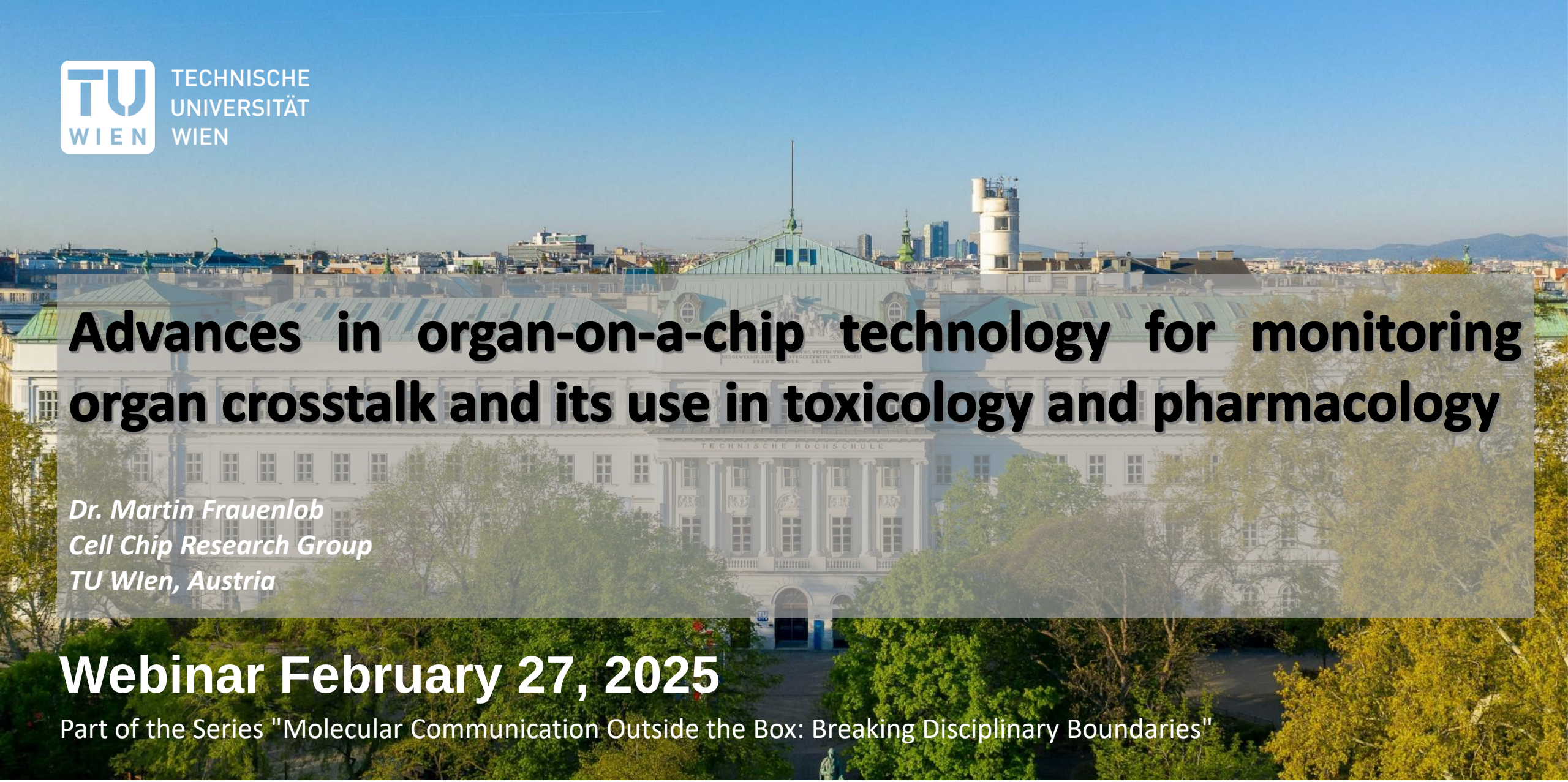


TECHNISCHE UNIVERSITÄT WIEN

Advances in organ-on-a-chip technology for monitoring organ crosstalk and its use in toxicology and pharmacology

Dr. Martin Frauenlob
Cell Chip Research Group
TU Wien, Austria

Webinar February 27, 2025

Part of the Series "Molecular Communication Outside the Box: Breaking Disciplinary Boundaries"

Toxicology & Pharmacology:

Toxicology

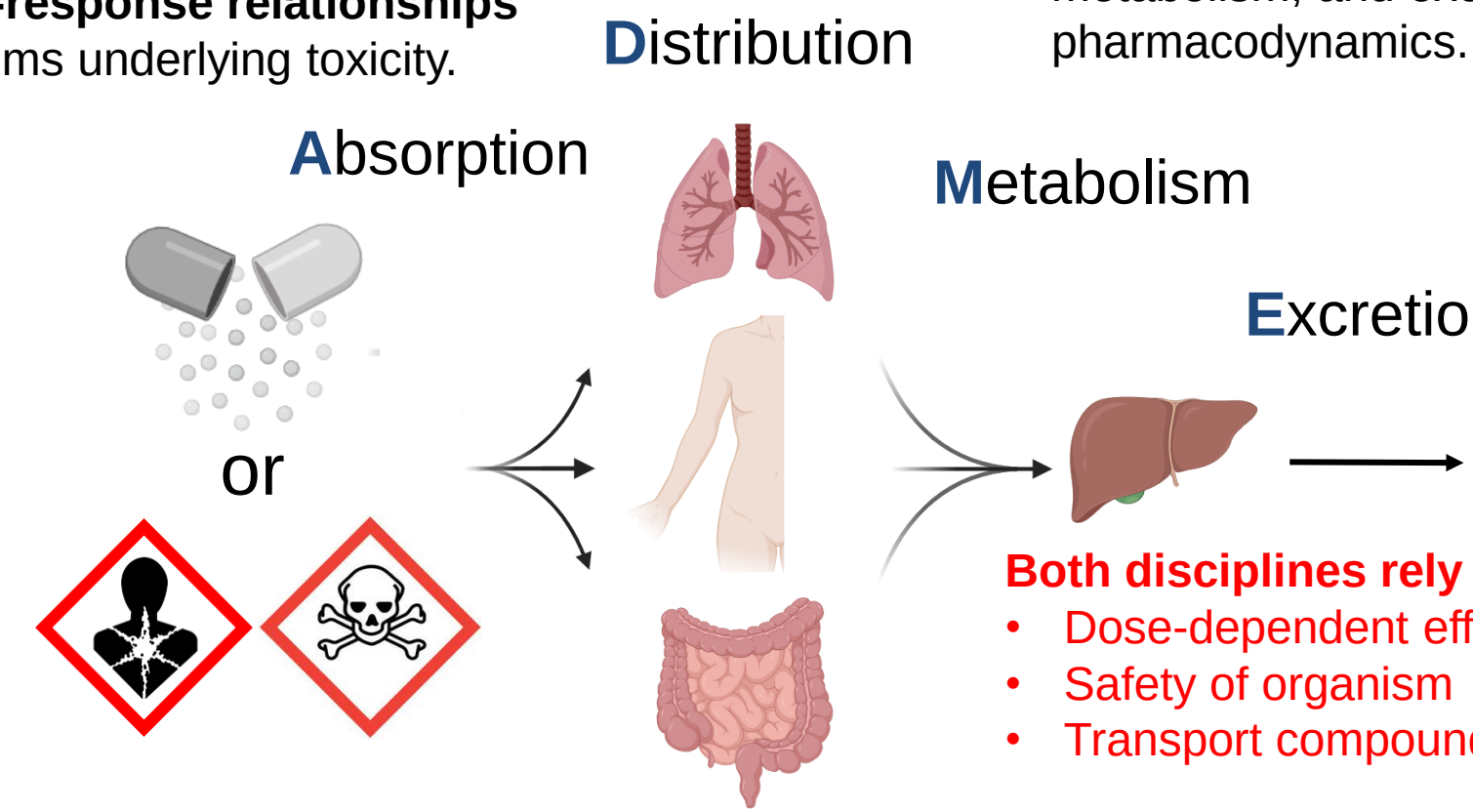
• The **science** of understanding the adverse effects of **chemicals and drugs** on living organisms.

• Examines **dose-response relationships** and the mechanisms underlying toxicity.

Pharmacology

• Focuses on how **drugs** interact with biological systems to identify **therapeutic effects**.

• Involves studying drug absorption, distribution, metabolism, and excretion (**ADME**) and pharmacodynamics.



Both disciplines rely on:

- Dose-dependent effects
- Safety of organism
- Transport compound between organ

Organ crosstalk:

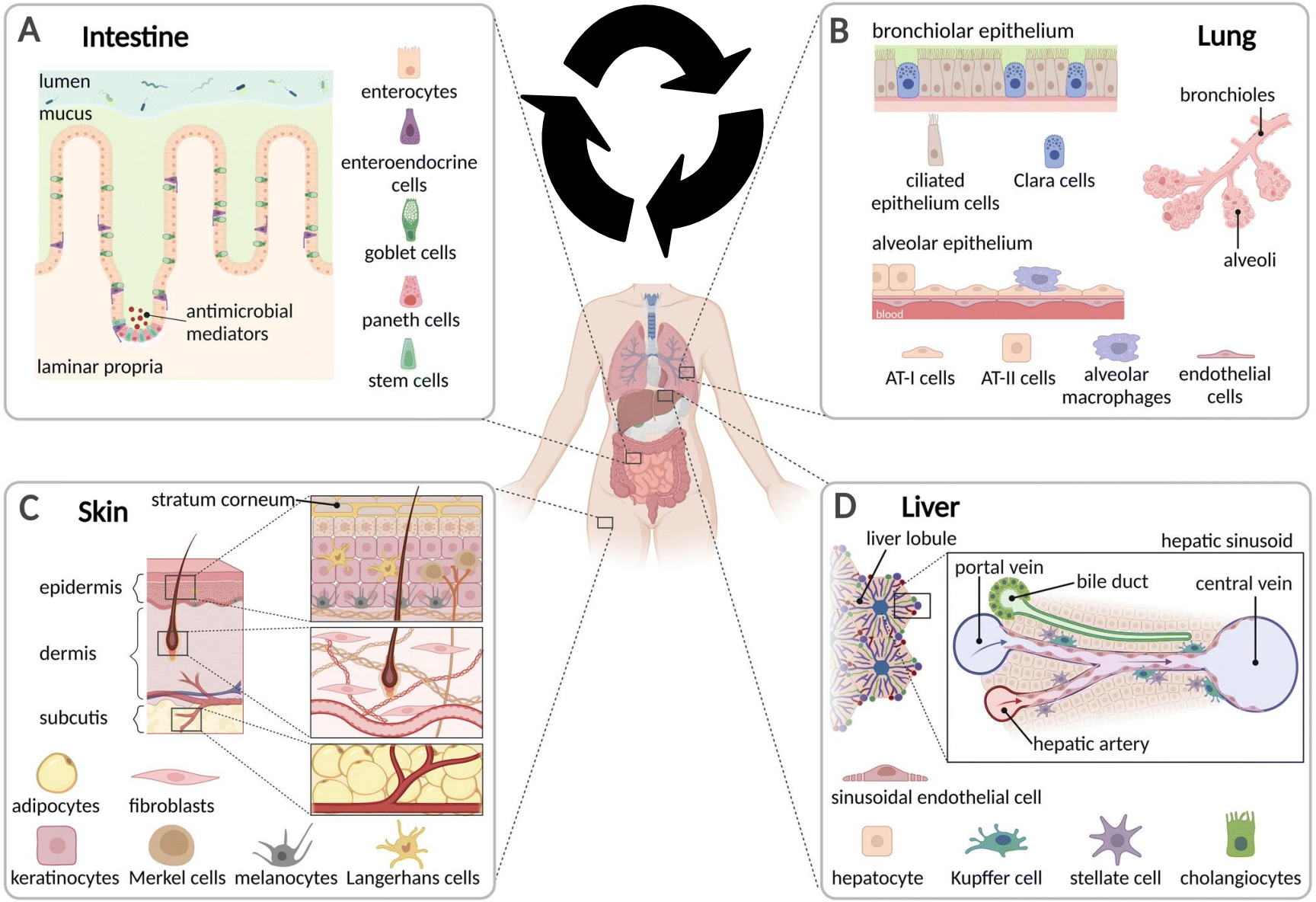
The dynamic, bidirectional **communication** between different organs or tissue systems through:

- Hormones
- Cytokines
- Metabolites
- Neural signals

Different entities of different structure and function that control each other.

Dysregulation can contribute to disease **pathogenesis** and altered drug responses.

Curing this state by administering drugs.
Can lead to **unintended actions** that occur when a drug interacts with receptors or proteins other than its intended target.

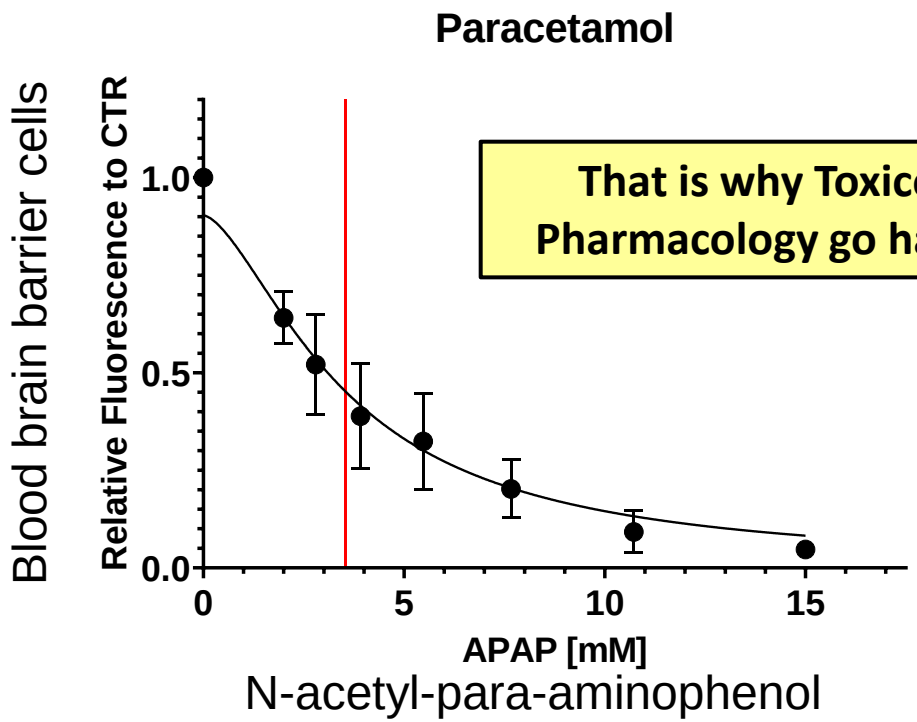


https://pubs.rsc.org/en/content/articlehtml/2025/lc/d4lc01011f

Pharmacology: On-Target / Off-target

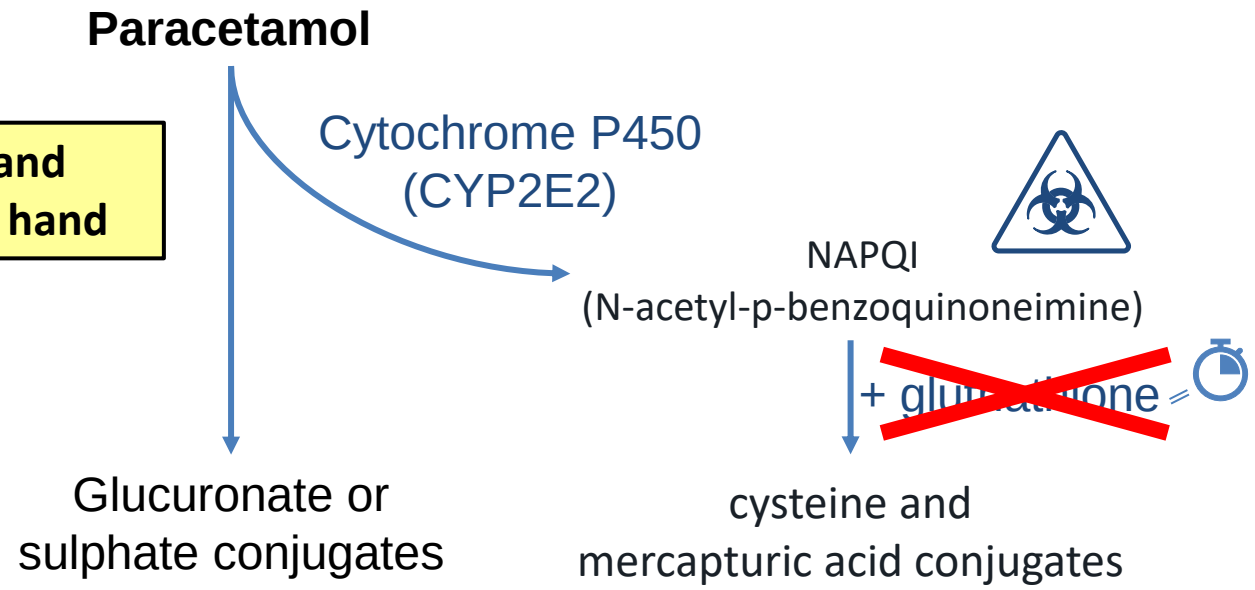
On-Target Effects:
•These are the desired, **primary effects** produced when a drug binds to its intended receptor or molecular target.
•They are responsible for the **therapeutic benefits** of the drug.

Off-Target Effects:
•These are **unintended actions** that occur when a drug interacts with receptors or proteins other than its intended target.
•Off-target effects can lead to side effects or **adverse reactions**.



