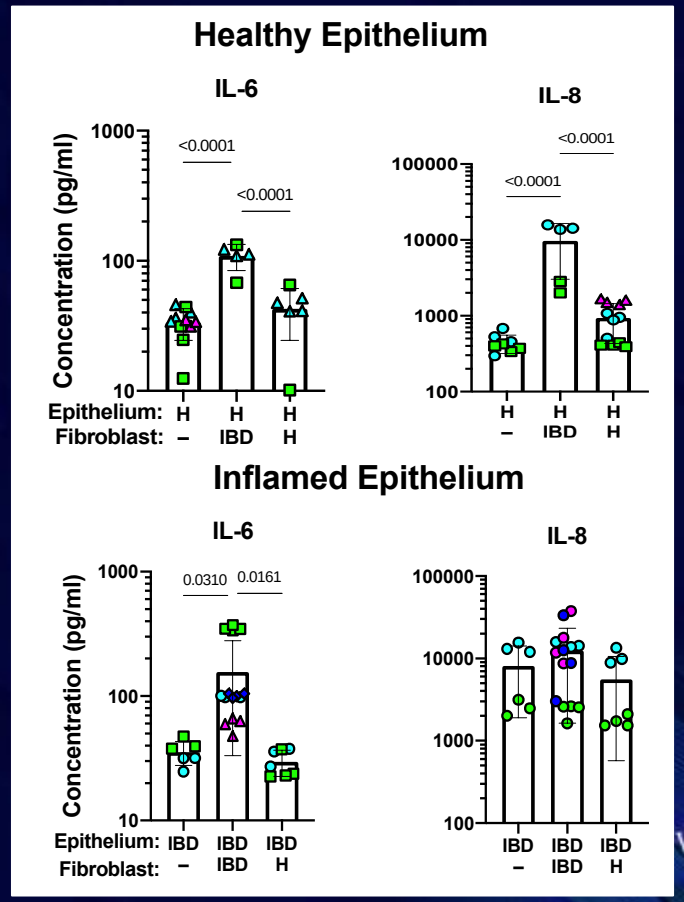




IBD Stroma
DISRUPTS Barrier Integrity



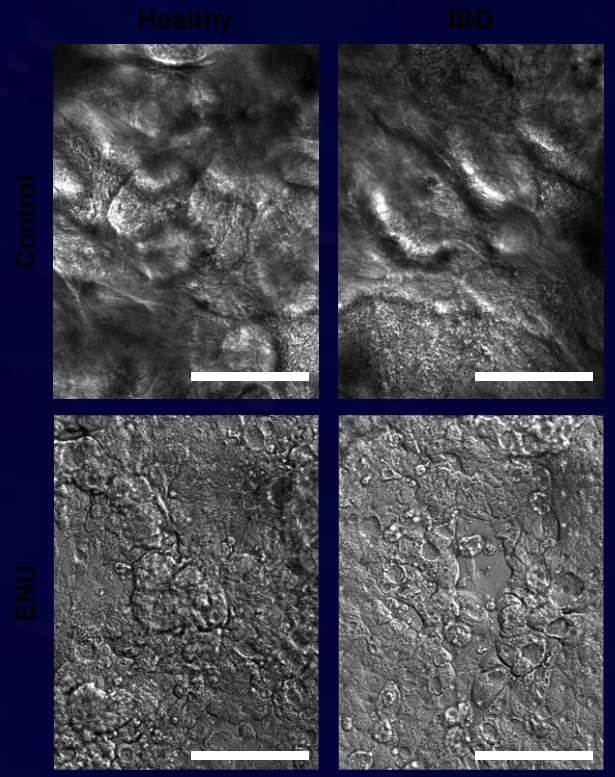
IBD Stroma
INCREASES Inflammatory Cytokines

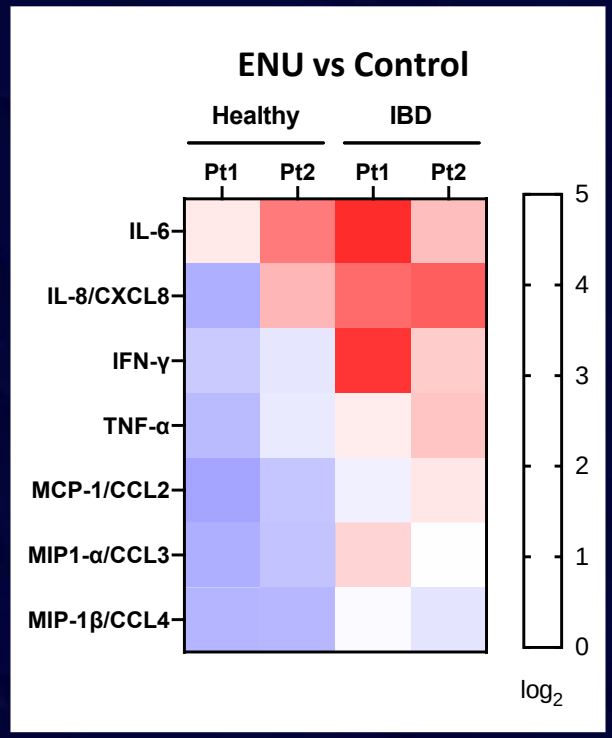


Wyss Institute

Modeling Carcinogen Exposure in Colon Chips

ENU carcinogen stimulates increased inflammation in IBD chips





- N-ethyl-N-nitrosourea (ENU) is a highly potent mutagen
- Healthy and IBD colon-chips were exposed to ENU for 3 weeks

ENU Only Induces Mutations in IBD Colon Chips

(w/ Stuart McDonald, Queen Mary University of London)

DNA copy number only increased in IBD Colon Chips

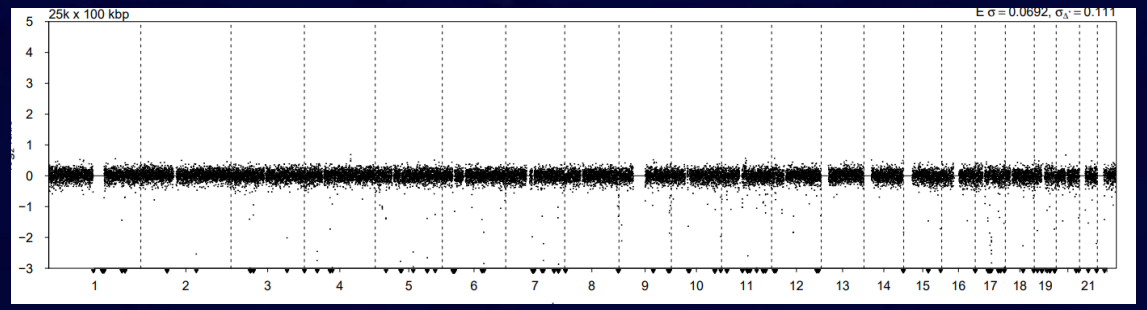
IBD Colon Chip - Patient 1

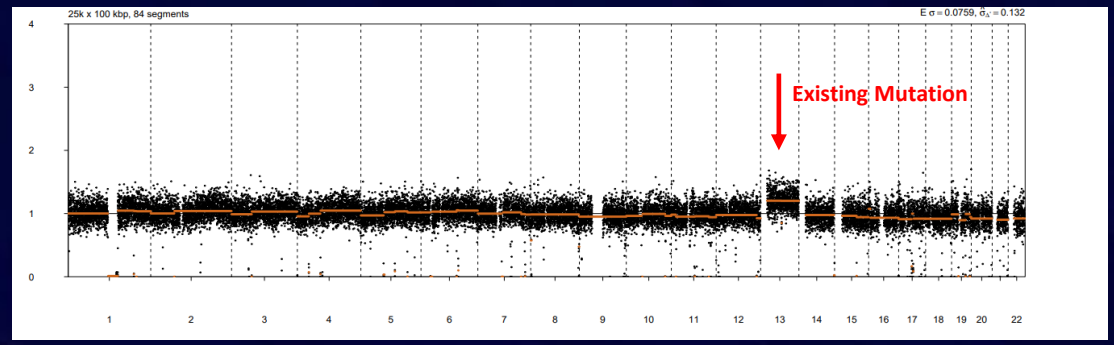
IBD Colon Chip - Patient 2

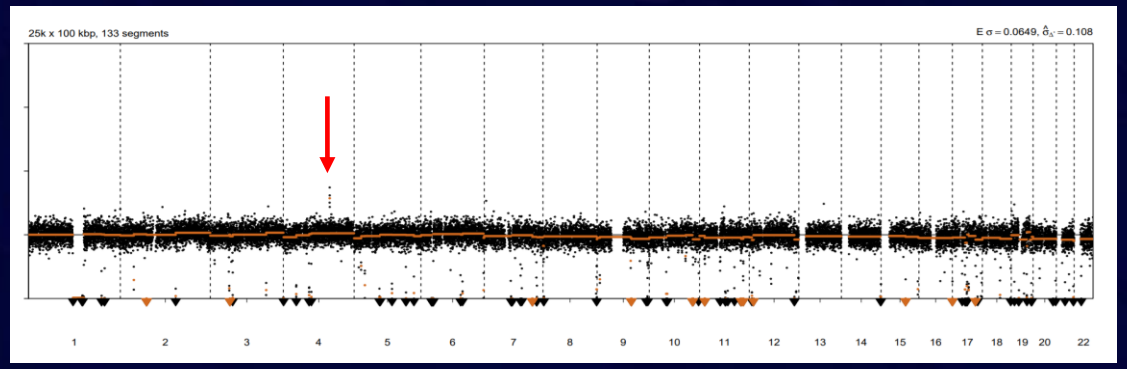
Control

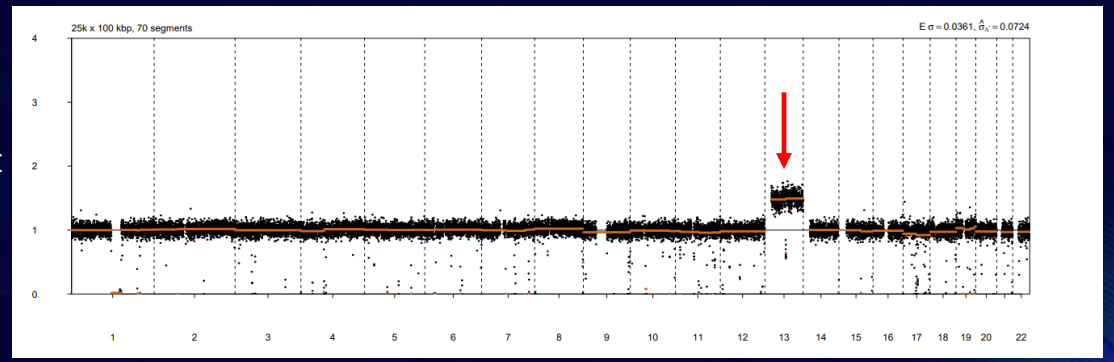
ENU (3 weeks)

DNA Copy Number







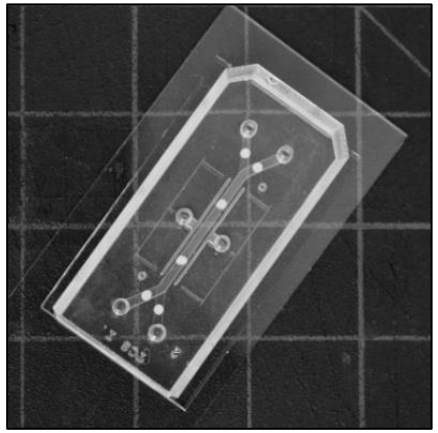


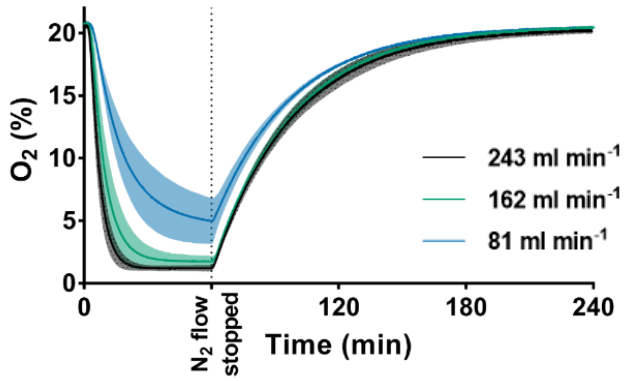
Wyss Institute

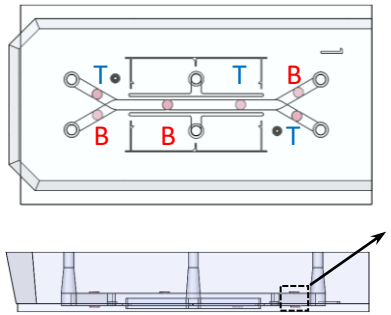
Integration of Aerobic & Anaerobic Gut Microbiome

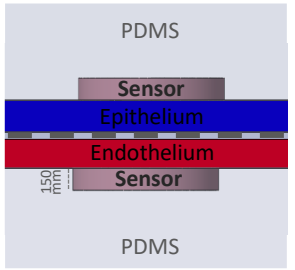
(Jalili-Firoozinezhad et al, *Nature Biomed.Engin.* 2019)

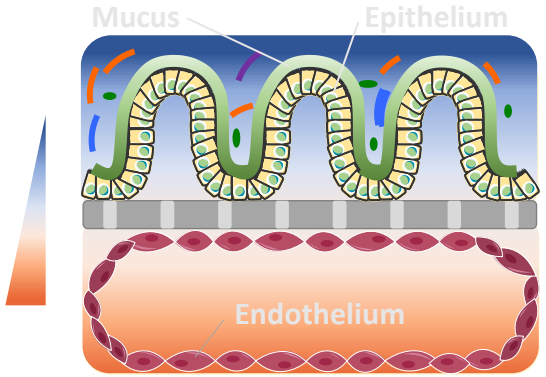
Generation of a Hypoxia Gradient On-Chip

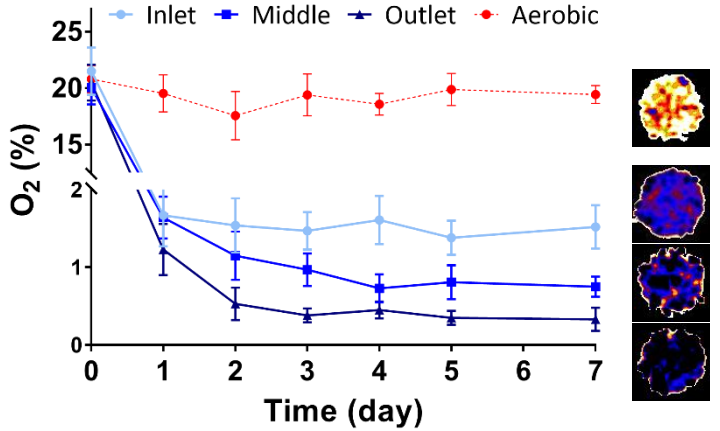








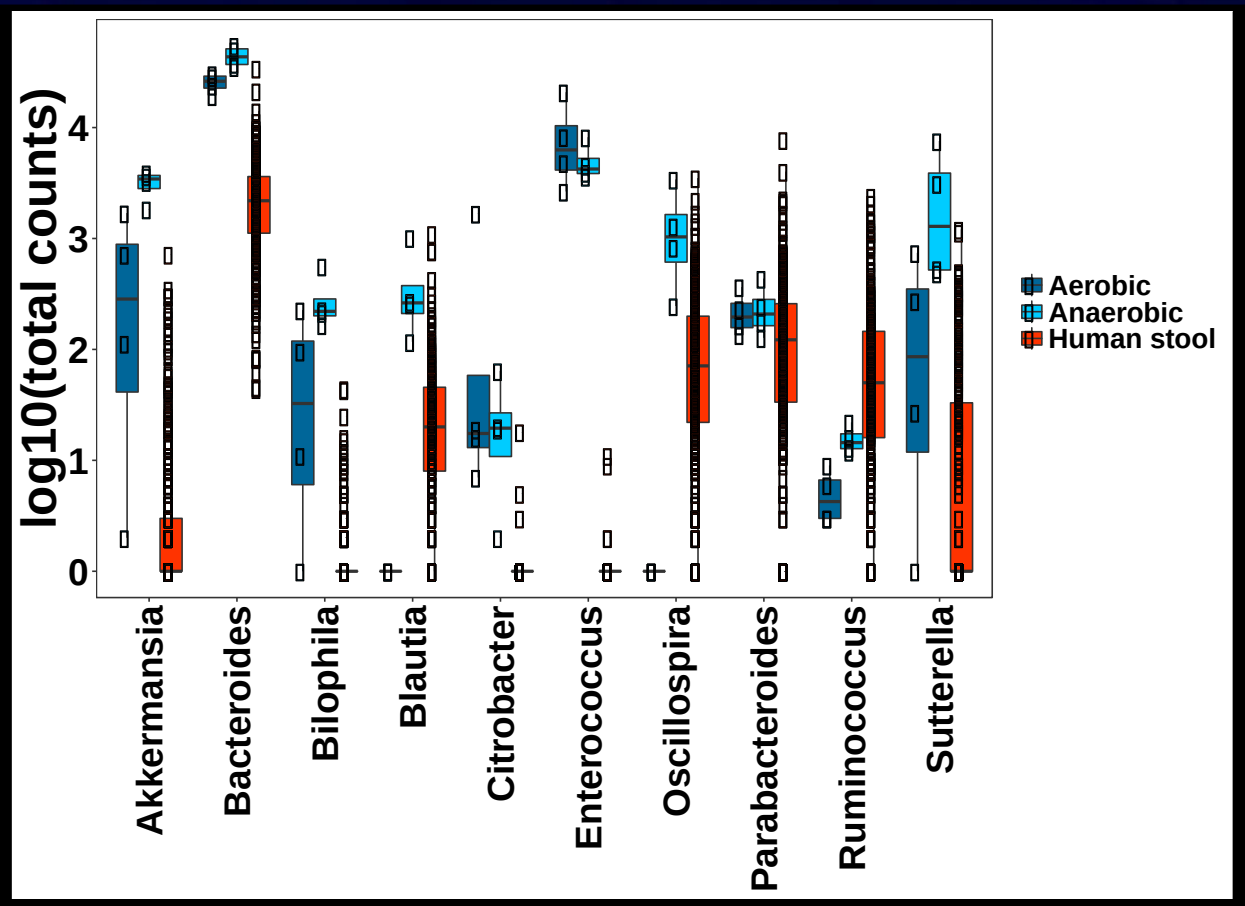




Intestine Chip Maintains Microbiome Complexity Similar to Human Stool

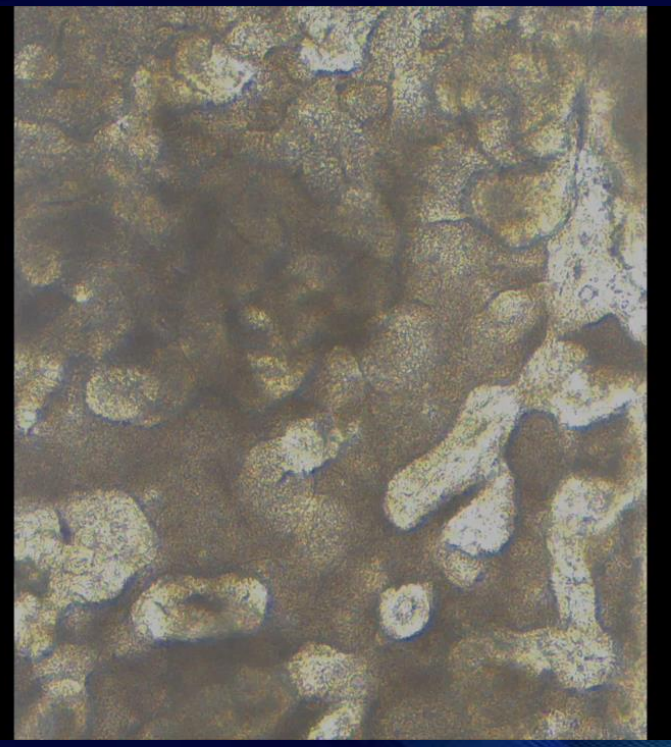
Bacteria on Mucus On-Chip

Includes Aerobes & Anaerobes



200 types of bacteria from 11 different genera

Preterm Infant Microbiome
3 days on-chip



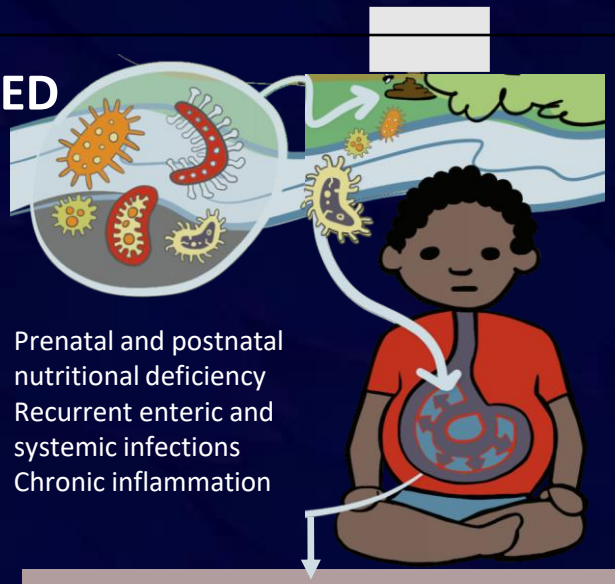
Real-Time Video

Wyss Institute

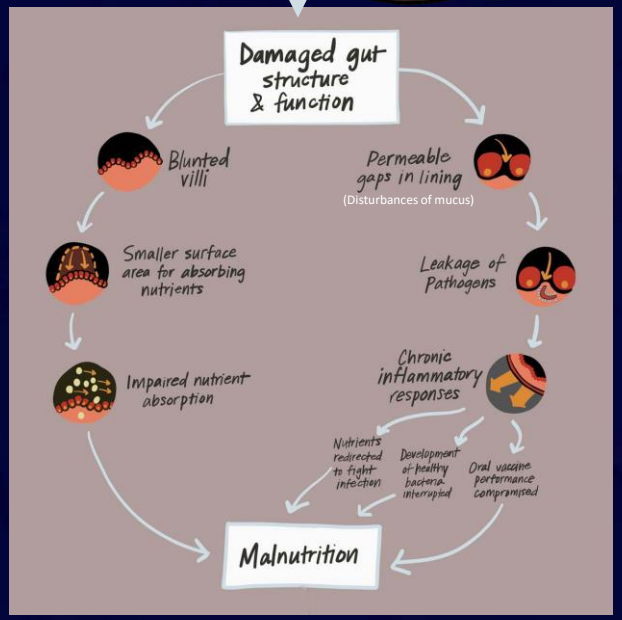
Funded by GATES Foundation

Environmental Enteric Dysfunction (EED) Chip

EED



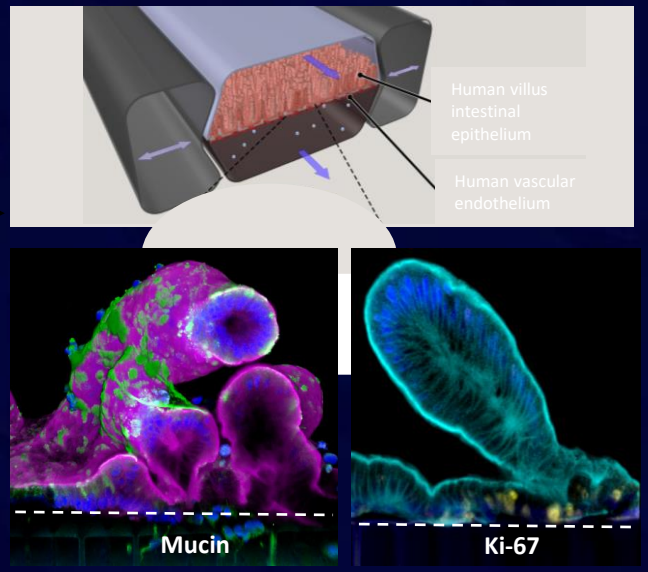
- Prenatal and postnatal nutritional deficiency
- Recurrent enteric and systemic infections
- Chronic inflammation



PRIMARY SMALL INTESTINE CHIP

(Sci Rep. 2018; 8:2871)

Seeding
Top – Intestinal Epithelial cells
Bottom – Intestinal microvascular cells

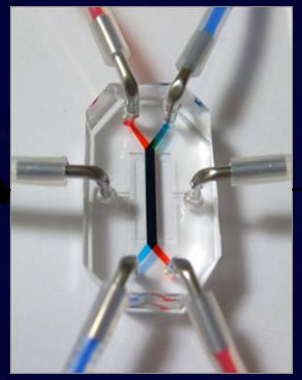


FORM:
- Villus-like structures
- Multi-lineage differentiation

FUNCTION:
- Mucus
- Epithelial barrier
- Digestion
- *In vivo*-like transcriptome

EED CHIP

- Malnutrition (-N/-T)
- Dysbiosis
- Pathogen Exposure
- Immune Response



Healthy or EED Derived Primary Epithelial Cells

Human preclinical model with features of EED useful for:
- Contributory analysis
- Biomarker development
- Therapeutic screening

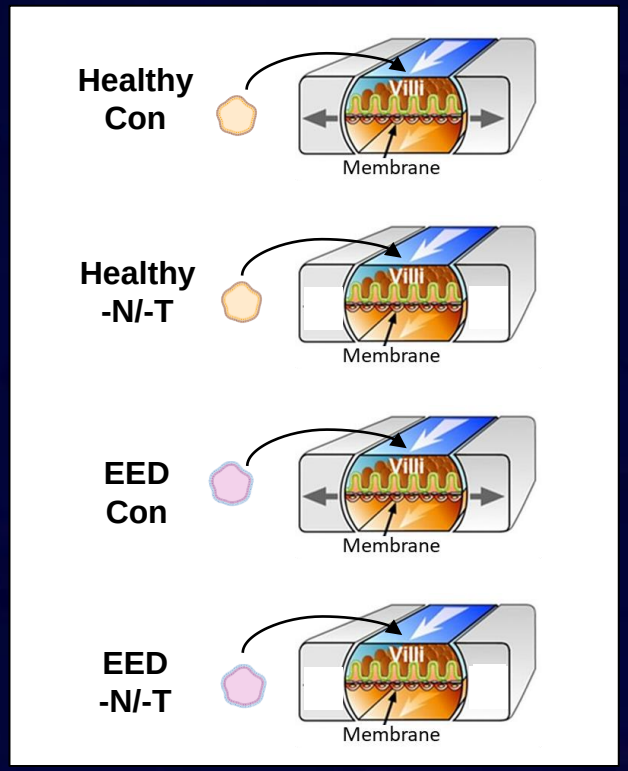
Wyss Institute

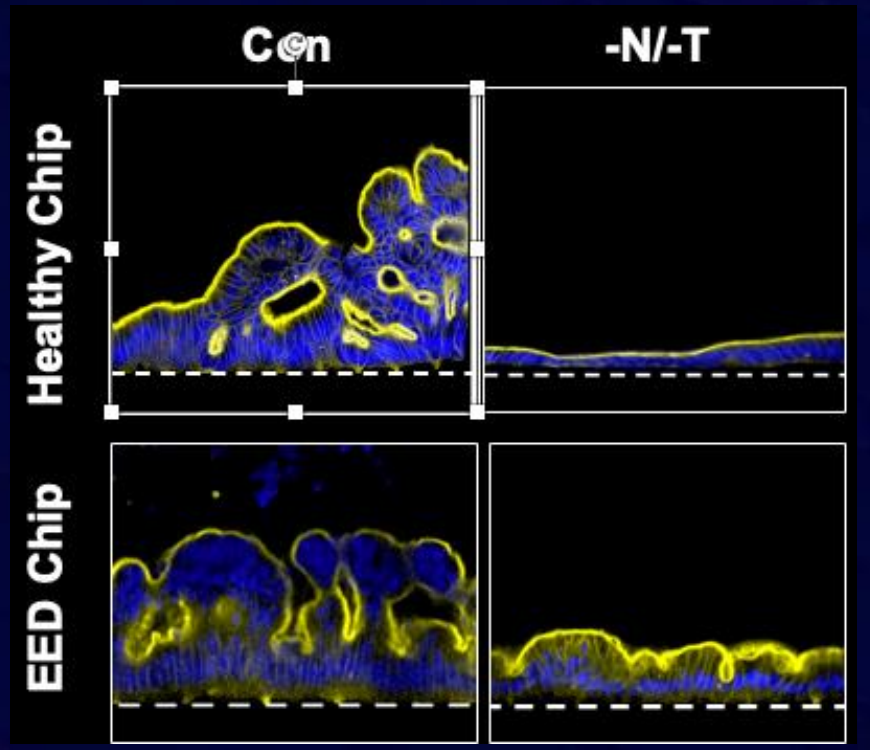
Funded by GATES Foundation

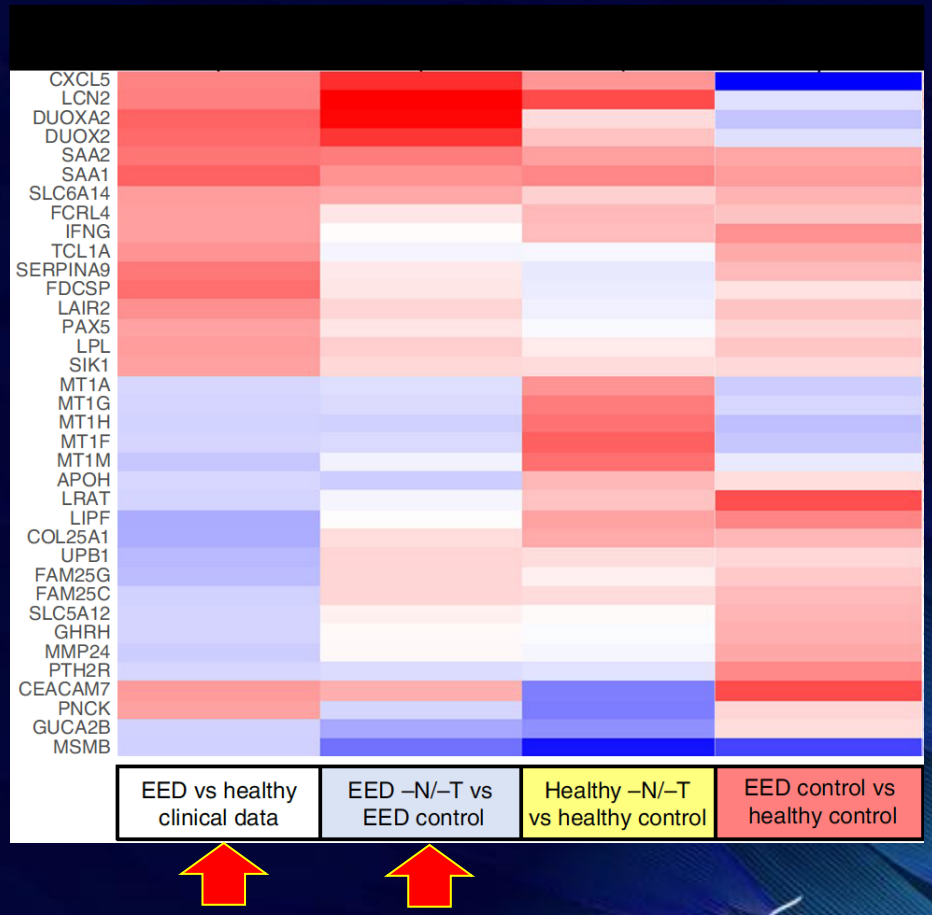
Intestine Chips with EED Patient Cells + Nutritional Deficiency Mimic Clinical EED Signature

(AMIR BEIN & CECILY FADEL et al, *Nature Biomed. Engin. 2022*)

EED Patient Duodenal ORGANOID-derived Epithelium On-Chip







-N/-T = Medium DEPLETED of Nicotinamide & Tryptophan

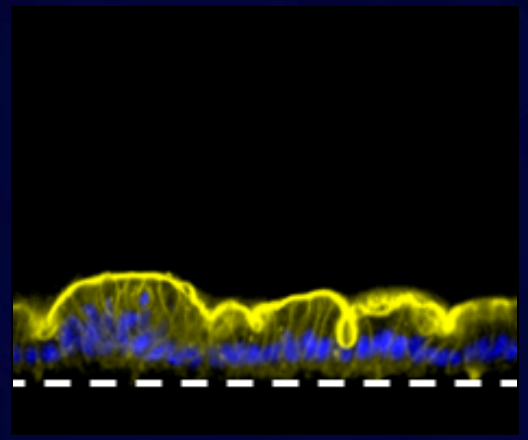
Wyss Institute

Effect of Living Microbiome

Patient Intestine Chip + Patient Microbiome reveal EED-Associated Inflammation and Barrier Compromise

(consortia provided by Jeff Gordon, Wash. U.)

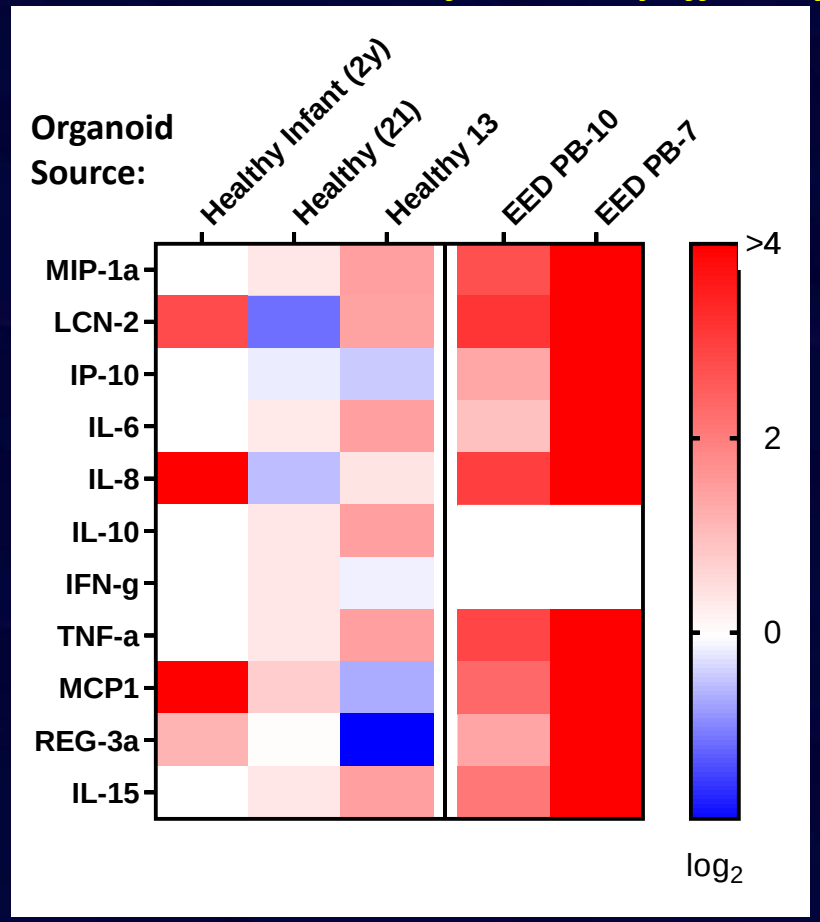
EED Chip

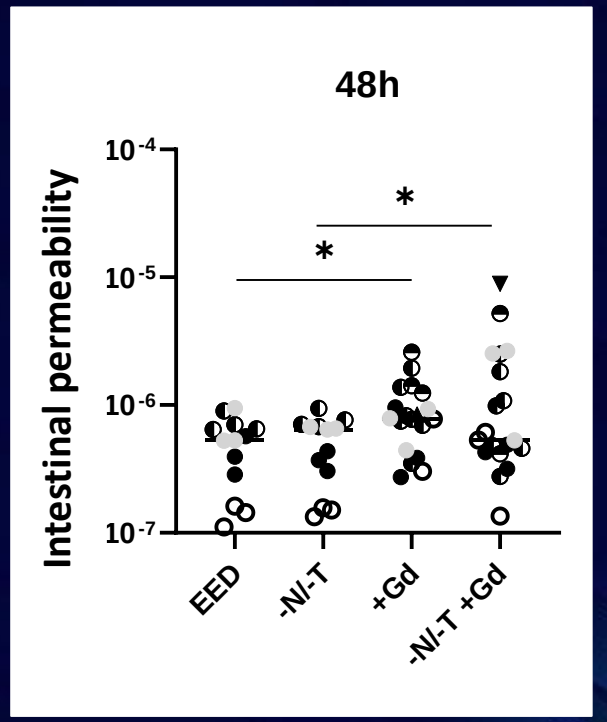


EED microbiome

22 different commensals

Inflammatory Effects of EED Microbiome





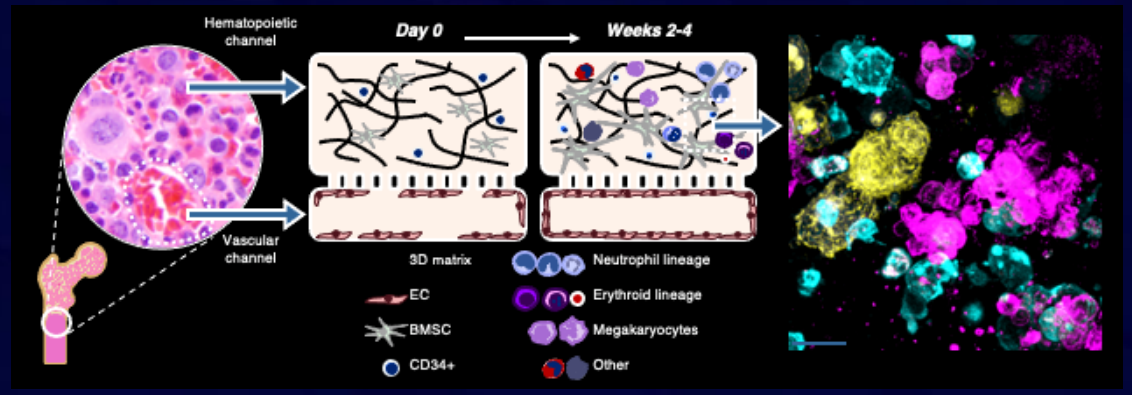
Wyss Institute

Other Key Goals

- To predict responses to drugs using *clinically relevant dose exposures*
- To develop *personalized disease models* for individual patients
- To create models that replicate *complex immune responses*
- To carry out a *head-on comparison with existing animal models*

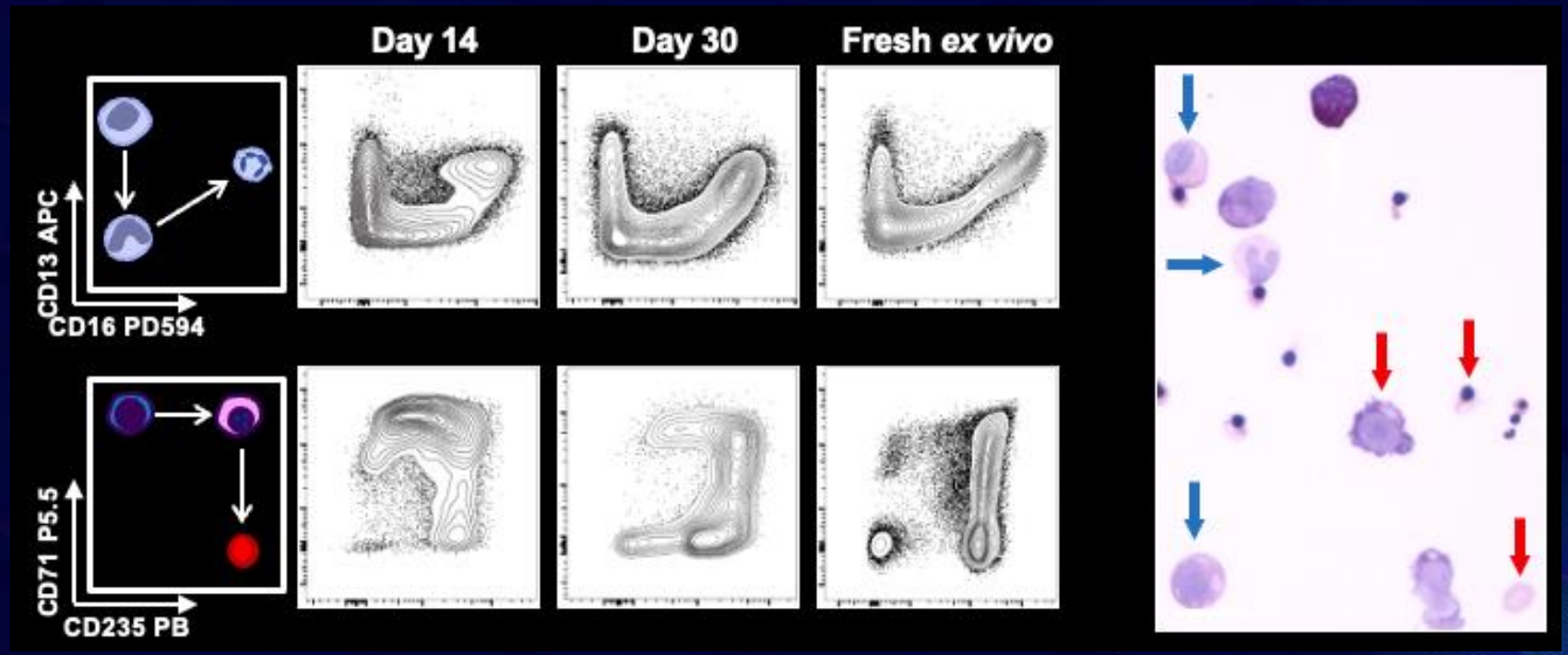
Human Bone Marrow Chip

(DAVID CHOU et al., *Nature Biomed. Engin. 2020*)



Neutrophil maturation

Erythroid maturation

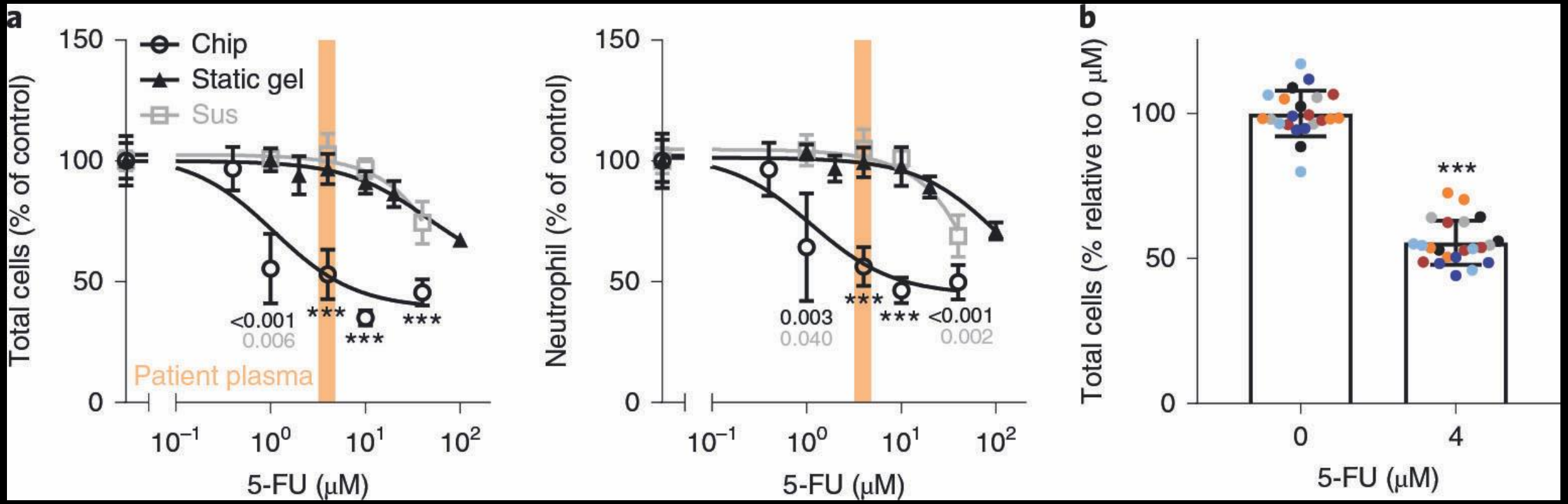


Wyss Institute

Funded by the FDA

Recapitulation of 5-FU Marrow Toxicity at Human-Relevant Drug Exposures

2 Day infusion as in patients (plasma concentrations ~ 3.2 - 4.8 µM)



Replicating Human Toxicities with Clinical Drug Exposures

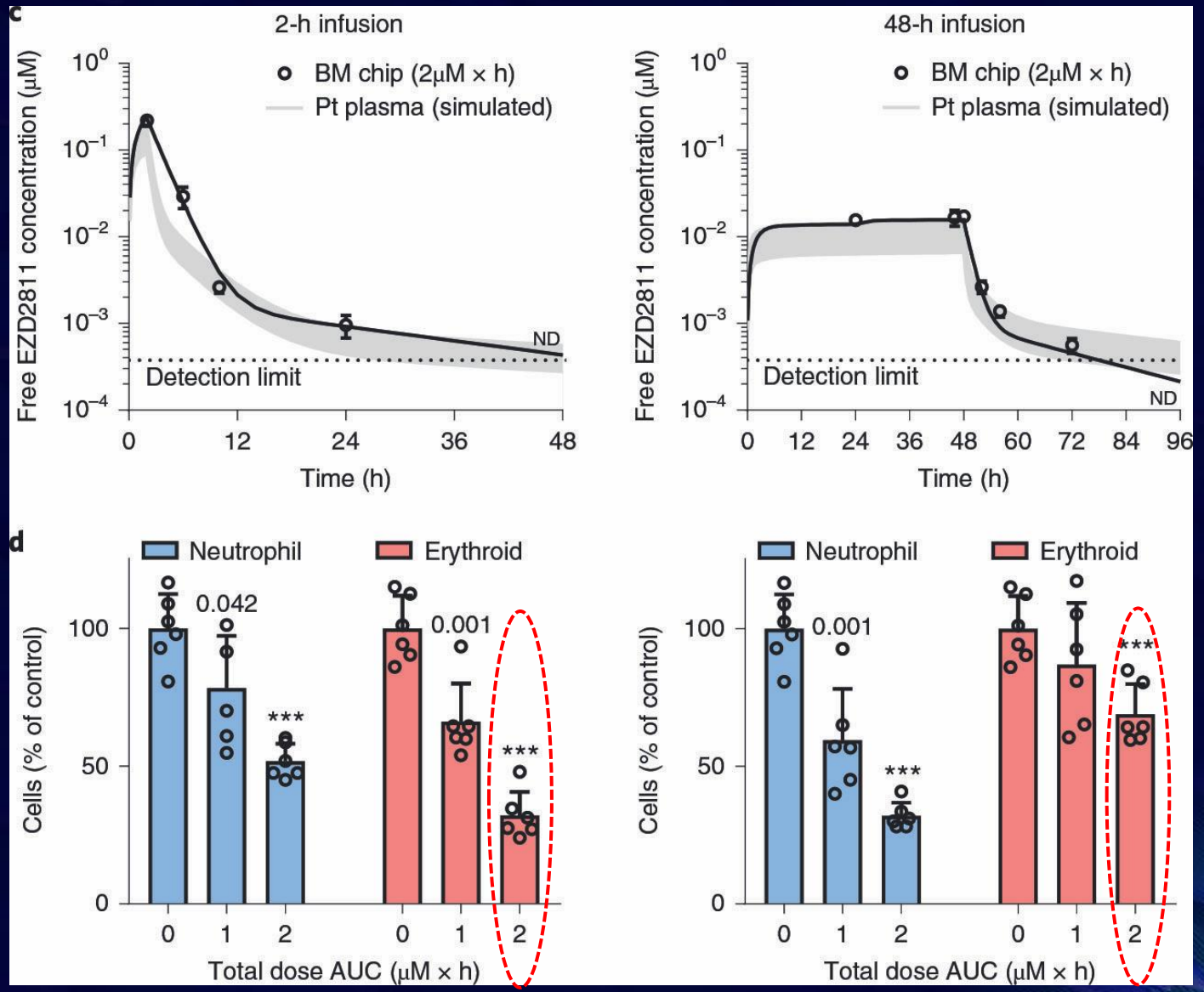
(collaboration with Astrazeneca)