That is why Toxicology and Pharmacology go hand in hand

Liver vs. Blood brain barrier

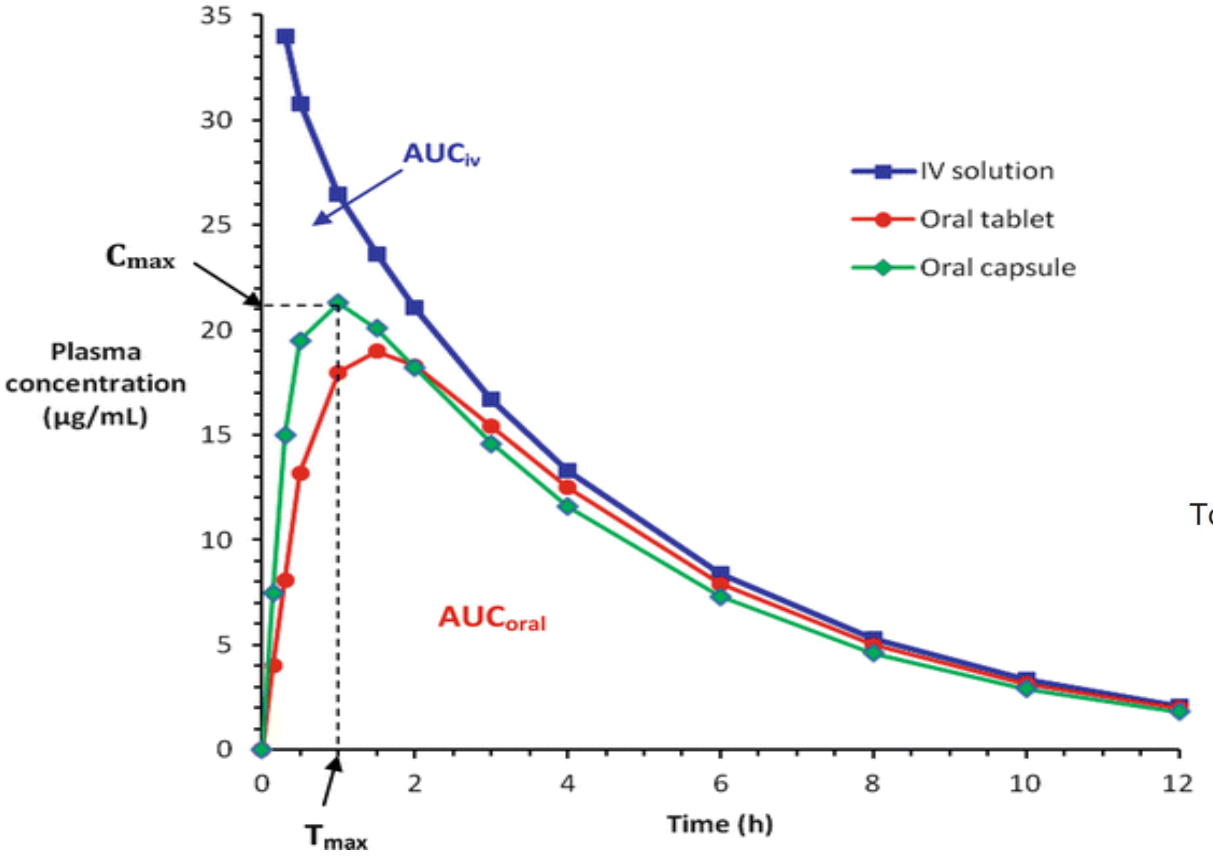


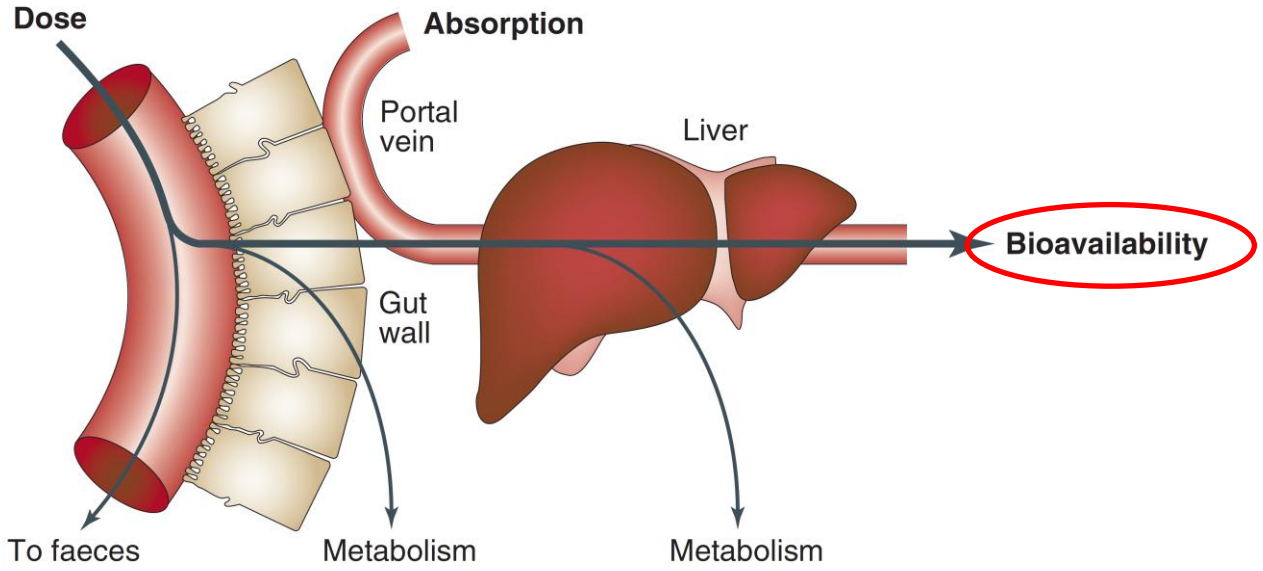
- https://go.drugbank.com/drugs/DB00316
- https://www.ncbi.nlm.nih.gov/books/NBK548162/

Pharmacokinetics:

Time distribution of a drug in the body and specific regions

ADME studies (adsorption, distribution metabolism, excretion) of a drug results in important parameters:





Bioavailability of a drug is the key knowledge for dosing in medicine!

https://basicmedicalkey.com/drug-absorption-and-bioavailability/

Physiologically based Pharmacokinetics

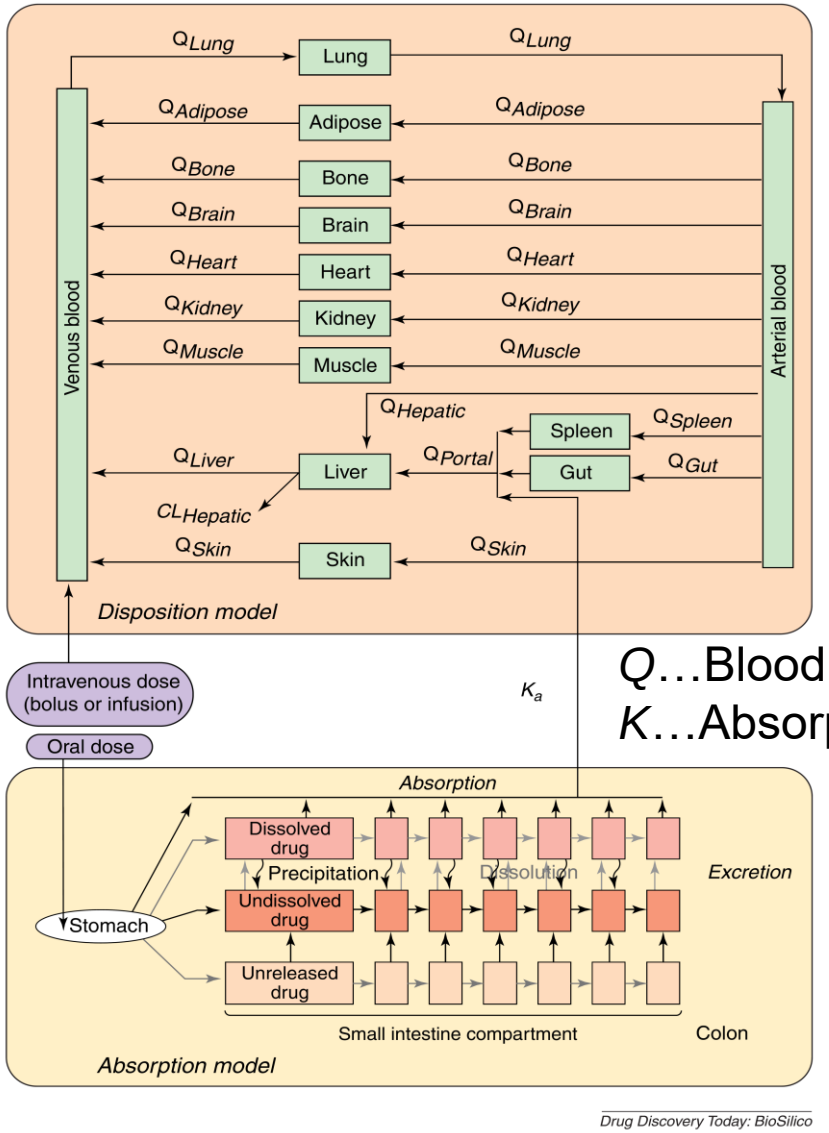


Figure 2. Conceptual PBPK model structure linked to an absorption model [23]. Blood flows are indicated as Q_{organ}, whereas K_a is the rate of absorption.