Clinical Observation:	2h dosing	48h dosing
	Neutropenia	Neutropenia
	Anemia	

Clinical Drug Exposure Profiles (PK) Recreated On-Chip

Chip Toxicity Results Replicate Clinical Findings with same Dosing

(Not observed in Suspension Cultures)



WYSS INSTITUTE

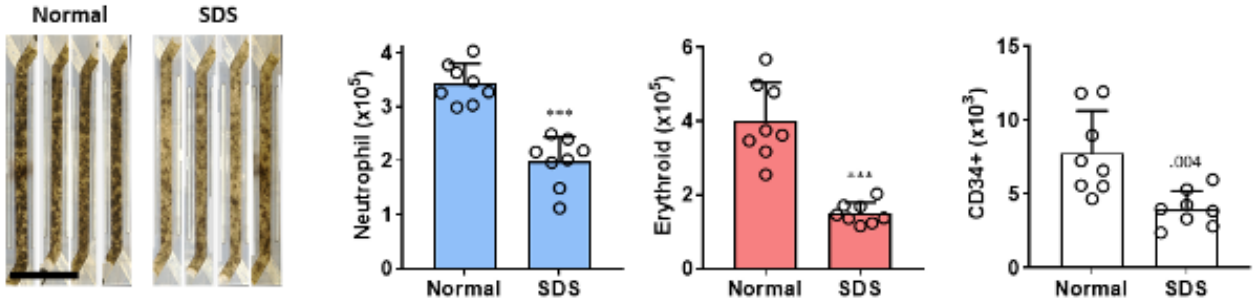
Shwachman-Diamond Syndrome Chip

(with Akiko Shimamura and Carl Novina, BCH & DFCI)

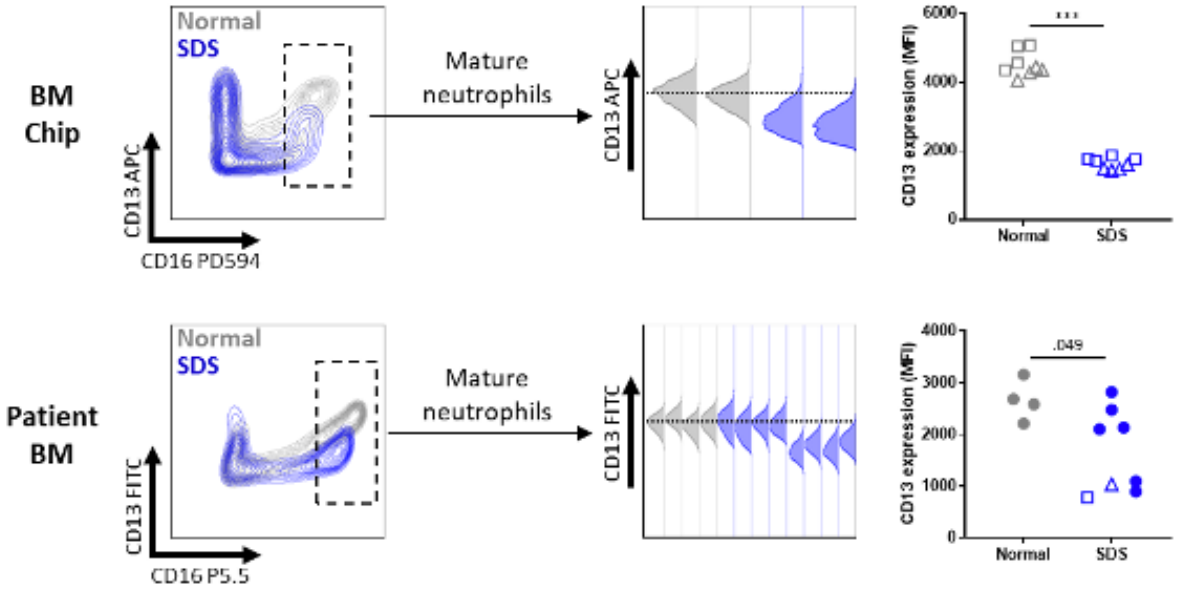
Using Patient Cells

Results correctly predict undescribed neutrophil maturation abnormality

Impaired neutrophil + erythroid development in Shwachman-Diamond syndrome

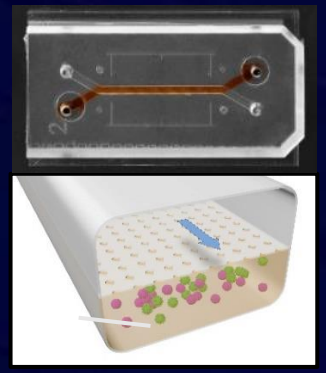


Altered neutrophil maturation in BM chip is validated in patient BM aspirates

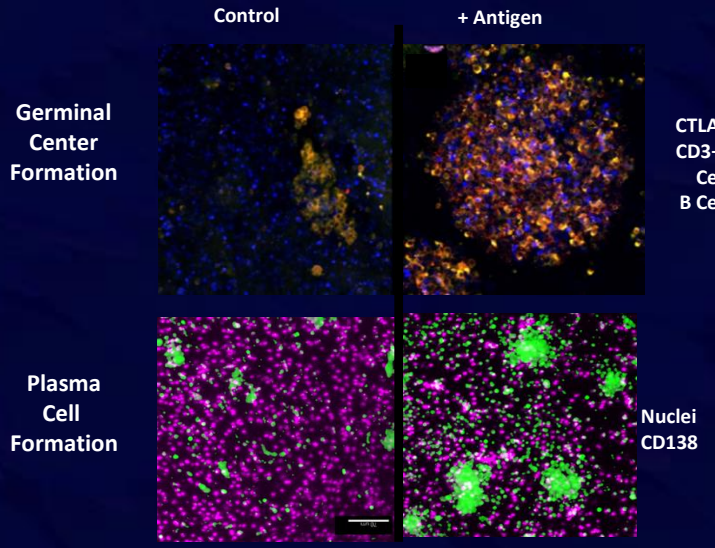


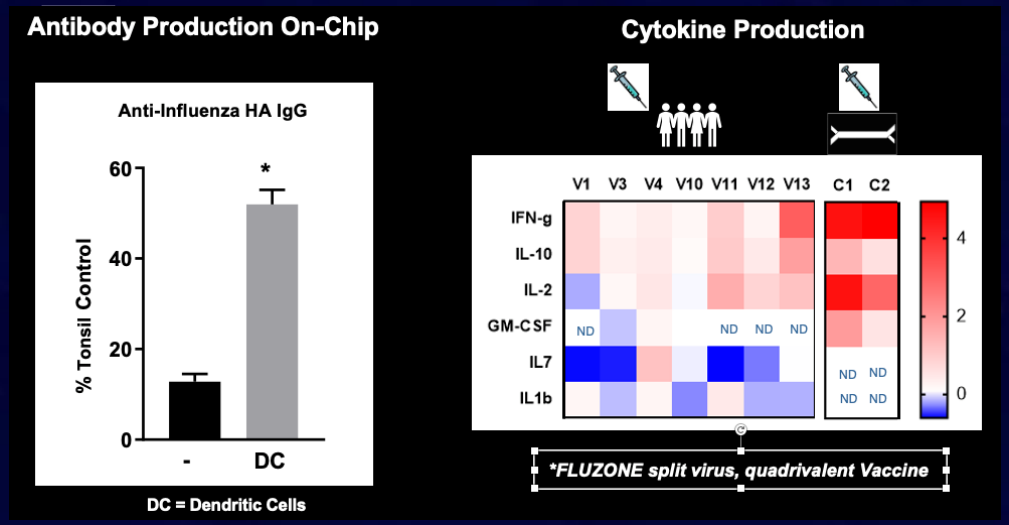
Human Lymphoid Follicle Chip

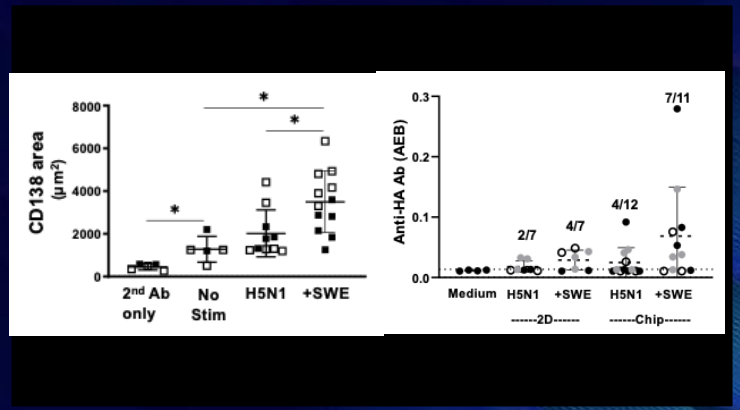
(GIRIJA GOYAL et al., ***Adv. Sci. 2022***)



+ Germinal center formation
+ Expansion with antigen stimulation & expression of correct biomarkers
+ Plasma cell formation
+ Antibody Class Switching
+ Vaccination response with Ag-specific IgG and Cytokine production in vitro
+ Now being used to test & validate new Adjuvants with GATES Foundation & Pharma



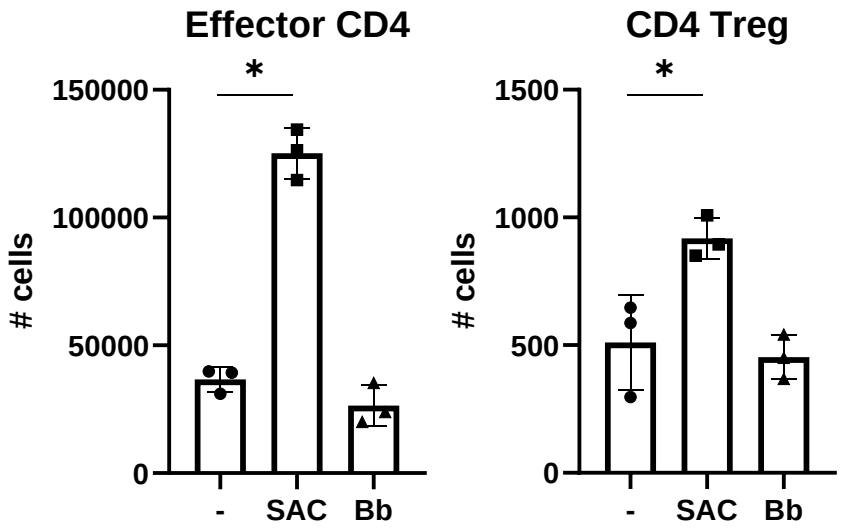




WYSS INSTITUTE

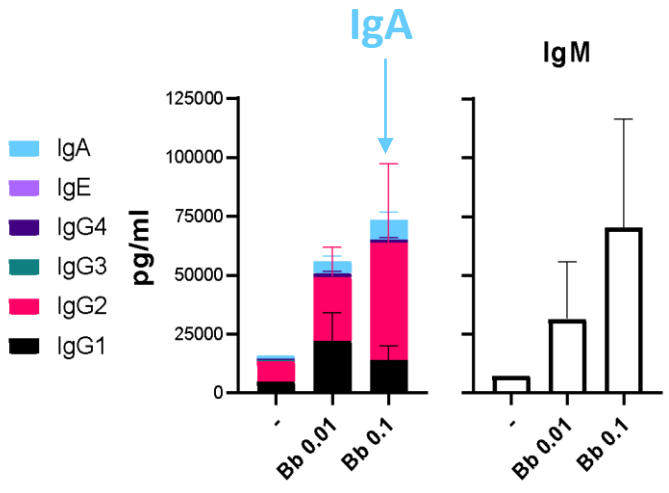
Lyme Disease: Modeling Infection-Induced Autoimmunity in the human LF Chip

7/7 health donors display *aberrant T cell immunity* with *Borrelia* infection



SAC: heat killed *S. aureus* Cowan I
Bb: *Borrelia burgdorferi*

3/7 healthy donors show hypergammaglobunemia

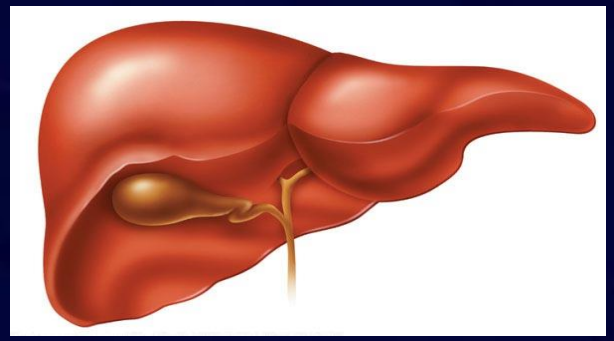


Bb – Borrelia
MOI = 0.1 or 0.01 (Borrelia vs. human cells

- Clearance of *Borrelia* requires antibiotic therapy
- Persistent inflammation may set the stage for *chronic* Lyme Disease
  - *In antibiotic-refractory Lyme arthritis, Treg number correlates with time to resolution*
- Excessive antibodies target host proteins

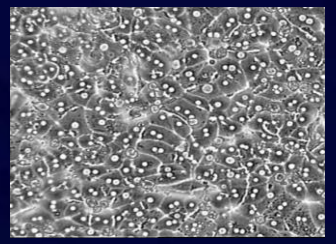
Species-Specific Liver Chips

(KYUNG-JIN JANG et al., ***Science Trans. Med.* 2019**; w/ Emulate Inc., Astrazeneca & Janssen Pharm.)



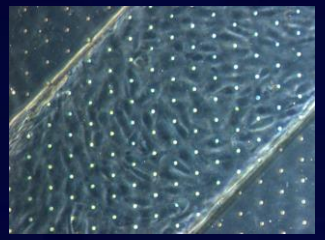
Primary HUMAN, DOG, or RAT

Hepatocytes

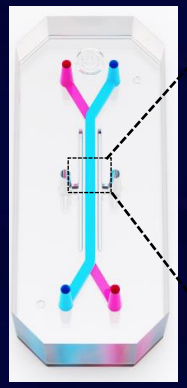


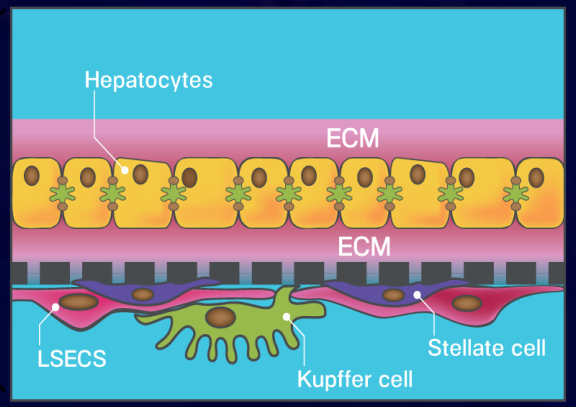
\+

Liver Sinusoidal Endothelial Cells

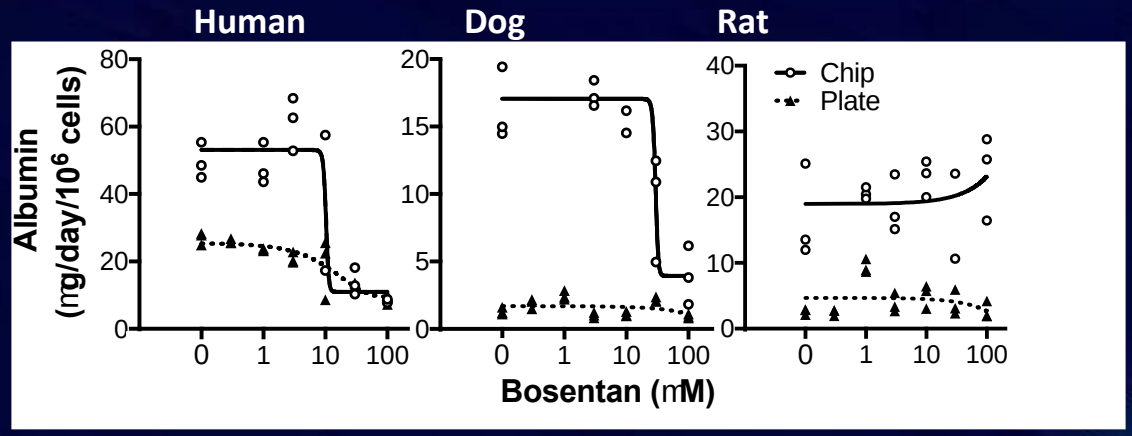


- Hepatocytes
- Liver sinusoidal endothelium
- Kupfer cells
- Stellate cells





Liver Chips Mimic Species-Specific Bosentan Toxicities

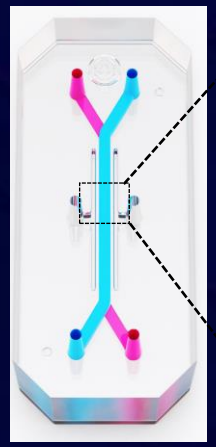


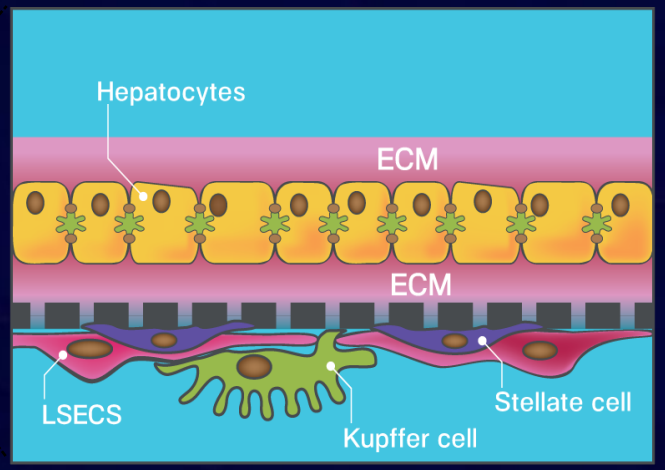
Faithfully recapitulated hepatocellular injury, steatosis, cholestasis, and fibrosis + species-specific toxicities with multiple compounds

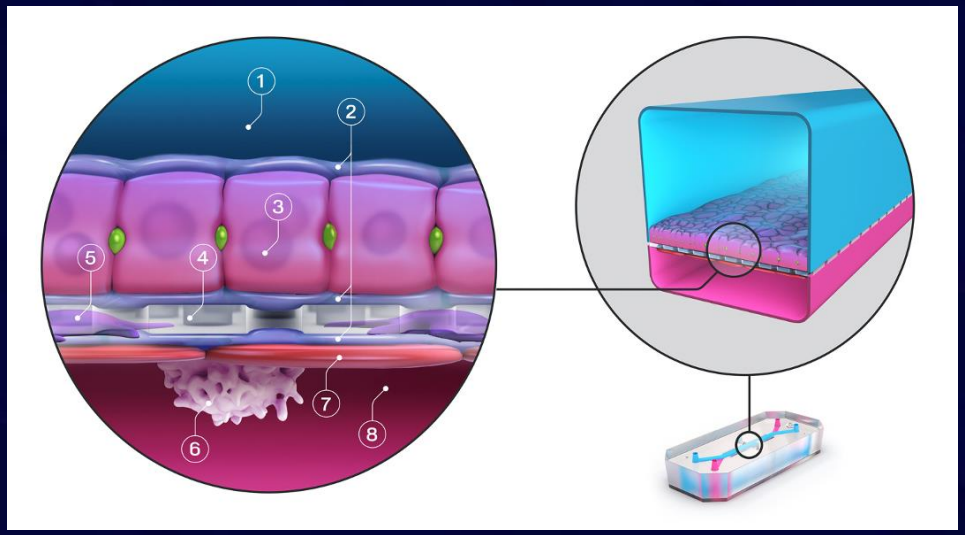
Wyss Institute

Human Liver Chips are Better Predictors of Drug-Induced Liver Injury than Animal Models

(Ewart et al. ***Commun. Med. 2022***; led by *Emulate, Inc.*)







- **870 Human Liver Chips analyzed** (cells from 3 donors)
- **Tested blinded set of 27 hepatotoxic and non-toxic drugs** (identified by pharma IQ Consortium)
- **Human toxicities of many drugs had been missed in animal models**
- ***Predicted human DILI with 87% sensitivity and 100% specificity***