Q…Blood flow
K…Absorption

PBPK…**P**hysiologically **B**ased **P**harmaco**k**inetic

- PBPK is a predictive model for ADME characteristics of a drug → complex model approaches (especially **Metabolism** with **cytochromes** being the most important enzymes)
- Important to know key parameters for PBPK modeling

Where do we get these key parameters from?

Dickens et al.:DDT: BIOSILICO Vol. 2, No. 1 January 2004

Classical drug testing: Animal model

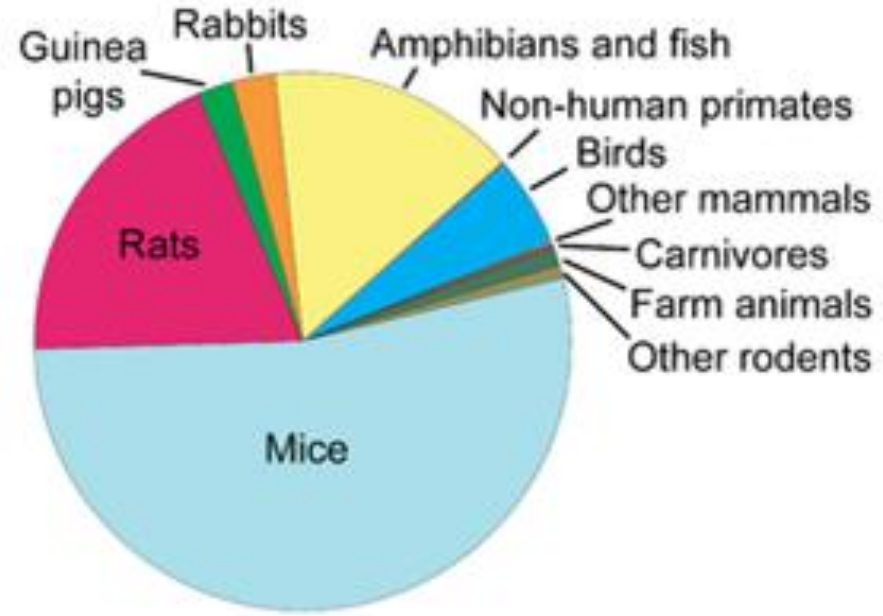
Golden standard with major drawbacks

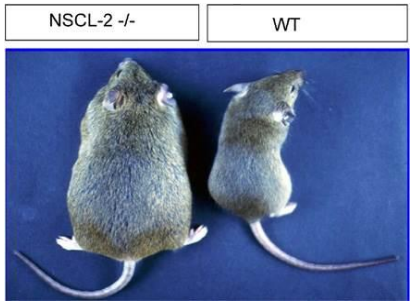
Reproducibility in human

http://www.nj.com/business/index.ssf/2013/07/merck_settles_vioxx_claim_to_p.html

Introduced as anti-inflammatory drug 1999 by Merck, withdrawn in 2004 because of increased risk of heart attack. Linked to over 27.000 deaths between 1999 – 2003 and resulted in more than $5 billion in criminal and civil settlements.

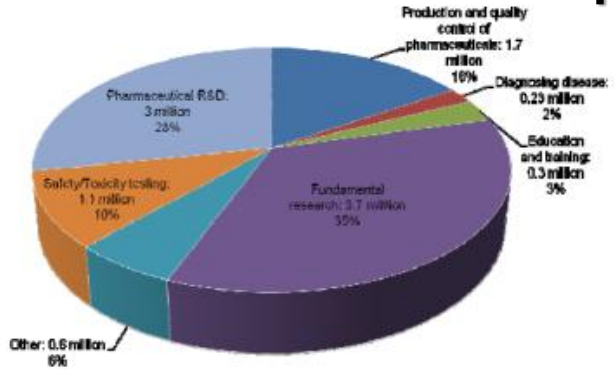
Ethical issue





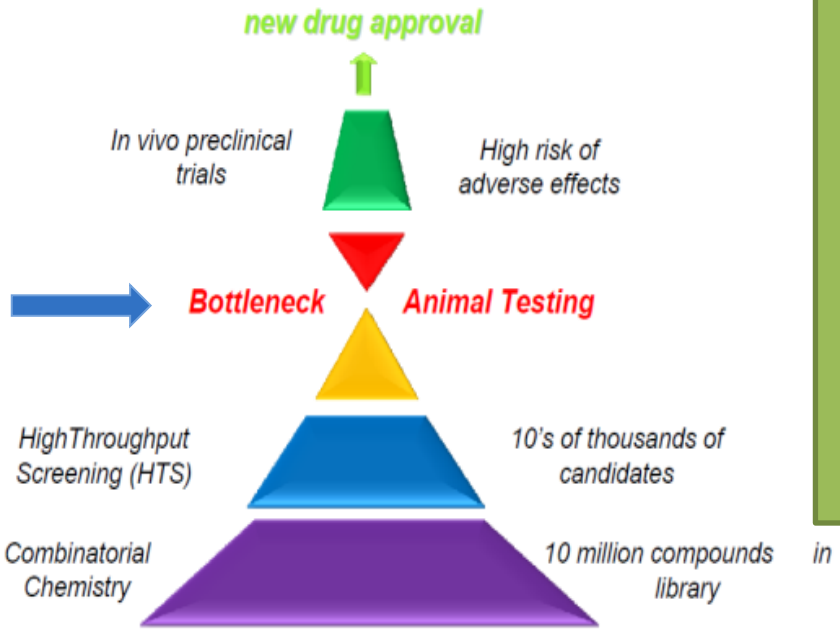
Animal testing in Europe

Approx. 9 million animal test per year



https://www.understandinganimalresearch.org.uk

- 39% fundamental research
- 28% pharmaceutical R&D
- 10% toxicity testing
- 10% quality control
- 3% education and training
- 2% diagnosing of diseases



Animal welfare

- **Animal suffering!**

Cost

Human health

- **Misleading animal test**
  - Lack of validity for *in vivo* validity
  - **Acute toxicity – 43%** concordance for rodent-human
  - **Reproductive toxicity – 50%** concordance for all animals-human
  - 9 out of 10 drug candidates fail in clinical trails

Scientific advisor

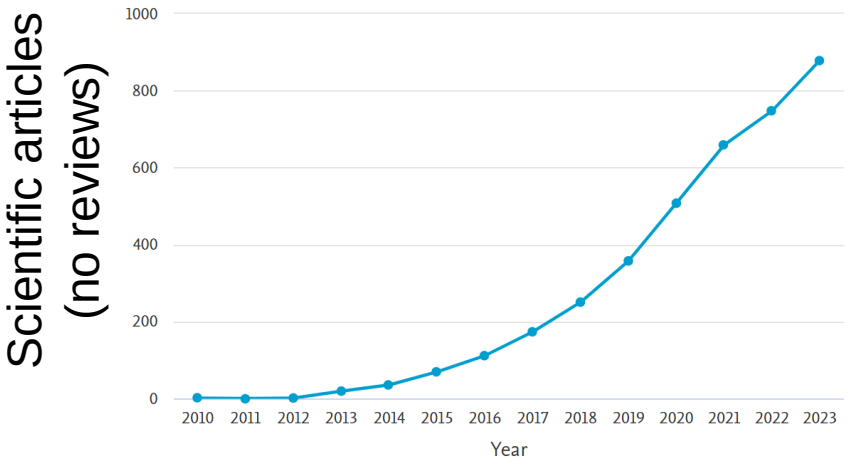
NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

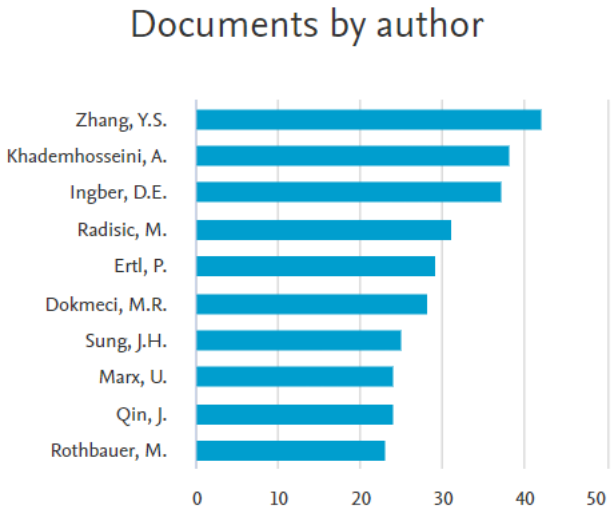
https://www.nc3rs.org.uk/

Activities: 1) funding research through grants and early career awards; 2) supporting commercialisation and uptake of 3Rs technologies and 3) office-led activities (in areas such as toxicology, experimental design and reporting, and animal welfare) for changes in policy, practice and regulation through data sharing and knowledge exchange, and dissemination through guidelines, publications, online resources and scientific events.