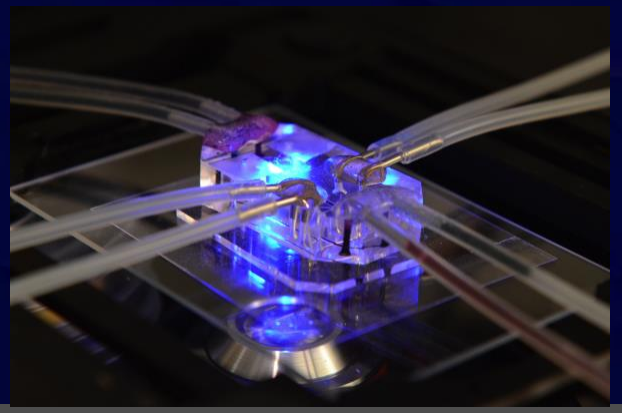
- 7-8x Better than Animal Models

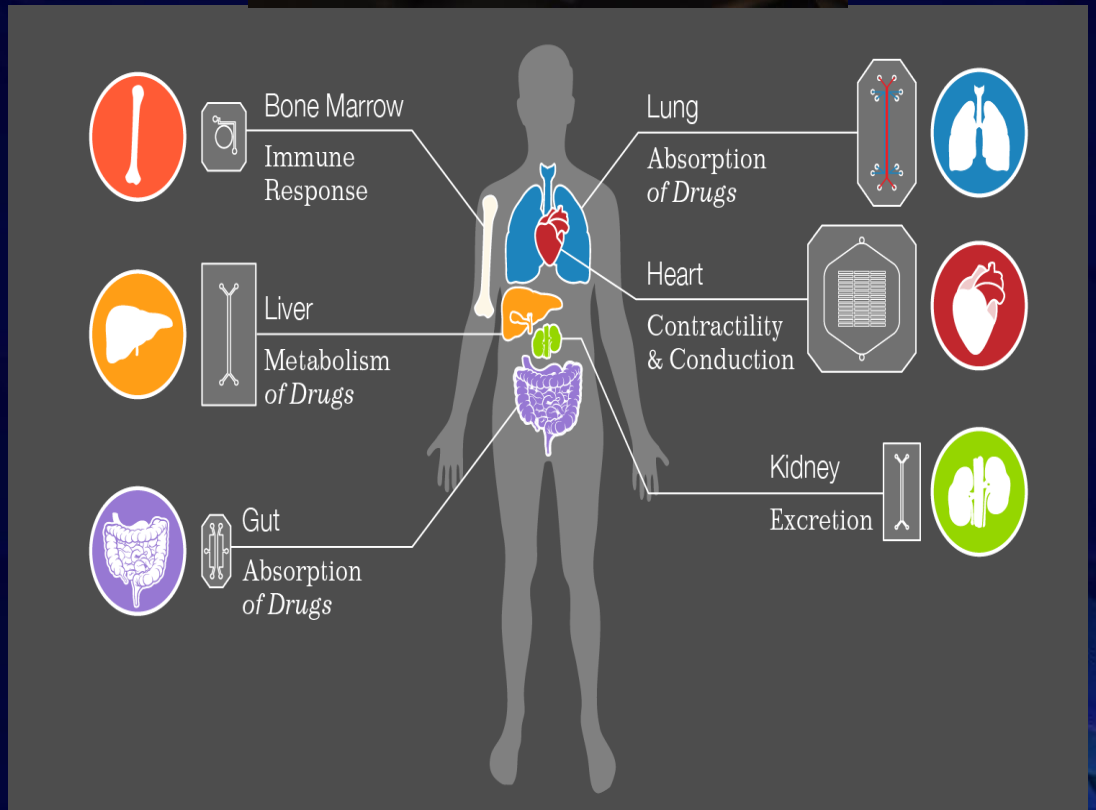
- Save Pharma Industry ~$2-3B per year

Wyss Institute

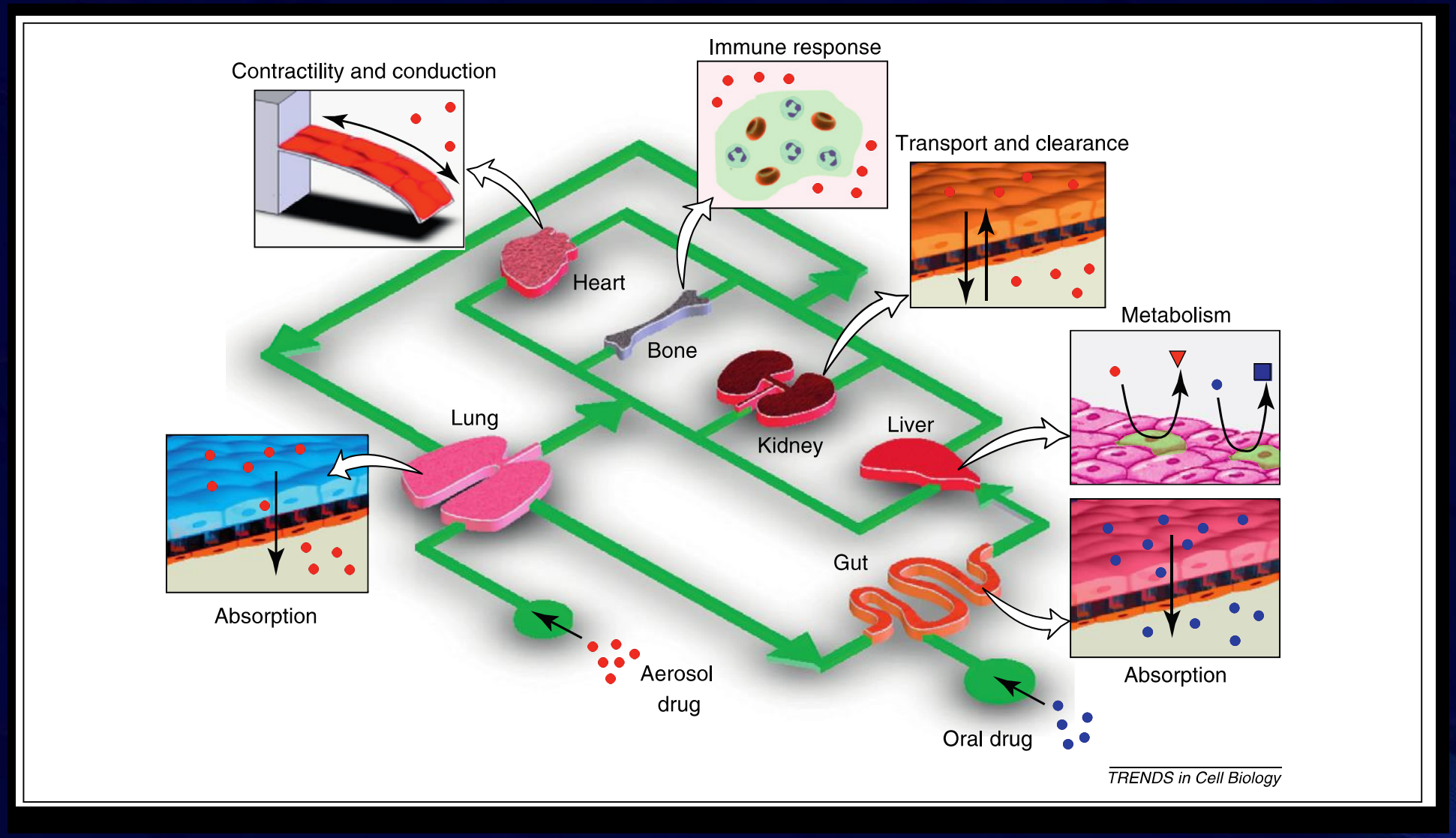
Organ Chip Technology Pipeline

- **Ongoing projects**
  - Lung Alveolus
  - Lung Small Airway
  - Liver
  - Small Intestine (duodenum, jejunum, ileum)
  - Large Intestine
  - Kidney Proximal Tubule
  - Kidney Glomerulus
  - Bone marrow
  - Skin
  - Lymphoid Follicle
  - Orthotopic Cancers
  - Blood-Brain Barrier
  - Esophagus
  - Vagina
  - Cervix
  - Brain Neurons *(Kit Parker)*
  - Heart *(Kit Parker)*
  - Skeletal Muscle *(Kit Parker)*
  - ……





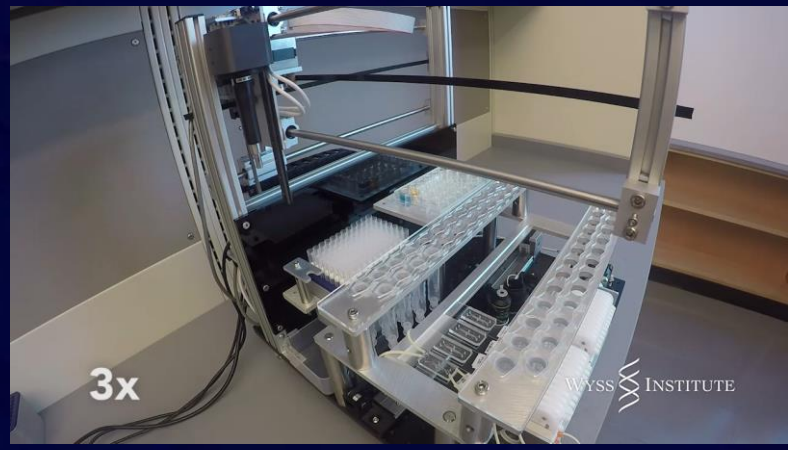
Integrated Human Body-on-Chips

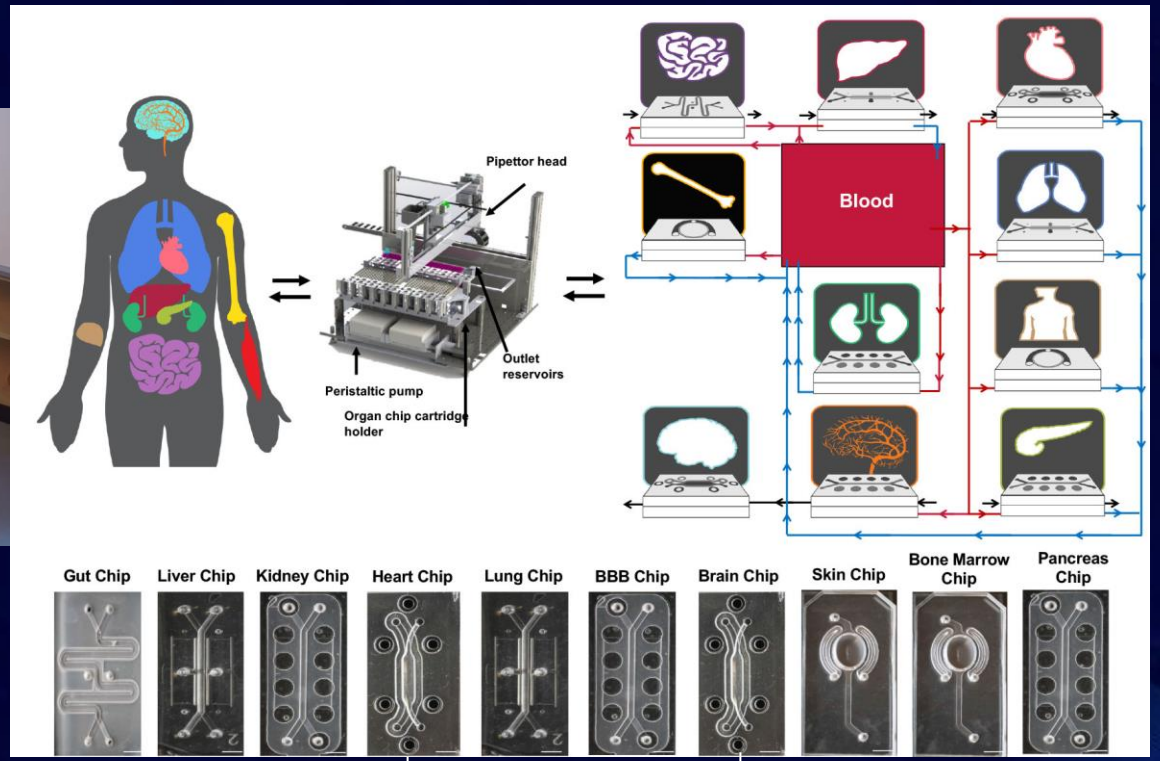


Wyss Institute

Automated Coupling of up to 10 Organs for 4 Weeks

(Novak et al., ***Nature Biomed. Engin. 2020***)

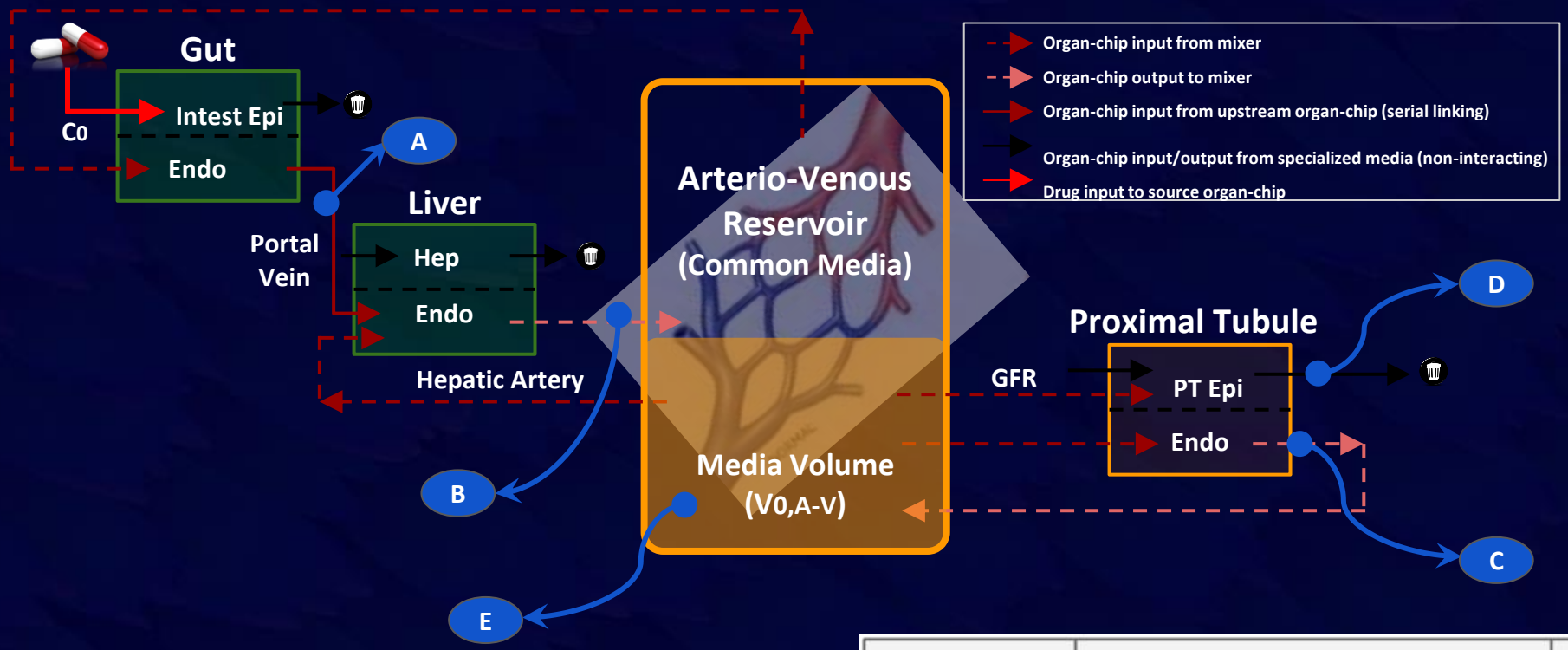




Use of Common"Blood Substitute" medium is possible due to Endothelium-lined Vascular Channels

Wyss Institute

In Vitro-to-In Vivo Translation of PK Parameters



Organ-Chip	PK Metrics	Sampling Location
Gut	Drug absorption (F_a) Apparent permeability (P_{app})	A
Liver	Drug metabolism (CL_{int})	B
Proximal Tubule	Secretion & Reabsorption	C
Kidney	Renal clearance (CL_R)	D

Organ-Chip	PK Metrics	Sampling Location
AV Reservoir	Maximum (or peak) plasma drug concentration (C_{max})	E
AV Reservoir	Half-life ($t_{1/2}$)	E

(PRANTIL-BAUN et al., *Ann. Rev. Pharm. Toxic.* 2018)

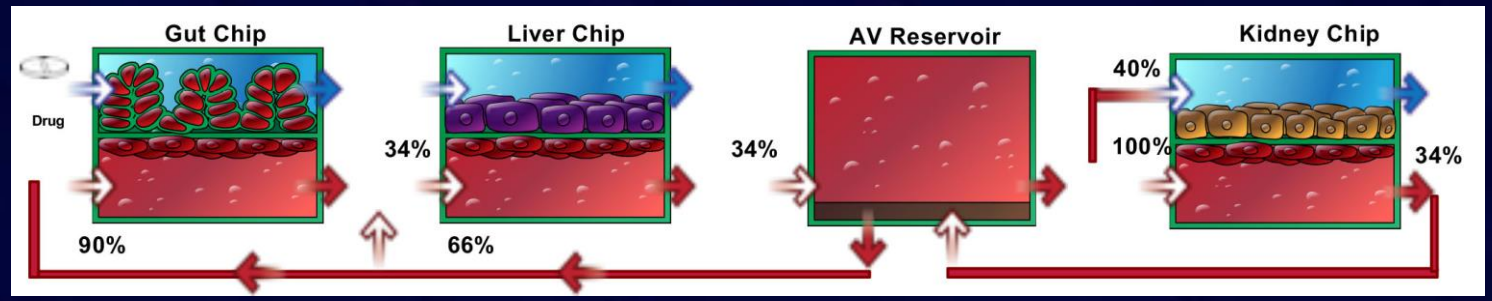
WYSS INSTITUTE

In Vitro-to-In Vivo Translation of PK Parameters

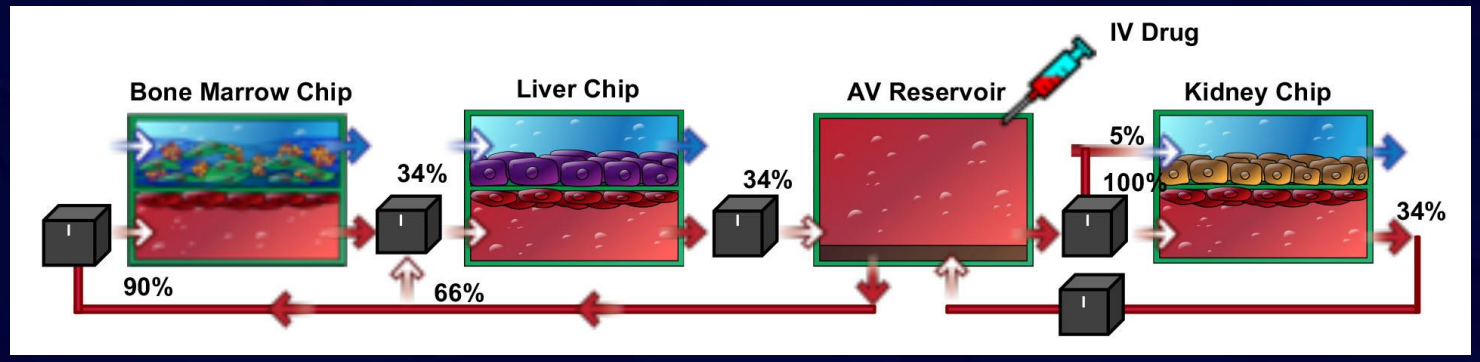
(ANNA HERLAND et al., *Nature Biomed. Engin. 2020*)

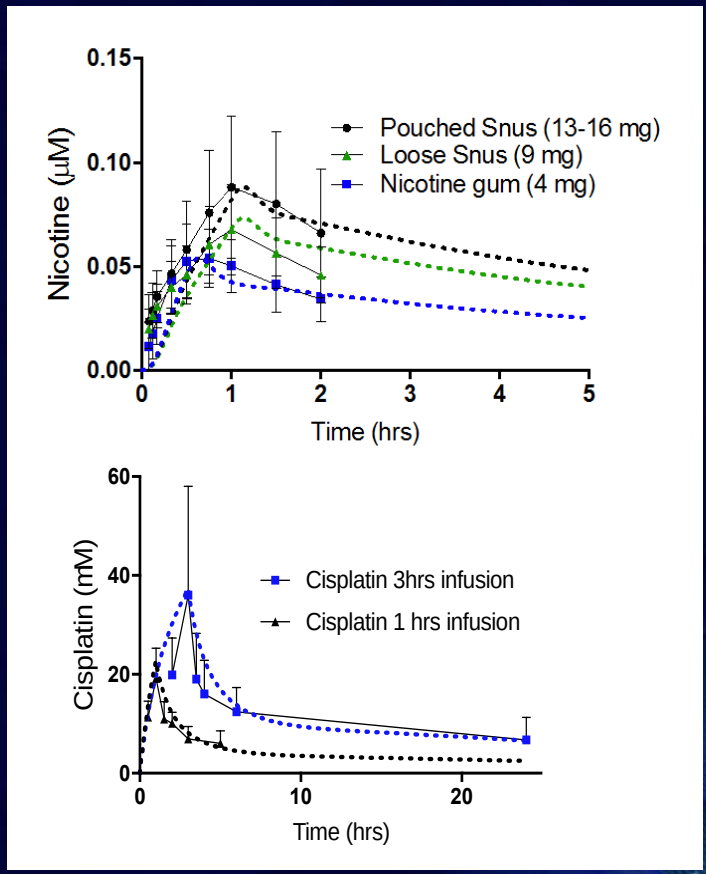
Human Body Chip Model QUANTITIVELY PREDICTS CLINICAL PK DATA for 2 different drugs

Oral NICOTINE



Intravenous CISPLATIN





Summary

Our 2-channel Organ Chips CAN:

- **faithfully recapitulate human pathophysiology**
- **mimic human responses to drugs & radiation**
  using clinically relevant dose exposures
- **quantitatively predict human drug PK parameters**

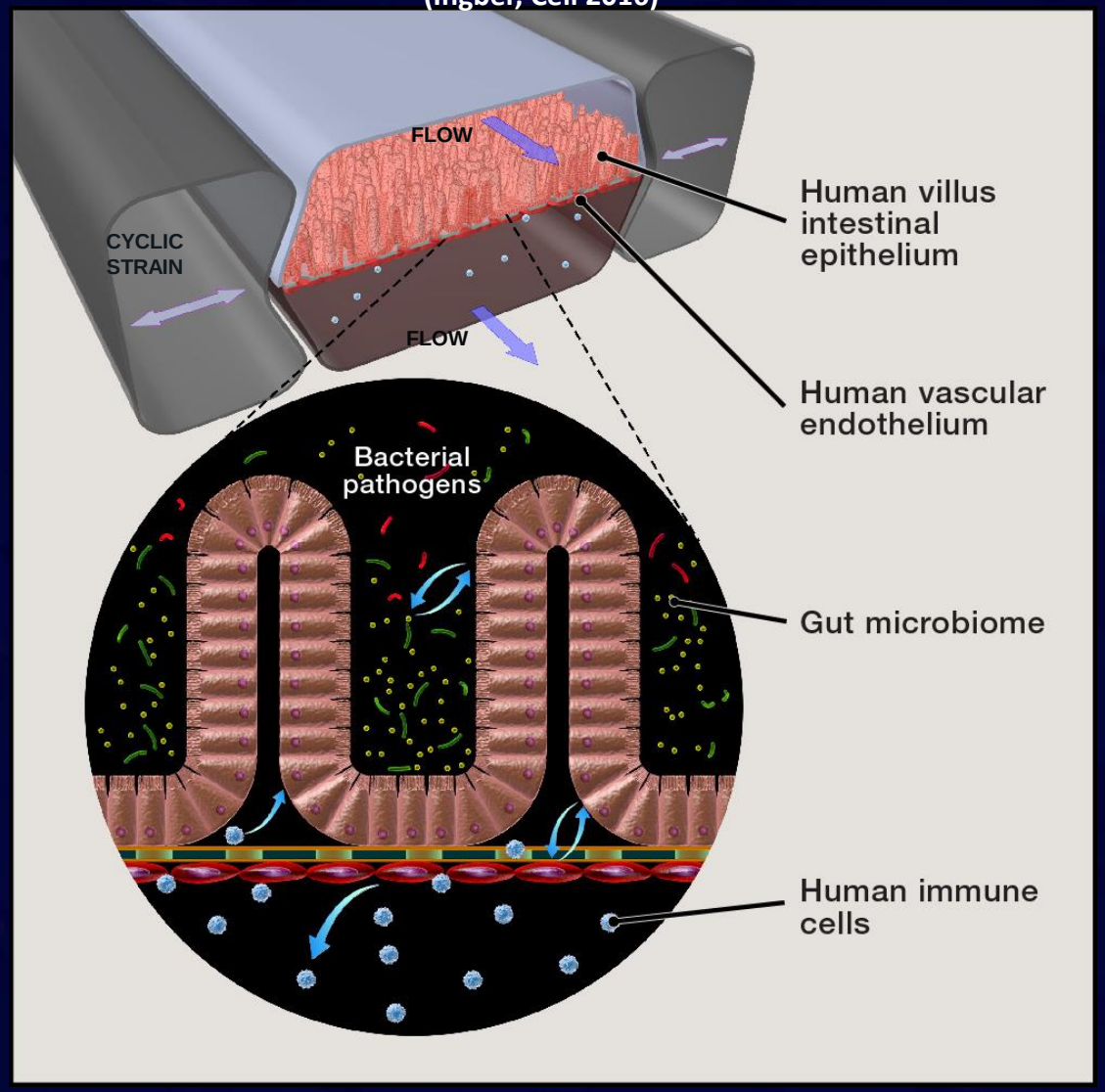
We believe that these Organ Chips are now ready to be integrated into the Drug Development Pipeline

WYSS INSTITUTE

Tools for Reverse Engineering Human Pathophysiology

(Ingber, Cell 2016)

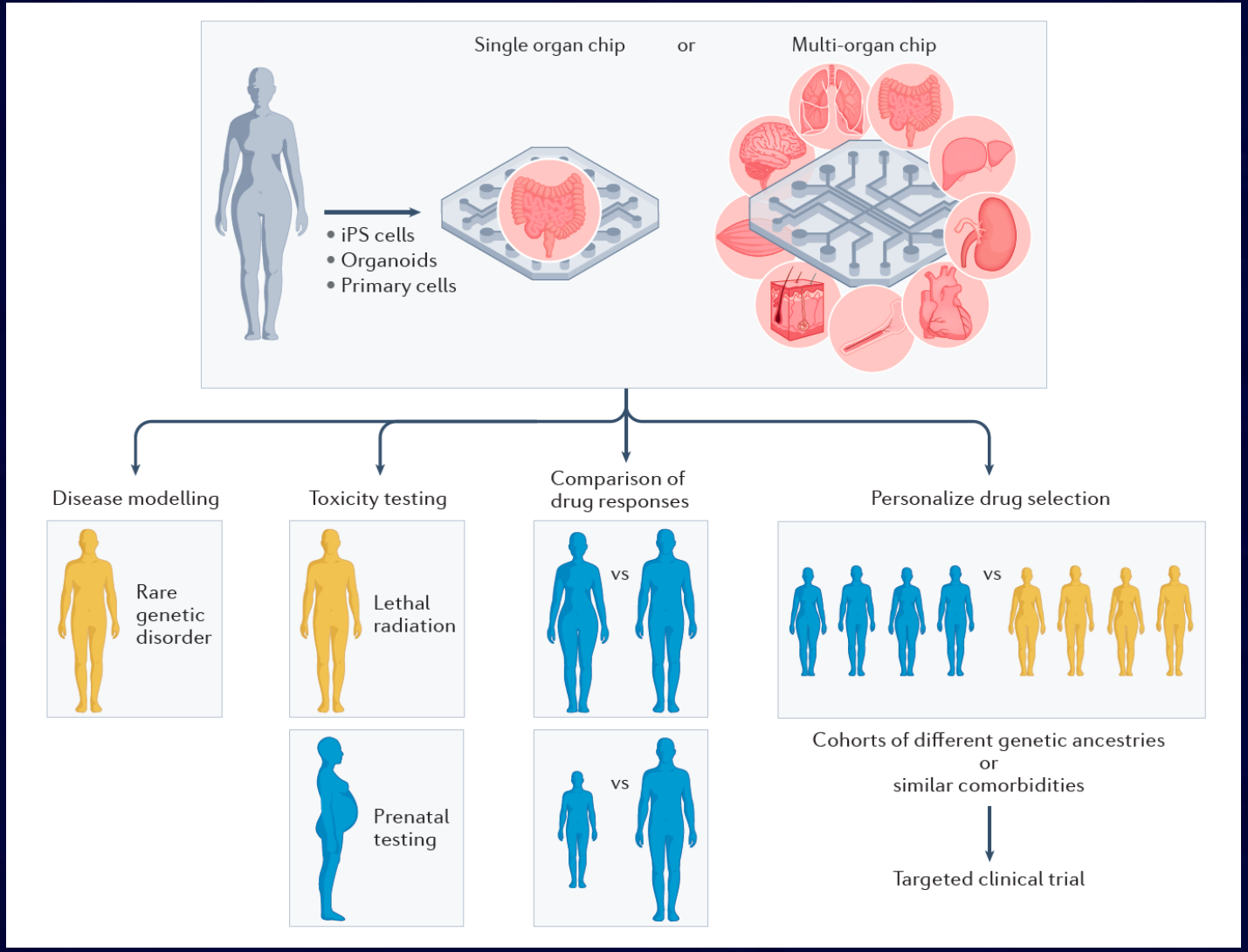
Insight into
Disease Mechanism
+
Drug Mechanism
of Action
+
Drug Mechanism
of Toxicity



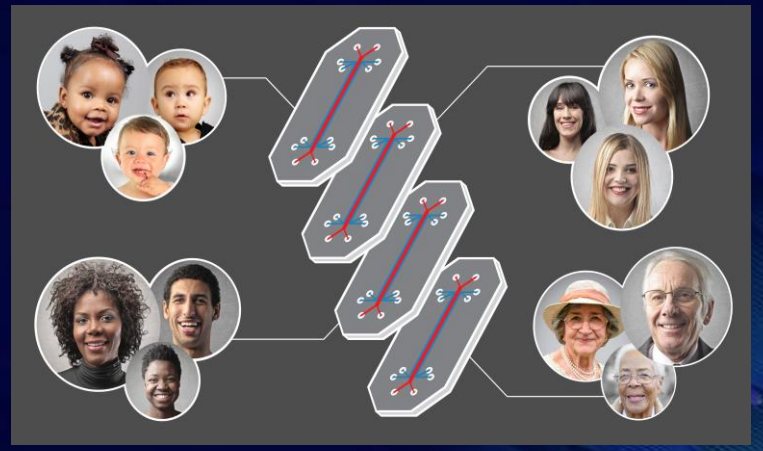
WYSS INSTITUTE

Implications for Personalized Medicine

(Ingber, ***Nature Rev. Gen.*** 2022)



Personalized Clinical Trials



WYSS INSTITUTE

FDA Modernization Act Passed by U.S. Congress

117TH CONGRESS
2D SESSION

S. 5002

To allow for alternatives to animal testing for purposes of drug and biological product applications.

IN THE SENATE OF THE UNITED STATES

SEPTEMBER 29, 2022

Mr. PAUL (for himself, Mr. BOOKER, Mr. BRAUN, Mr. CRAPO, Mr. MARSHALL, Ms. COLLINS, Mr. KING, Mr. PADILLA, Mr. SANDERS, M[illegible]. TU[illegible] of Florida) introduced the following bill; which was read twice, considered, read the third time, and passed

---

A BILL

To allow for alternatives to animal testing for purposes of drug and biological product applications.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "FDA Modernization Act 2.0".

SEC. 2. ALTERNATIVES TO ANIMAL TESTING.

(a) IN GENERAL.—Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) is amended—

(1) in subsection (i)—

(A) in paragraph (1)(A), by striking "preclinical tests (including tests on animals)" and inserting

(B) in paragraph (2)(B), by striking "animal" and inserting "nonclinical tests"; and

(2) after subsection (y), by inserting the following:

"(z) NONCLINICAL TEST DEFINED.—For purposes of this section, the term 'nonclinical test' m[illegible] a te[illegible] or a non-human in vivo test that occurs before or during the clinical trial phase of the investigation of th[illegible] animal tests, or non-animal or human biology-based test methods, such as cell-based assays, micr[illegible]physiolo[illegible]

(b) BIOSIMILAR BIOLOGICAL PRODUCT APPLICATIONS.—Item (bb) o[illegible] 262(k)(2)(A)(i)(II)) is amended to read as follows:

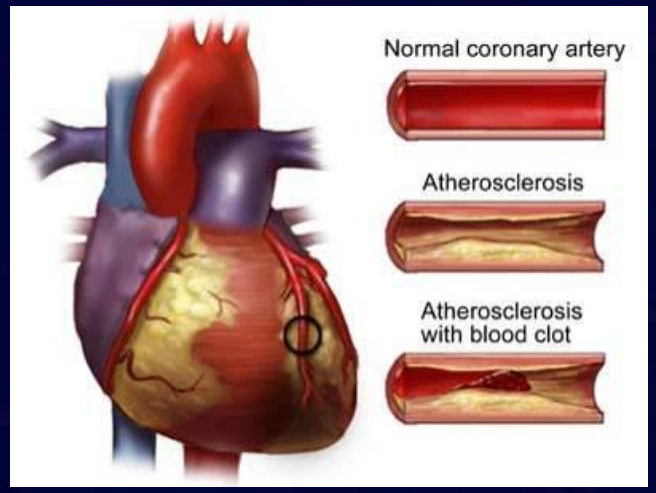
WYSS INSTITUTE

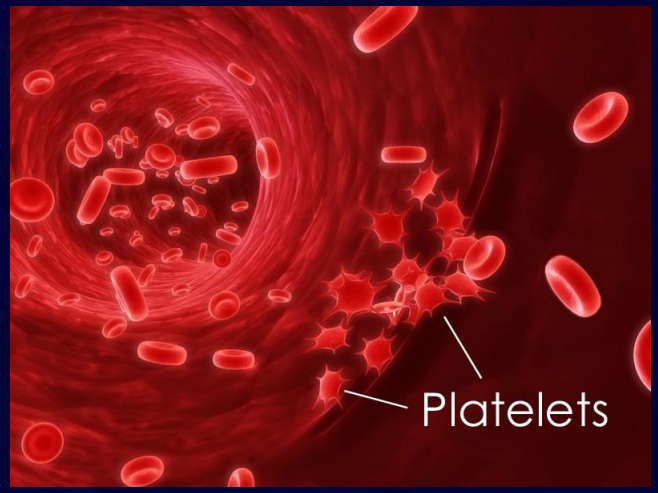
CHALLENGE 2:

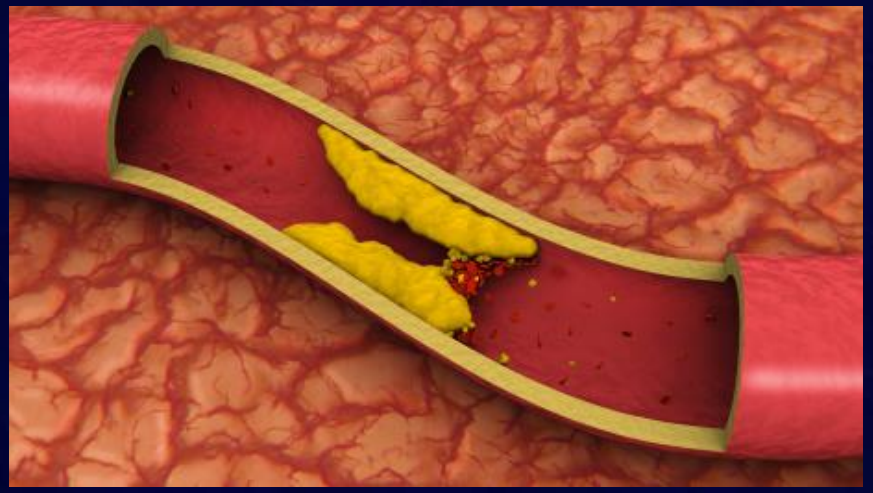
Can we develop ways to target drugs only to sites where they are needed?

WYSS INSTITUTE

Vascular Occlusion is Leading Cause of Death







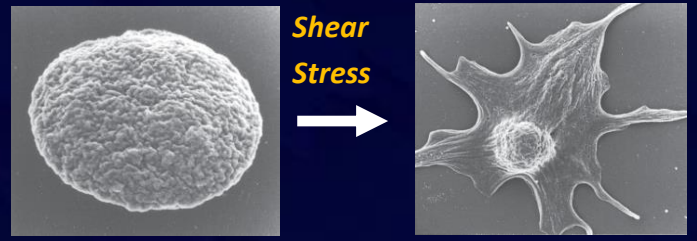
Platelets 'Activated' by Shear Stress

- Heart Attack
- Stroke
- Pulmonary Embolism
- Atherosclerosis
- Coronary Spasm
- Intimal Hyperplasia (Stent clogging)
- Pulmonary Vascular Disease
- …

Shear-Targeted Drug Delivery

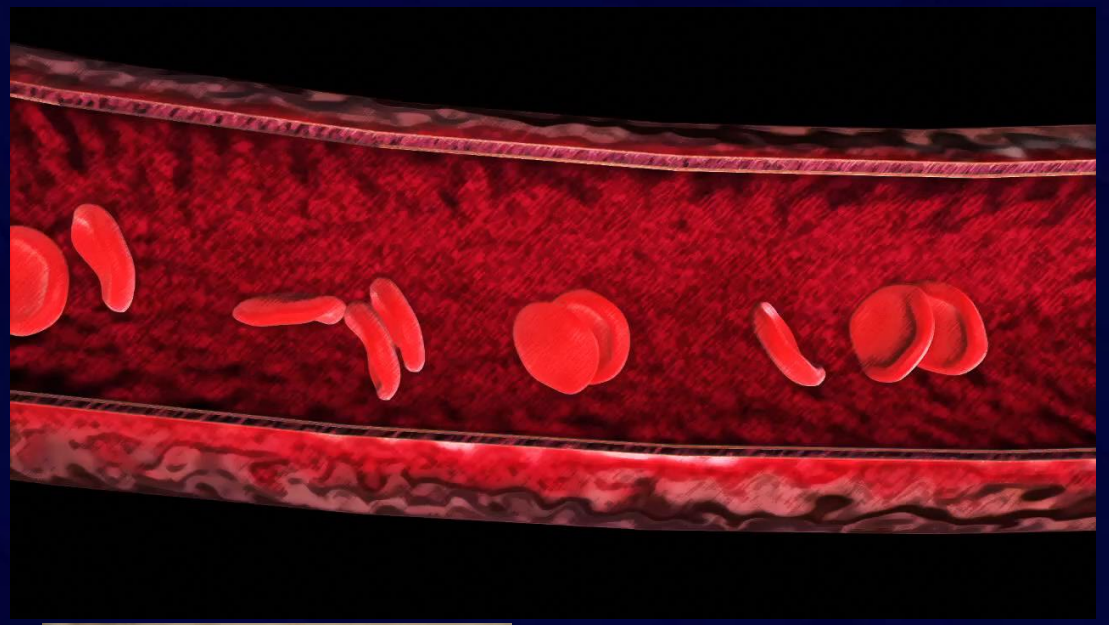
(Korin et al., *Science* 2012)

Shear-induced platelet activation



Synthetic ‘Platelet Mimetics’

Vascular Blockage-Targeted Drug Delivery

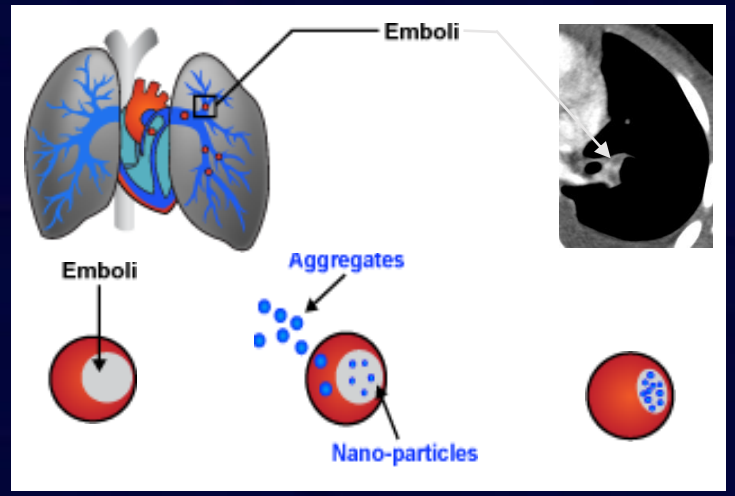


WYSS INSTITUTE

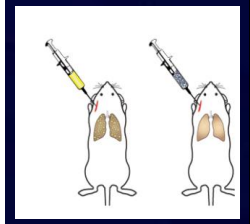
Therapeutic Responses in an Animal Model

(effective at 1/100th injected clinical dose of free tPA)

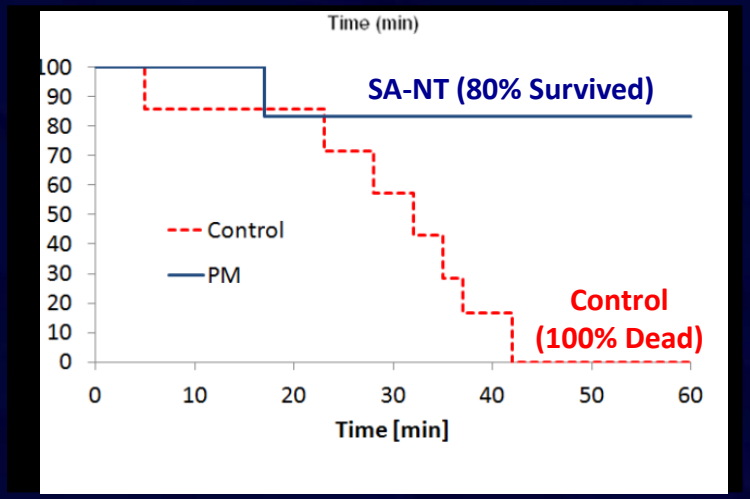
Targeting Pulmonary Embolism

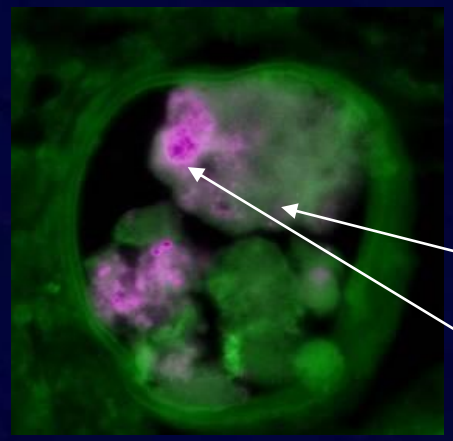


Pulmonary Embolism Model



Significant Increase in Survival





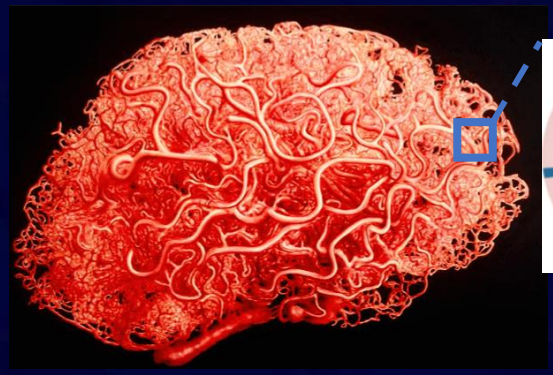
Embolus

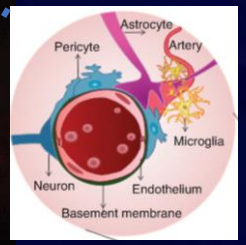
Released Nanoparticles

CHALLENGE 3:

Can we deliver drugs to the Brain with great efficiency?

Molecular Shuttles for Brain-Targeting





- Only 1 in 10,000 molecules of many drugs cross the Blood-Brain Barrier (BBB)
- Alzheimer's disease: More than 1700 clinical trials (>99.9%) have failed over the past 10 years
- Glioblastoma:

Neuro-Oncology

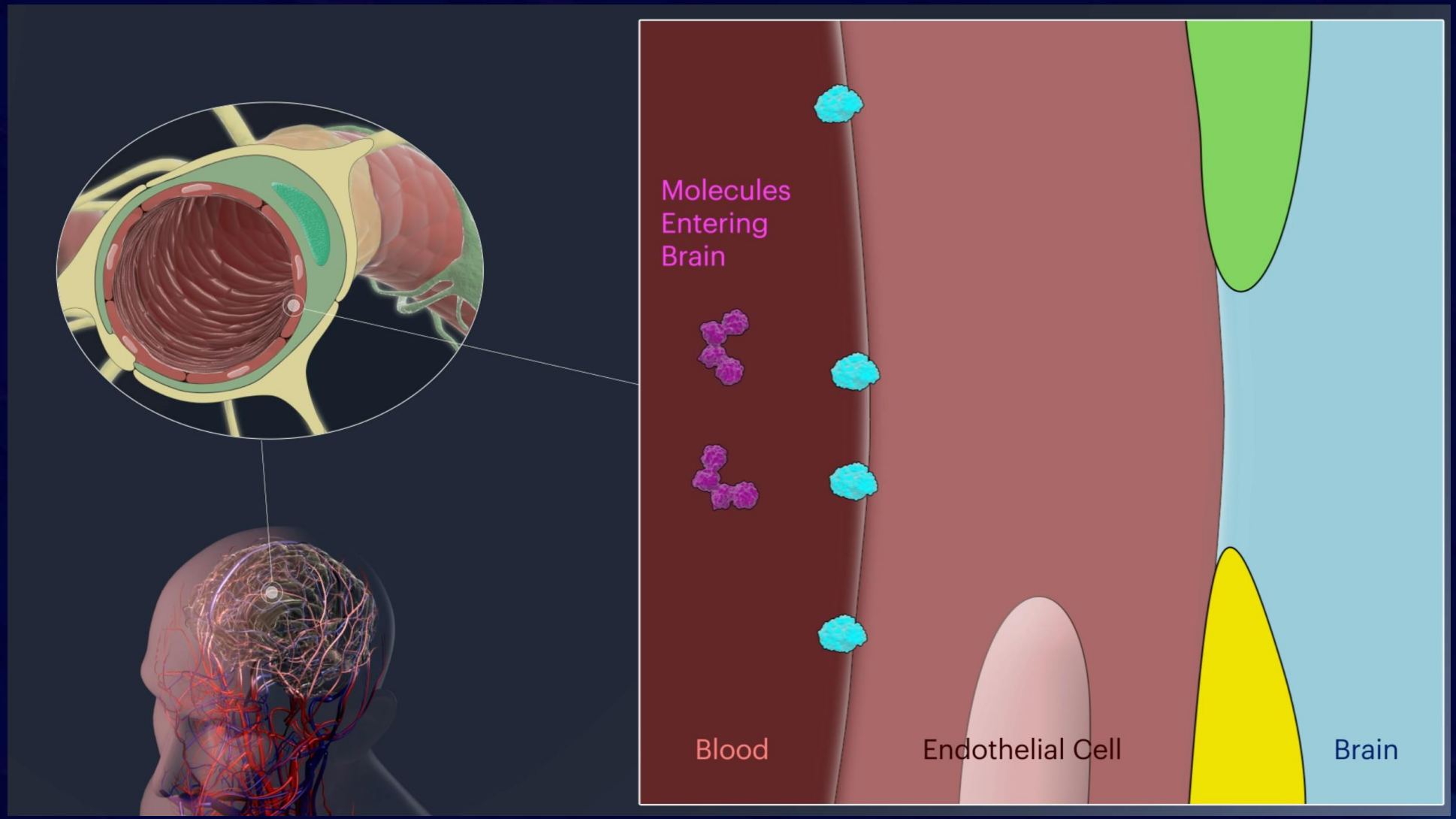
25(1), 1–3, 2023 | https://doi.org/10.1093/neuonc/noac226 | Advance Access date 18 October 2022

Negative trials over and over again: How can we do better?

J. Ricardo McFaline-Figueroa and Patrick Y. Wen

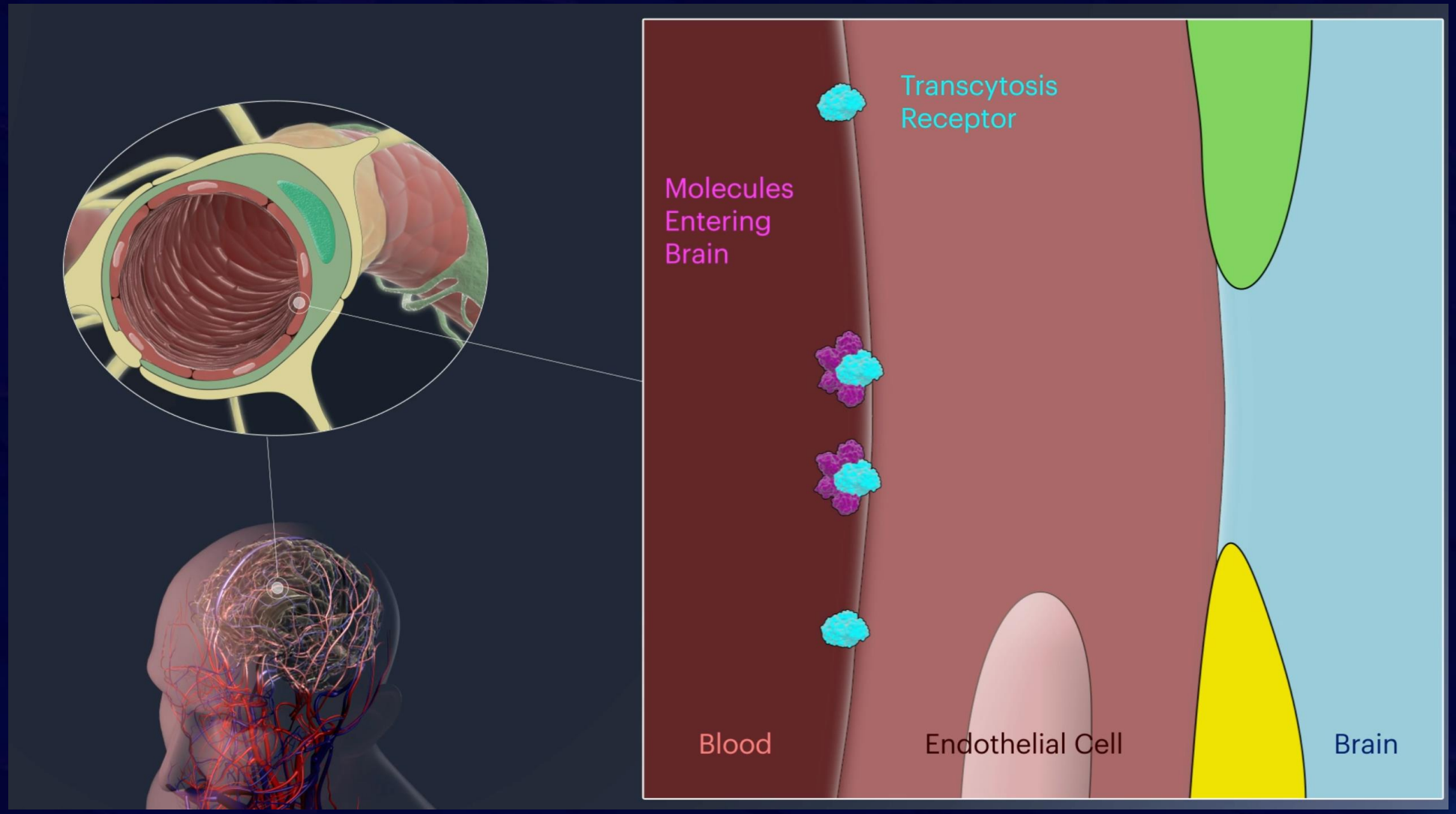
➢ **<u>Unmet Need</u>**: ***To dramatically increase the brain uptake of drugs***

Evading the Brain's Security System

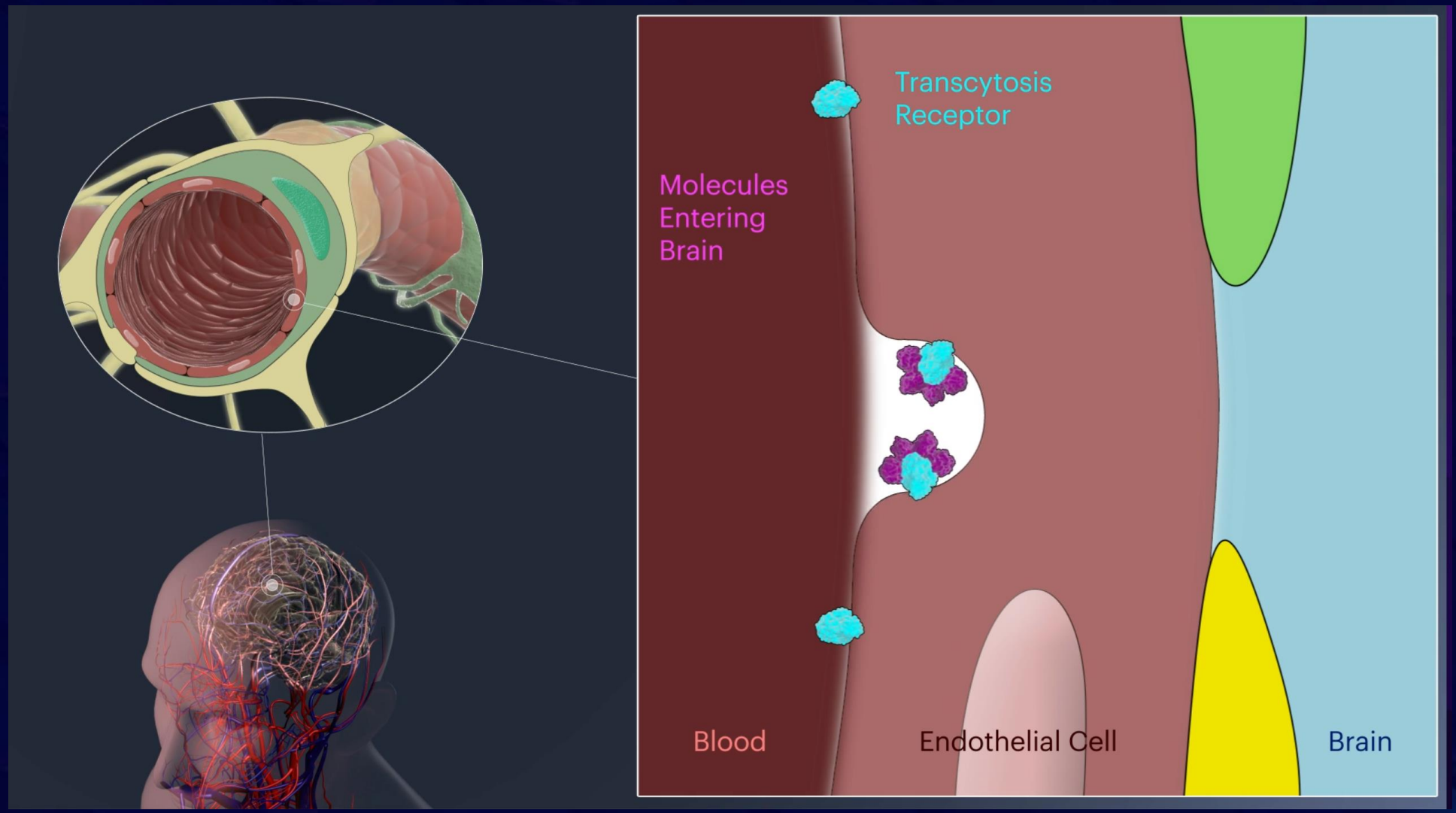


Wyss Institute

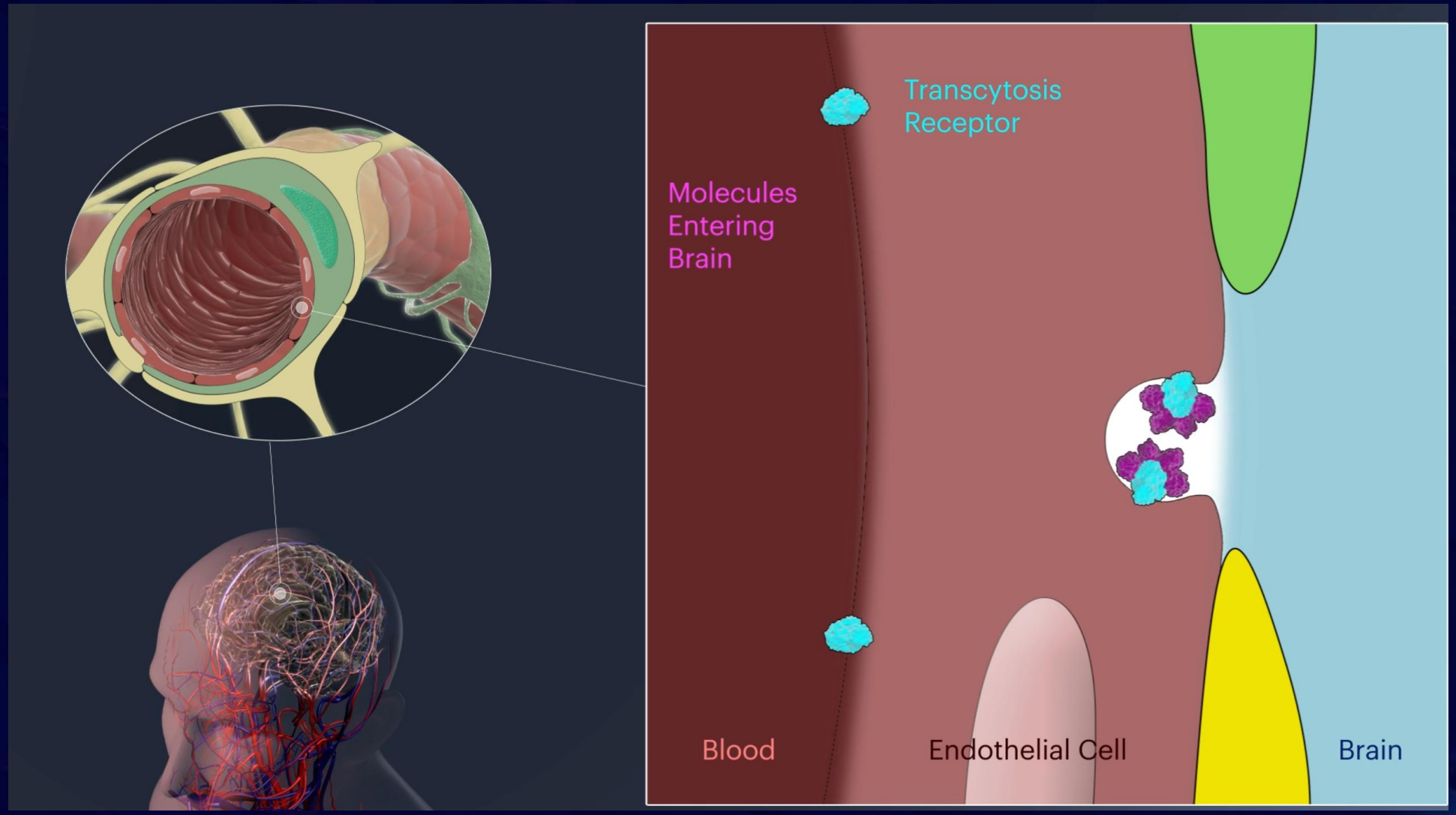
Evading the Brain's Security System



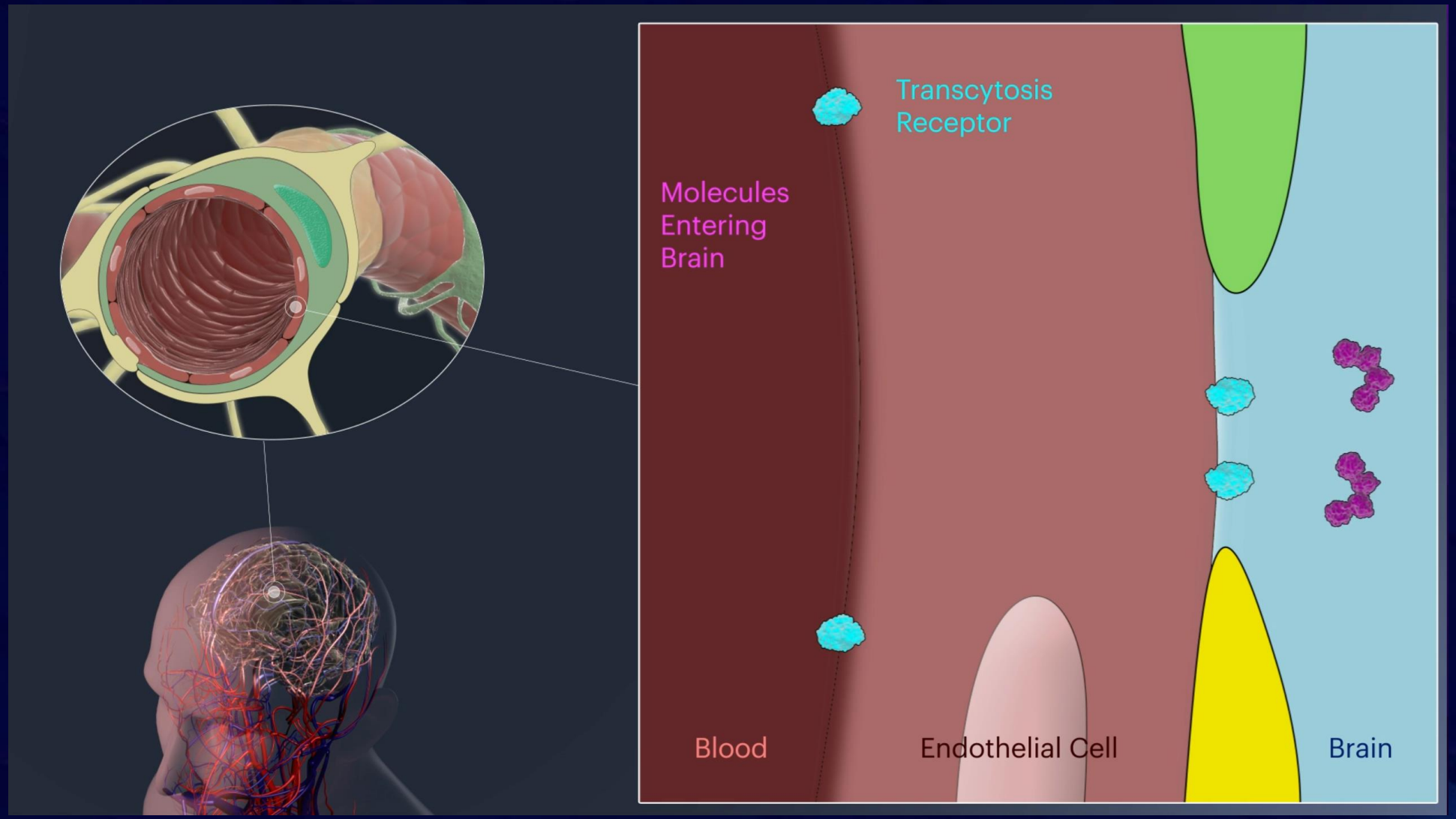
Evading the Brain's Security System



Evading the Brain's Security System

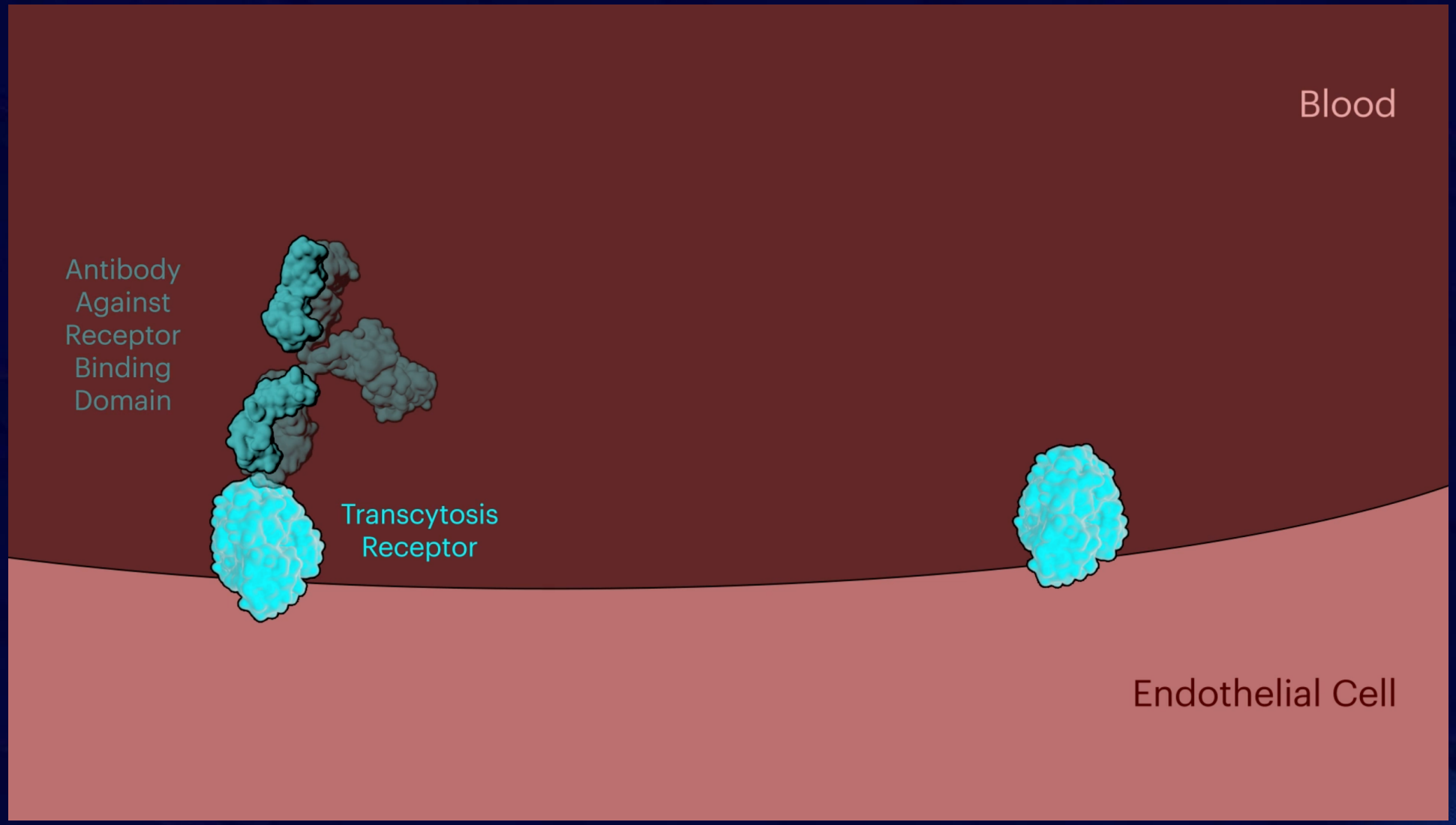


Normal BBB transport via transcytosis



Wyss Institute

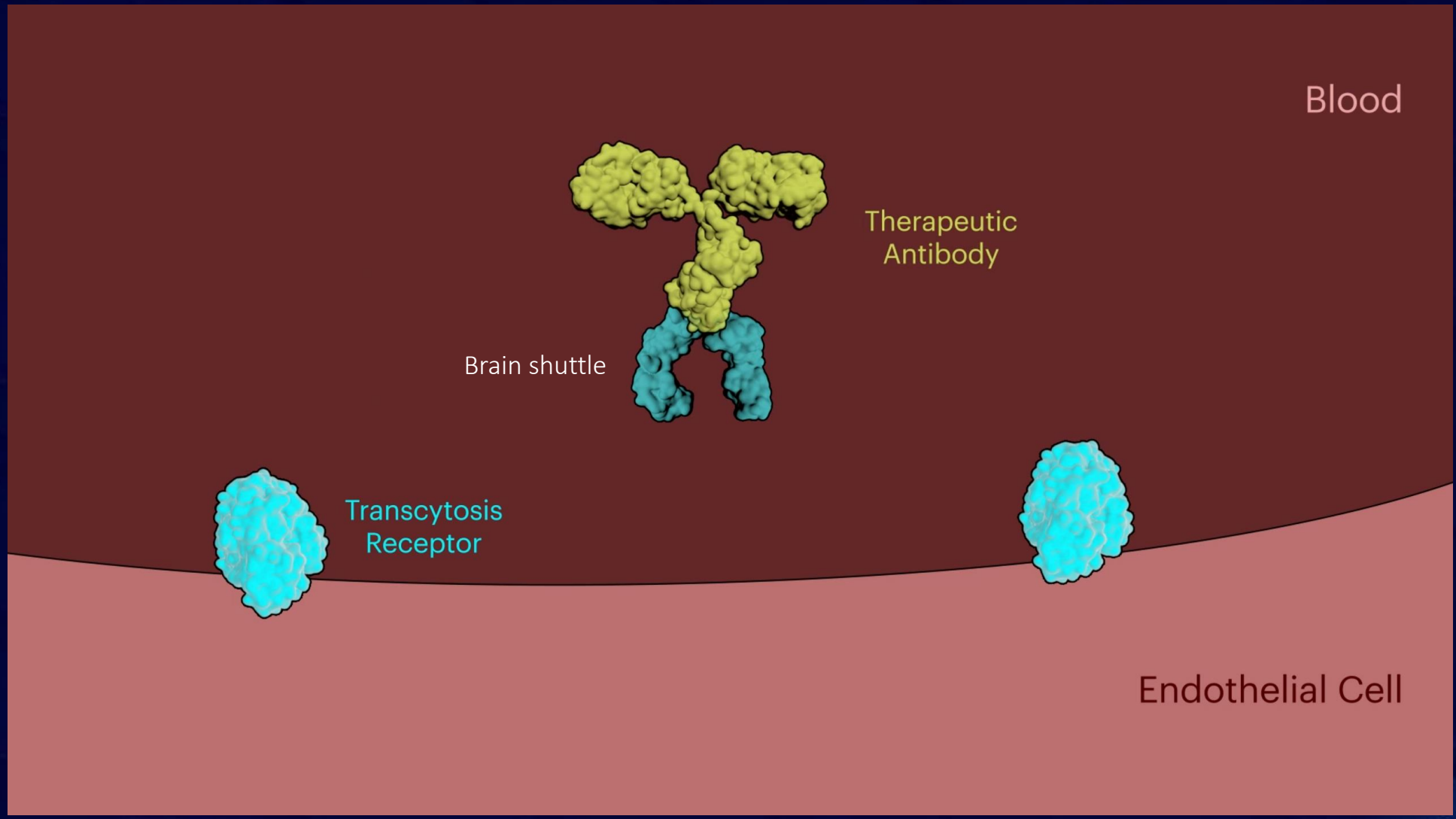
Designing Brain-Targeted Therapeutic Abs



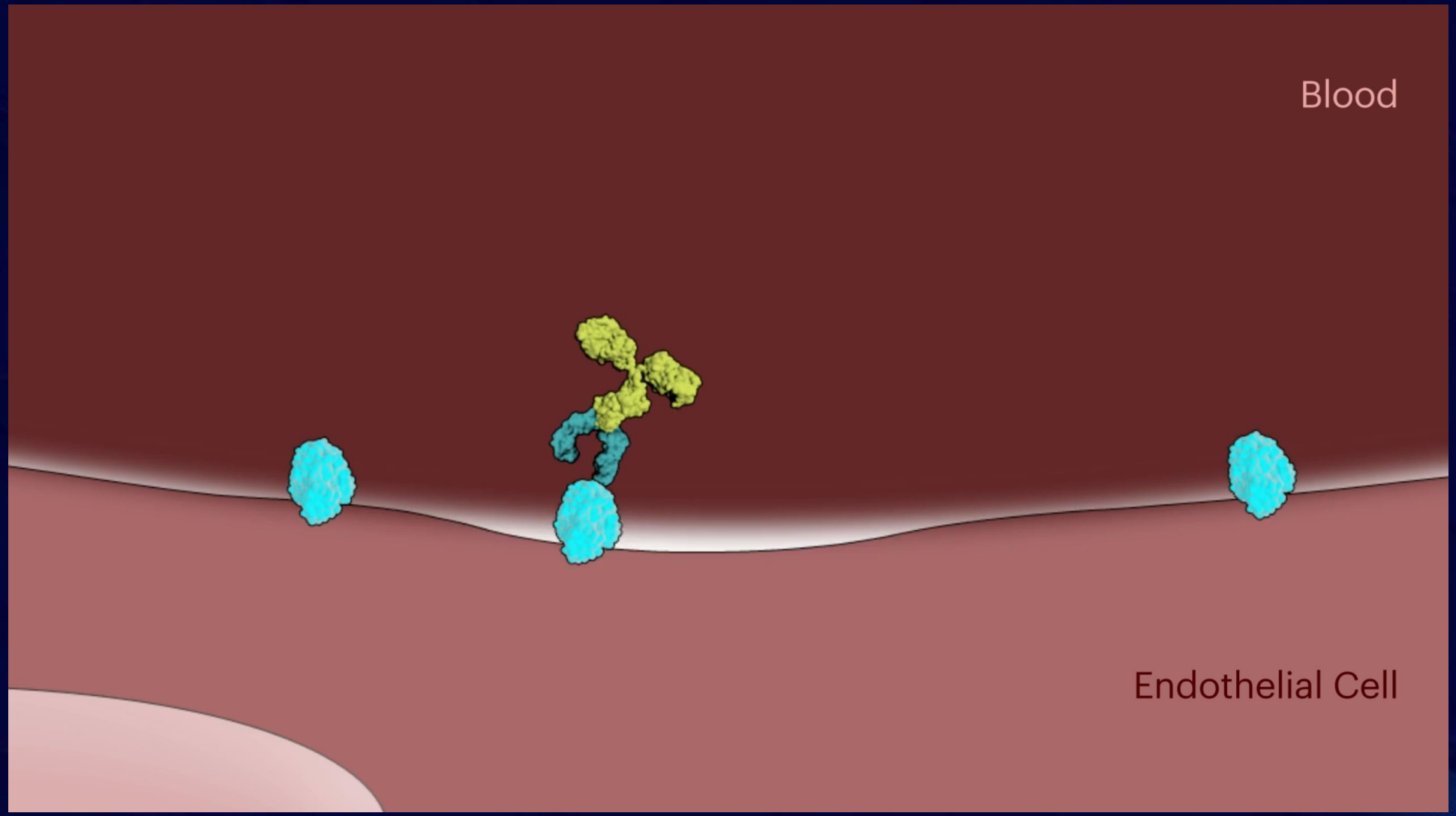
Wyss Institute

Designing brain-targeted therapeutic Abs

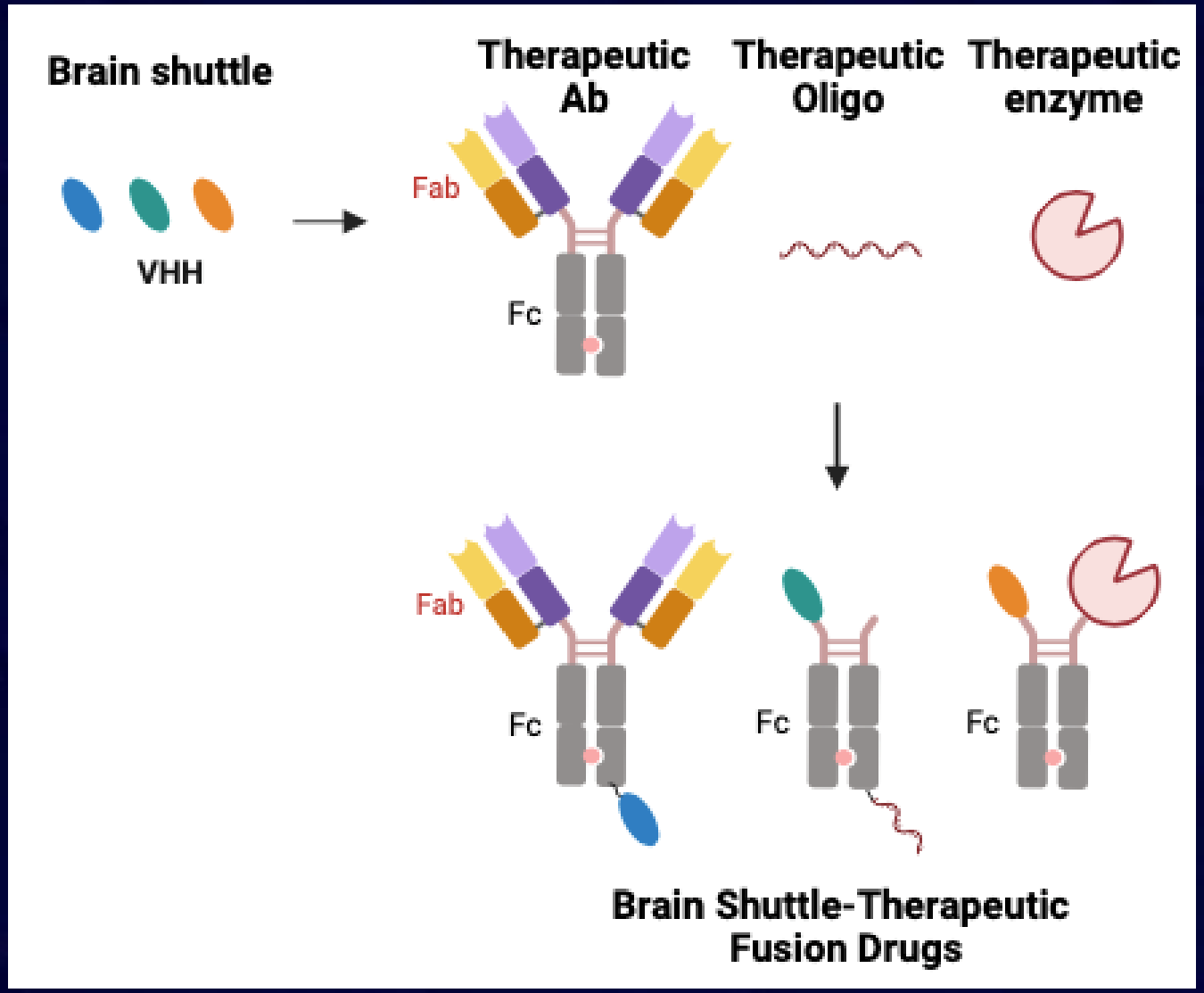
Designing Brain-Targeted Therapeutic Abs



Designing Brain-Targeted Therapeutic Abs



Ab Shuttle Platform Can Deliver Many Payloads



New Brain Target Discovery Approach

(*PRE-COMPETITIVE CONSORTIUM* Led by Jim Gorman, MD,PhD)

Consortium Members:

Eli Lilly
Merck
BMS
Anylam
Lundbeck
Visterra

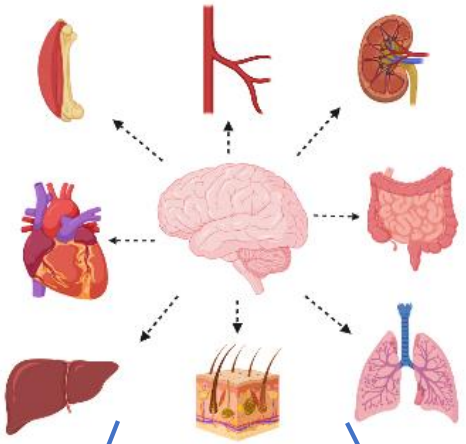
Development Partner:

Fair Journey

DATA COLLECTION

Human Tissue

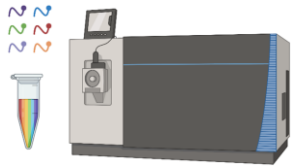
Fresh: Normal & Diseased



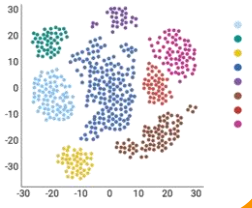
Process Tissue

Obtain Public Data

Proteomics



RNA-Seq

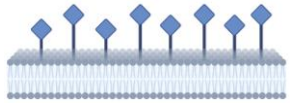


BIOINFORMATIC PROCESSING

Omics

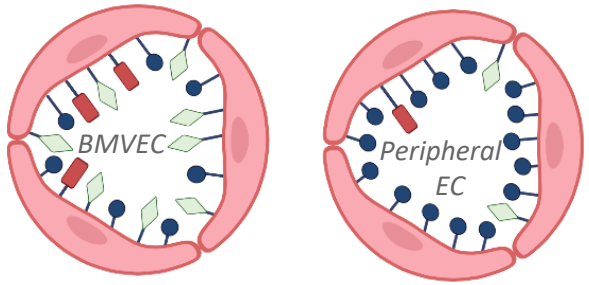
Normalize, clean data and filter genes
Identify ECs and EC subtypes

Filter for cell surface proteins



Metrics

1. Identify **Abundant** vs **Enriched** vs **Both**



2. Apply **functional metrics** to identify proteins:

Transcytosis potential

RANKING

Rank proteins to prioritize for wet lab validation

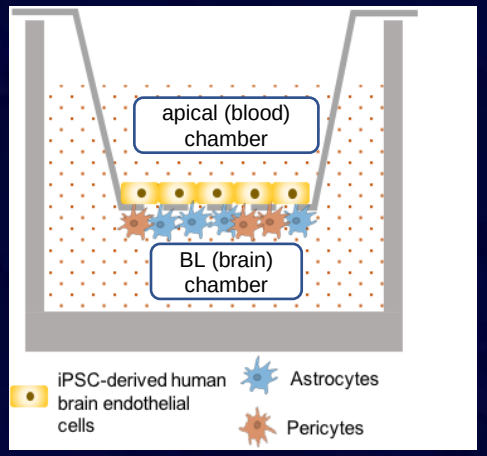
High potential targets

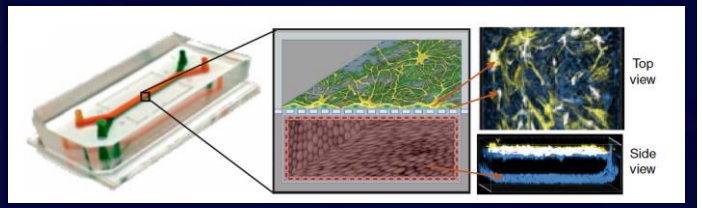
Proceed with Ab Panel

Wyss Institute

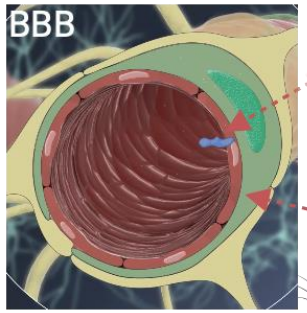
Functional Screens

In Vitro Models





Humanized Mice



Shuttle receptor: TfR, CD98hc, Target 3

Therapeutic IgG

Brain shuttle

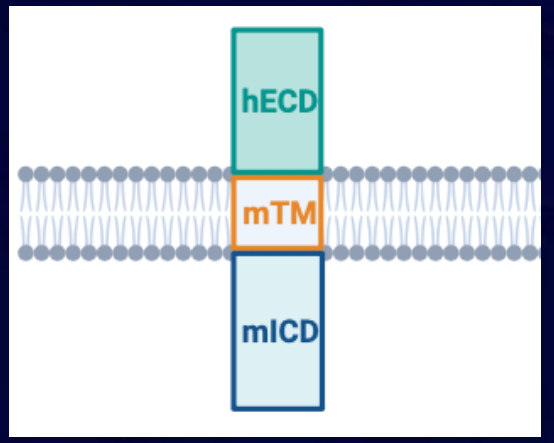
Humanized shuttle receptor knock-in mice

capillary depletion

parenchyma fraction

capillary fraction

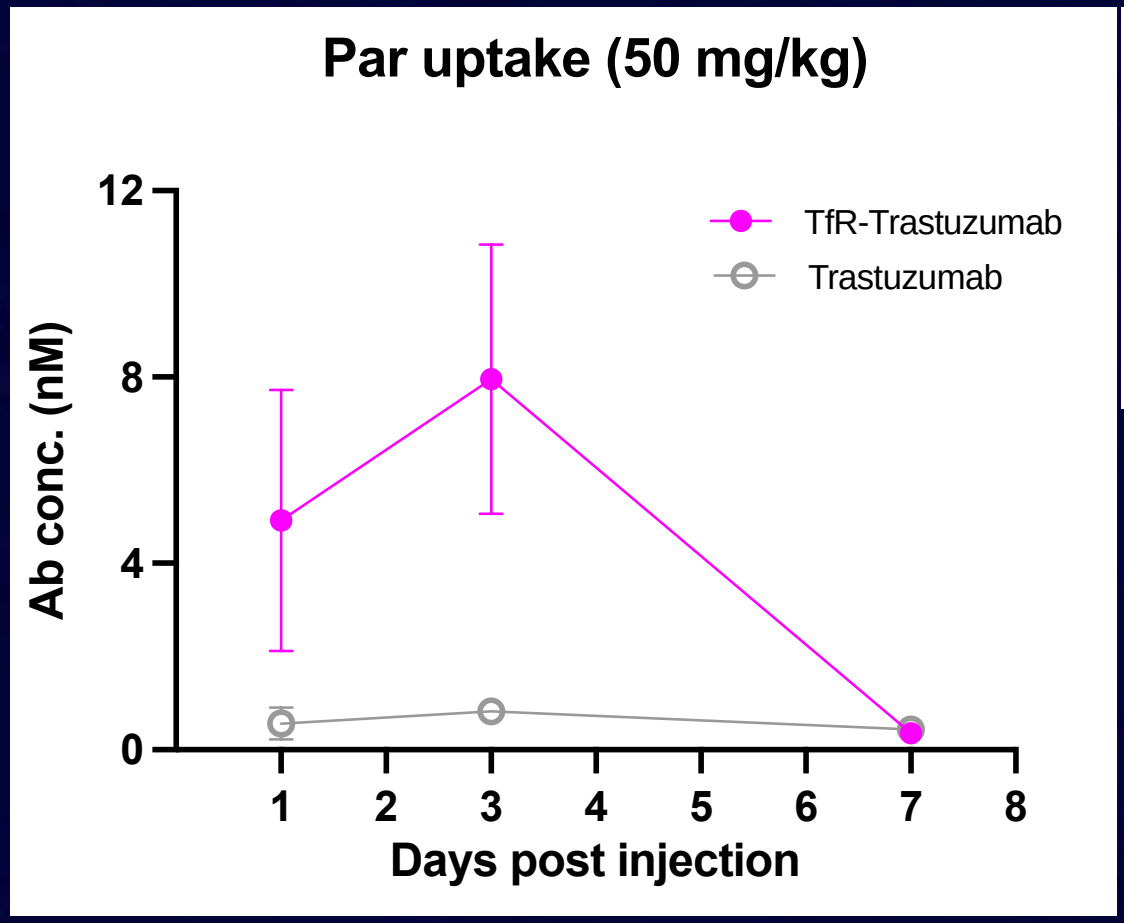
Determine Ab conc. in **parenchymal** brain lysate.
Rank hits.

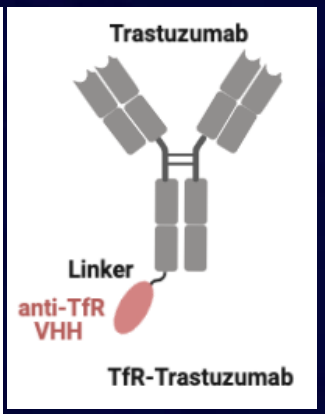


Humanized receptor

Brain PK of anti-Transferrin Receptor (TfR) shuttle

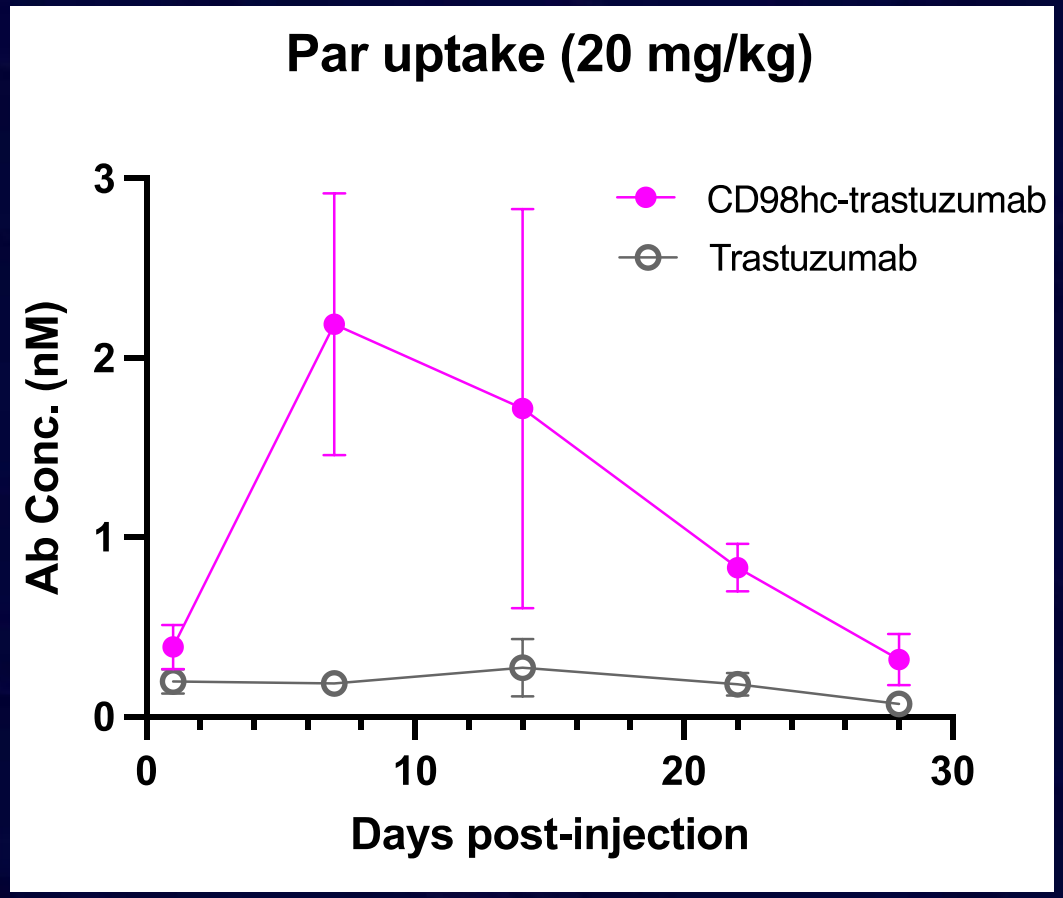
- 10-fold increased parenchymal brain uptake compared to control

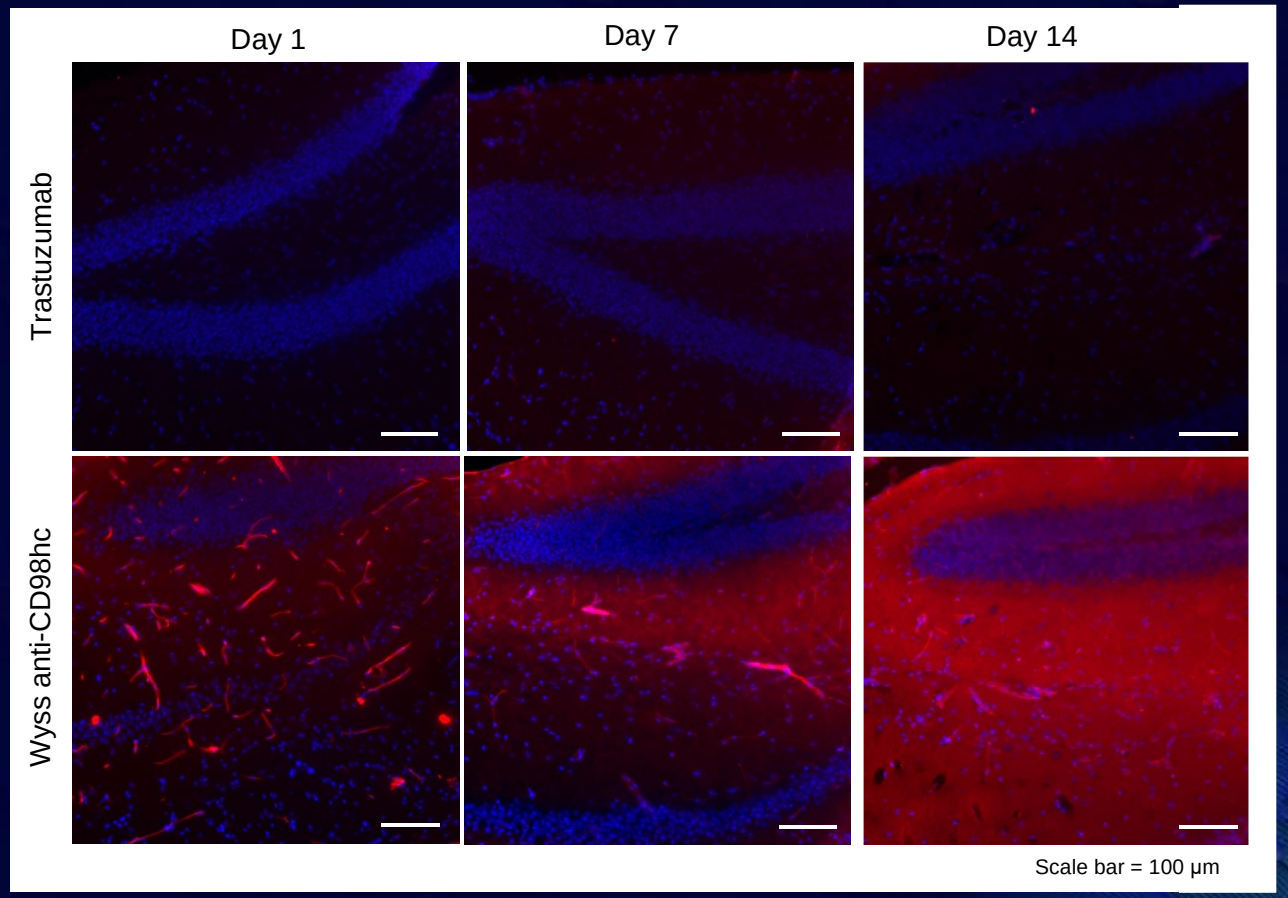




Brain PK of Anti-CD98hc Shuttle

Sustained brain exposure over 4 weeks!





CHALLENGE 4:

Can we develop companion diagnostics to increase likelihood of therapeutic success?

GOAL: A Quantitative Point-of-Care Diagnostic

OPTIMAL DESIGN: Handheld Sensor

ELECTROCHEMICAL SENSORS

ADVANTAGES:

- **Rapid**
- **Quantitative**
- **Miniaturized**
- **Highly sensitive**
- **Low cost**

PROBLEM:

- Biofouling
- Multiplexing

GOAL: A Quantitative Point-of-Care Diagnostic

OPTIMAL DESIGN: Handheld Sensor

ELECTROCHEMICAL SENSORS

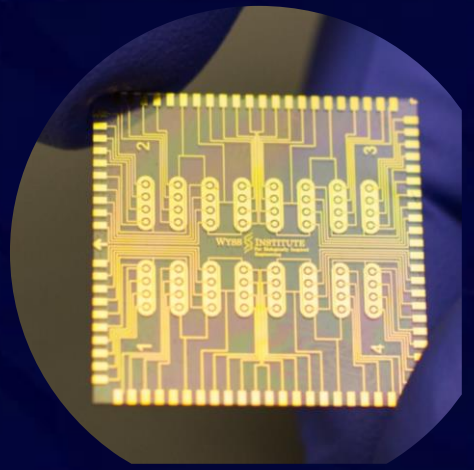
ADVANTAGES:

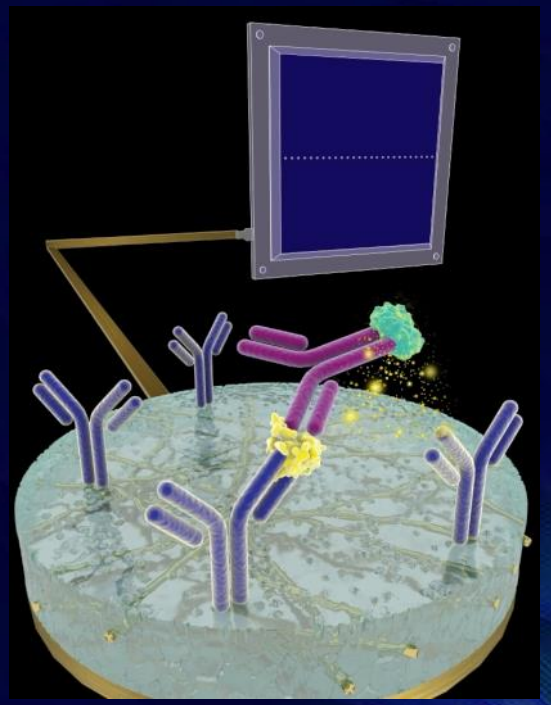
- **Rapid**
- **Quantitative**
- **Miniaturized**
- **Highly sensitive**
- **Low cost**

PROBLEM:

- Biofouling
- Multiplexing

SOLUTION: eRAPID Technology





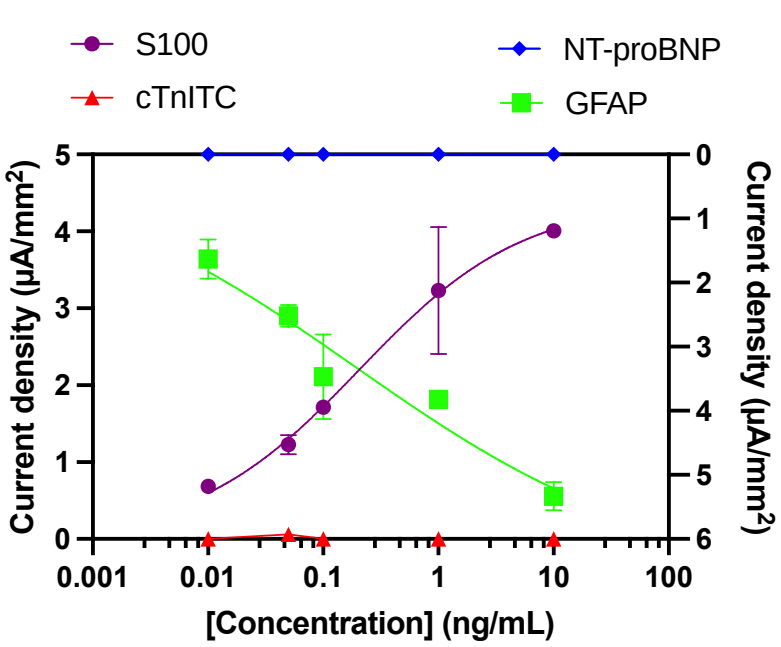
Wyss Institute

Detection of Potential Biomarkers for Heart Attack & Concussion

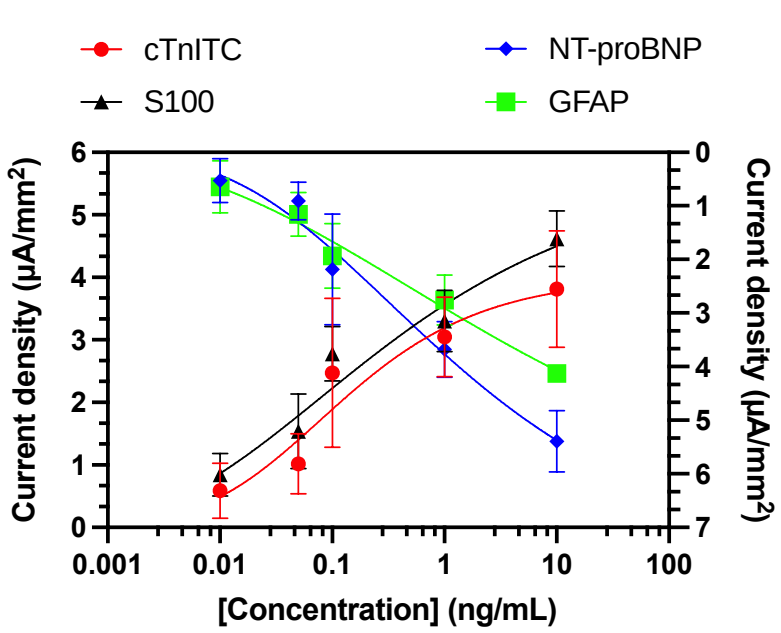
Multiplexed Panel: Troponin ITC (cTnITC), NT pro BNP, s100b, & GFAP

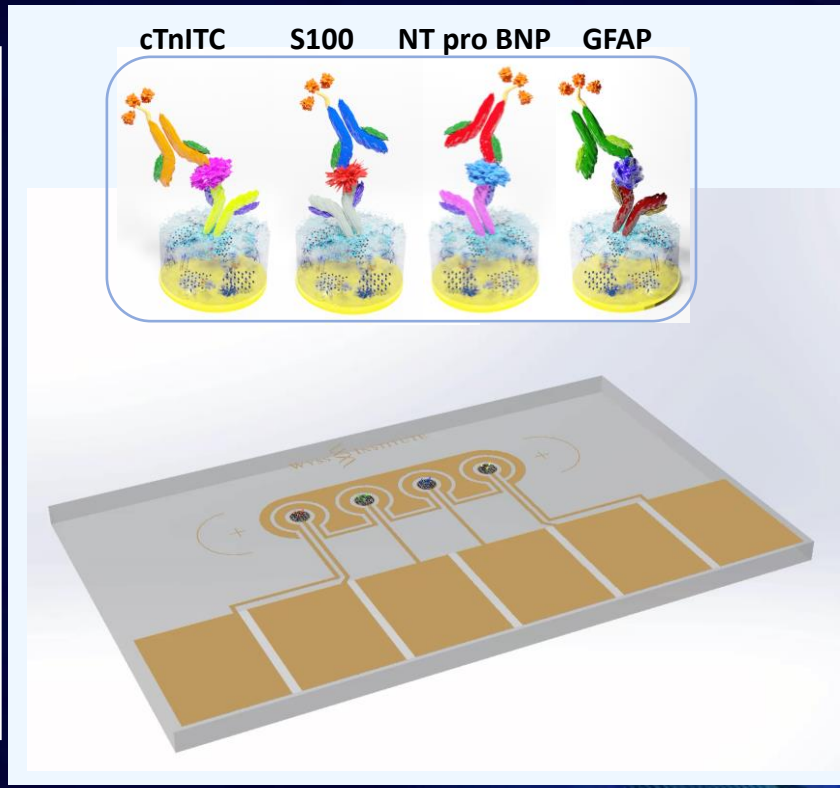
Detection Time: ~30 min in 15 µL human whole blood

2 markers demonstrate Excellent Selectivity



4 markers demonstrate Excellent Correlation



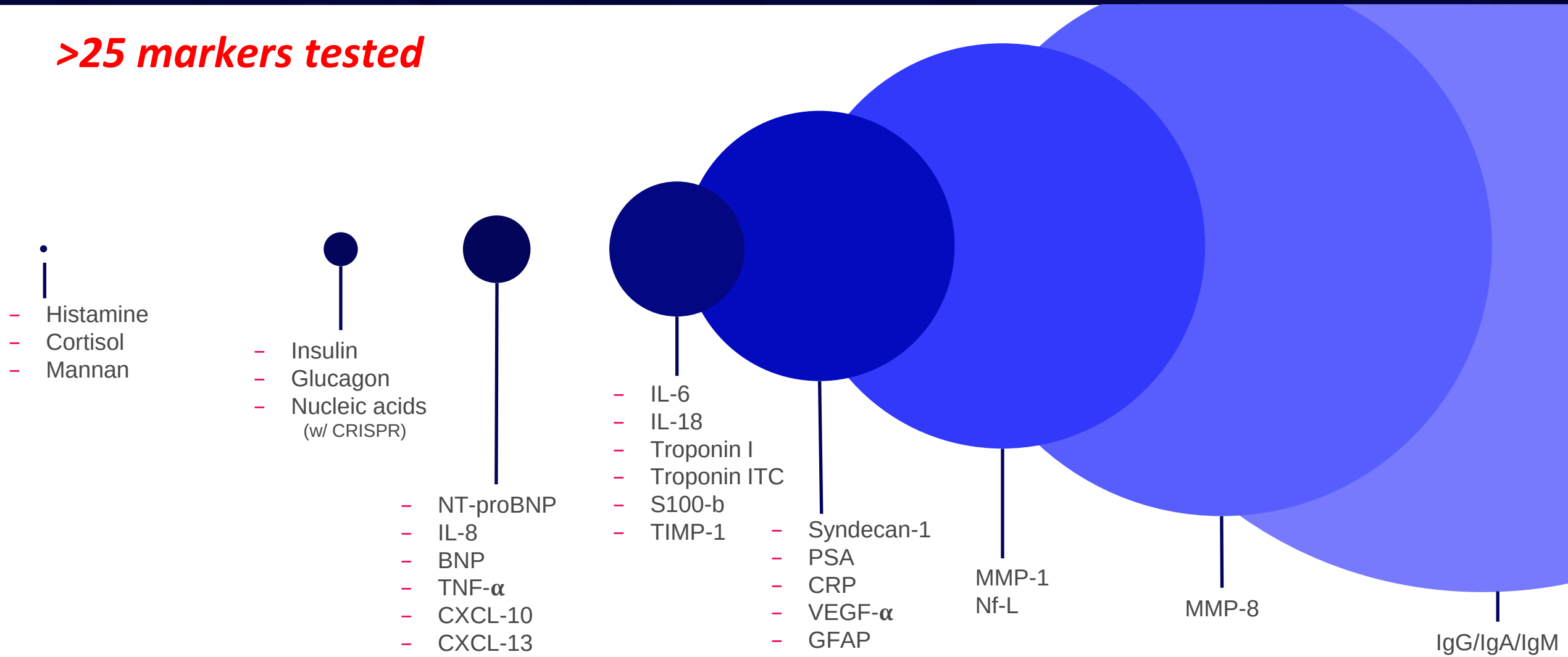


Timilsina et al. *AHM.* 2021

Wyss Institute

eRapid Platform Detects a Wide Range of Analytes

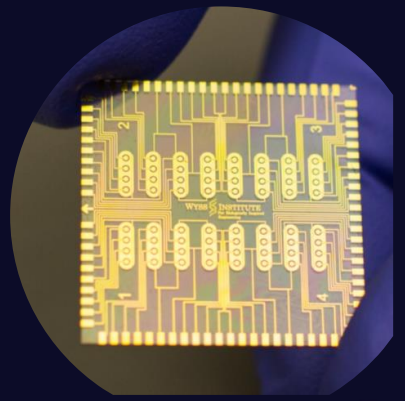
>25 markers tested



(Timilsina et al. *Acc.Chem. Res.* 2021)

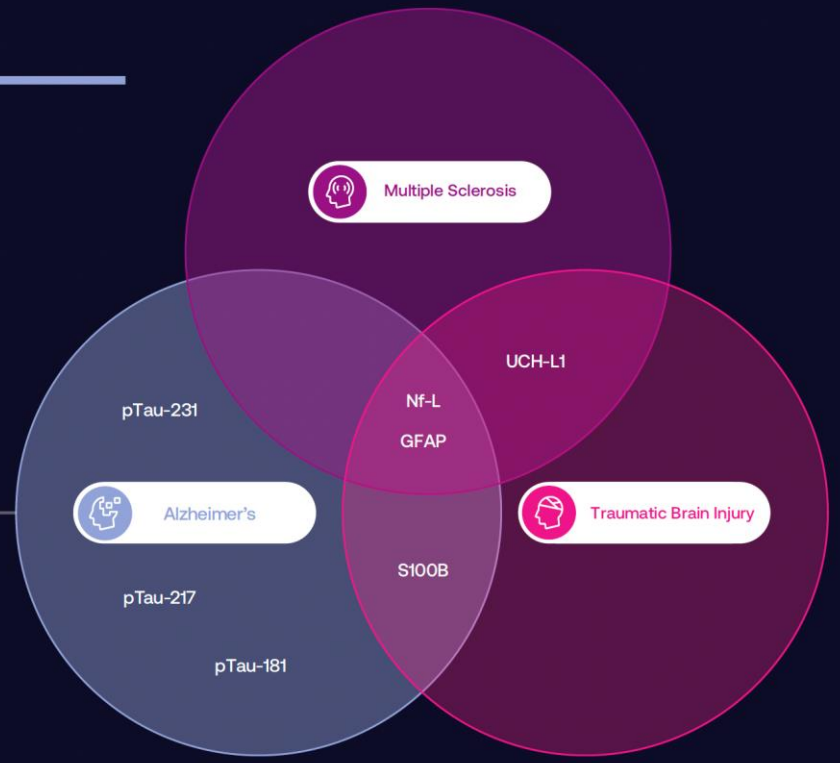
Wyss Institute

What if a simple finger-prick blood test could reduce dependence on the MRI?



STATA DX

We are the building the first point-of-care platform for Neurology



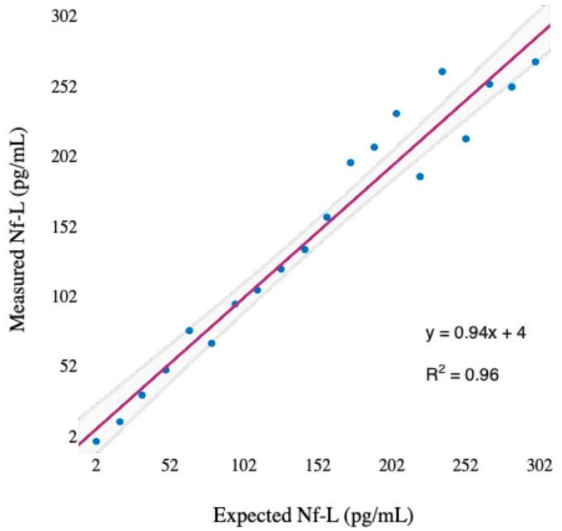
STATA DX

POC Diagnostics for Neurological, Cardiovascular and Renal Diseases

Clinical

Established clinical concordance for Nf-L with Quanterix Simoa at Universitat Basel

Universität Basel



COMPANION DIAGNOSTIC

Rapid Nf-L test for MS

Wyss Institute

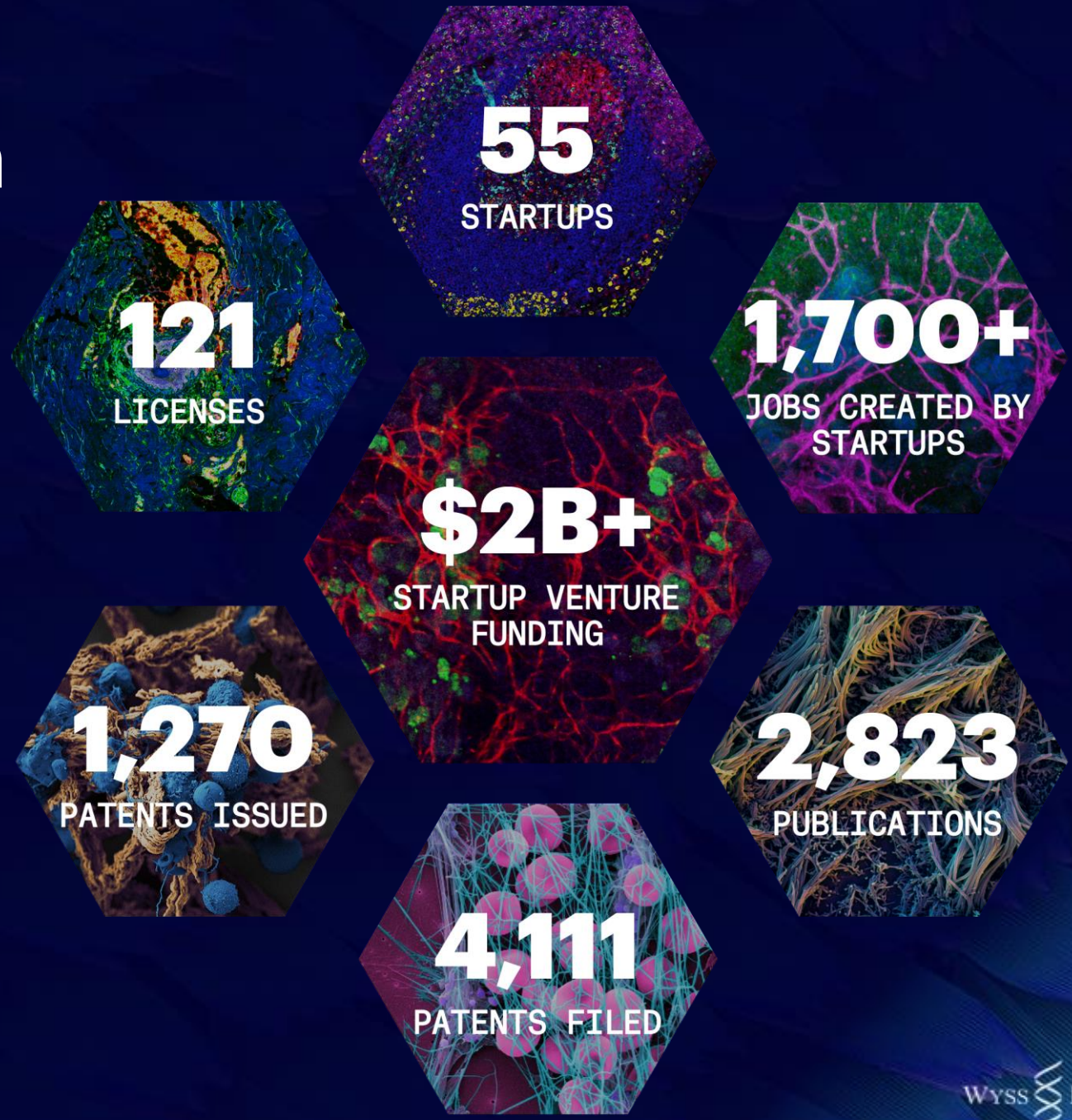
Take Home Message

- *Human Organ Chips are more than potential animal replacements*
- *They are also Mechanistic Drug Discovery Tools that*
  - *can provide new insight into human pathophysiology*
  - *can be combined with advanced analytical (AI) approaches*
  - *enable rapid drug repurposing*
  - *accelerate discovery of novel therapeutics and vaccines*
- ***Bioinspired Engineering offers a new approach to confront major challenges in pharmaceutical development***

WYSS INSTITUTE IMPACT SINCE 2009

Disruptive Innovation Inspired by Nature

We enable >20% of all Harvard IP & startups annually



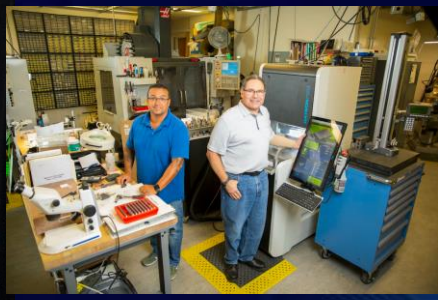
Wyss Institute

Multidisciplinary Team

BIOPHYSICS PHYSIOLOGY ENGINEERING MATERIALS

CELL BIOLOGY IMMUNOLOGY VIROLOGY MEDICINE

MOLECULAR BIOLOGY MICROBIOLOGY PHARMACOLOGY COMPUTATIONAL MODELING

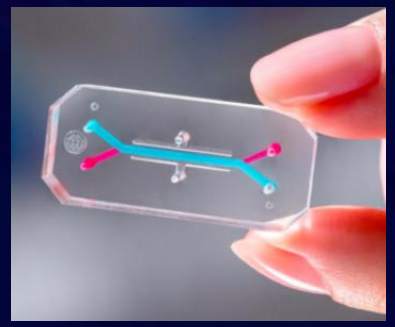


Wyss Institute

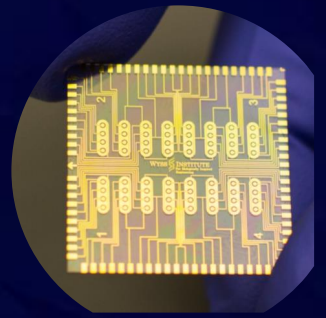
Disclosure Statement of Financial Interest:

- I hold equity, sit on the BODs & chair the Scientific Advisory Boards of:

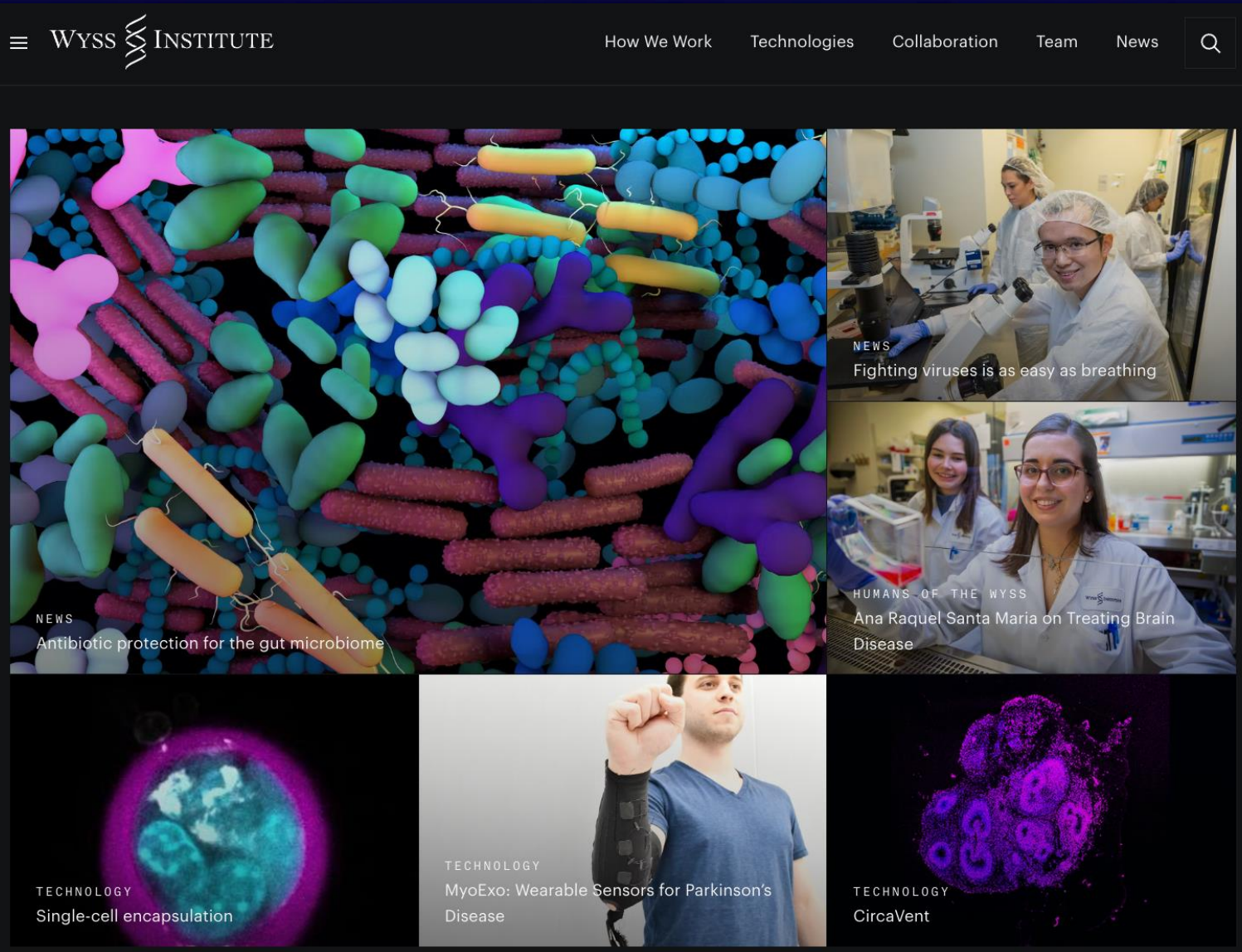
emulate

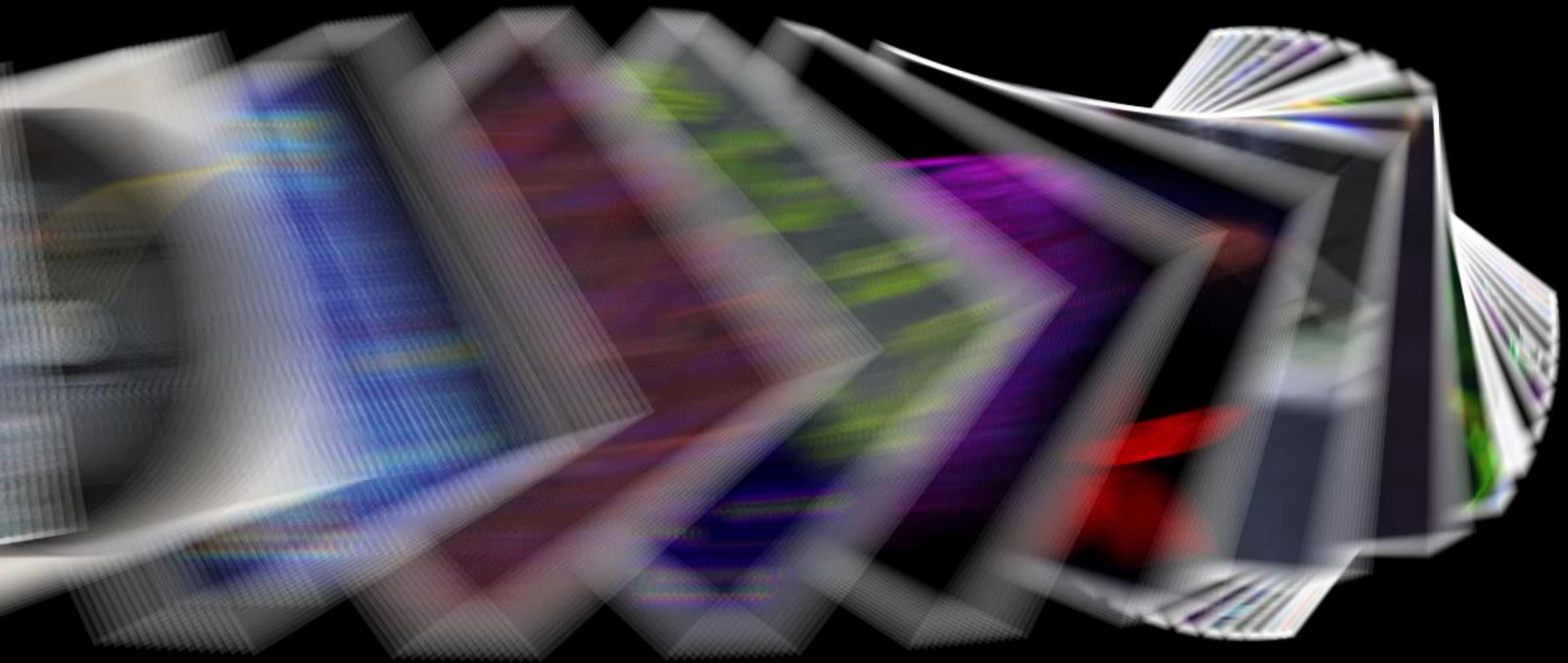


STATA DX



wyss.harvard.edu



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

WYSS INSTITUTE