The Paradigm Shift

Scopus search: Organ-on-a-Chip





Advancing New Alternative Methods at FDA

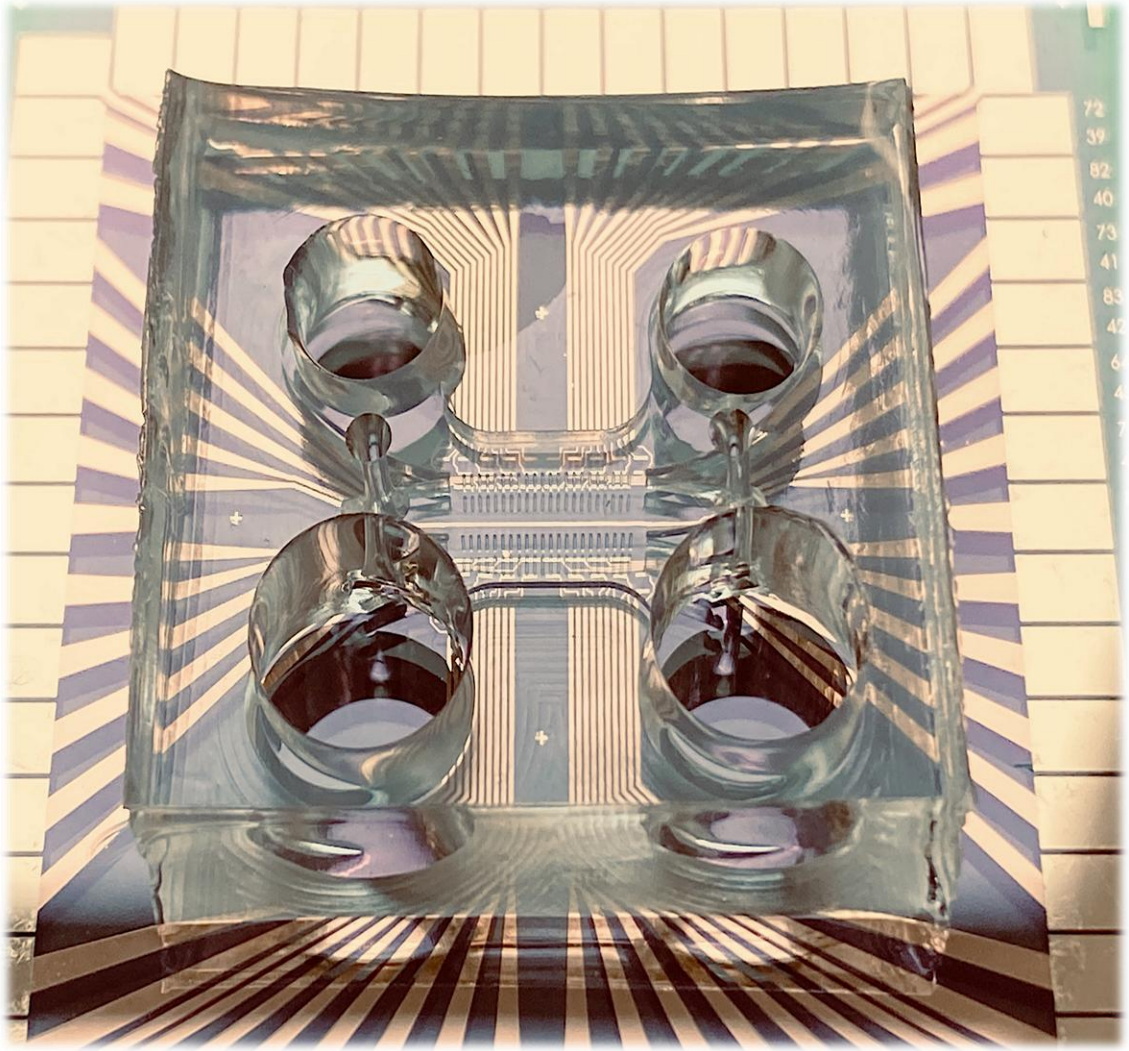
Food and Drug Omnibus Reform Act of 2022 (FDORA)

- Replaced “preclinical tests (including tests on animals)” with “nonclinical tests”

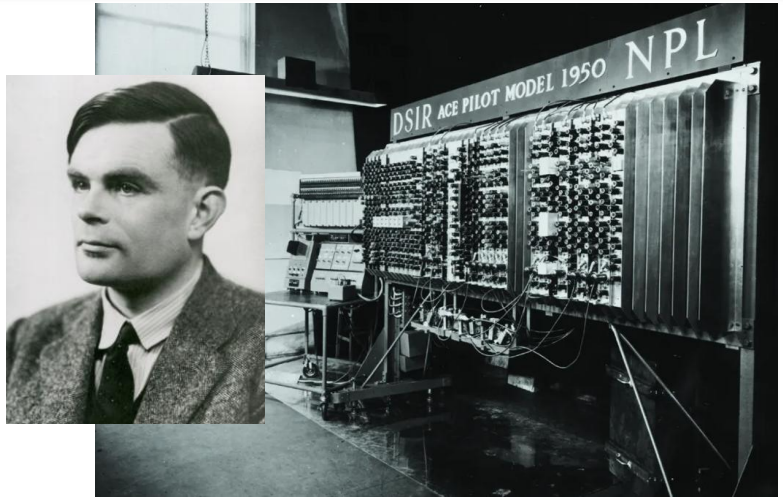
- Defined nonclinical tests as: “a test conducted *in vitro*, *in silico*, or *in chemico*, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such tests may include the following:

(1) Cell-based assays
(2) Organ chips and microphysiological systems 🥳🥳
(3) Computer modeling
(4) Other nonhuman or human biology-based test methods, such as bioprinting.
(5) Animal tests.”

How did Organ-on-a-Chip systems ended up on the list?



Miniaturization



Automated Computing Engine – ACE based on Alan Turings idea in 1950

Personal Computer IBM 5150 in 1981

Zanco Tiny T1 – Samsung Galaxy Z Flip

Relevant ?

Information technology - IT

Portable, Energy-efficient

Miniaturization / Integration / Automation

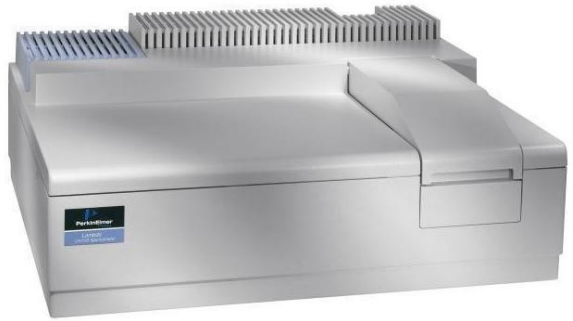
Analytical technology

Economic and Market Demand

UV/Vis Spectrophotometer

Cary Instruments 15 - 1961

Perkin Elmer Lambda 25 - 1992

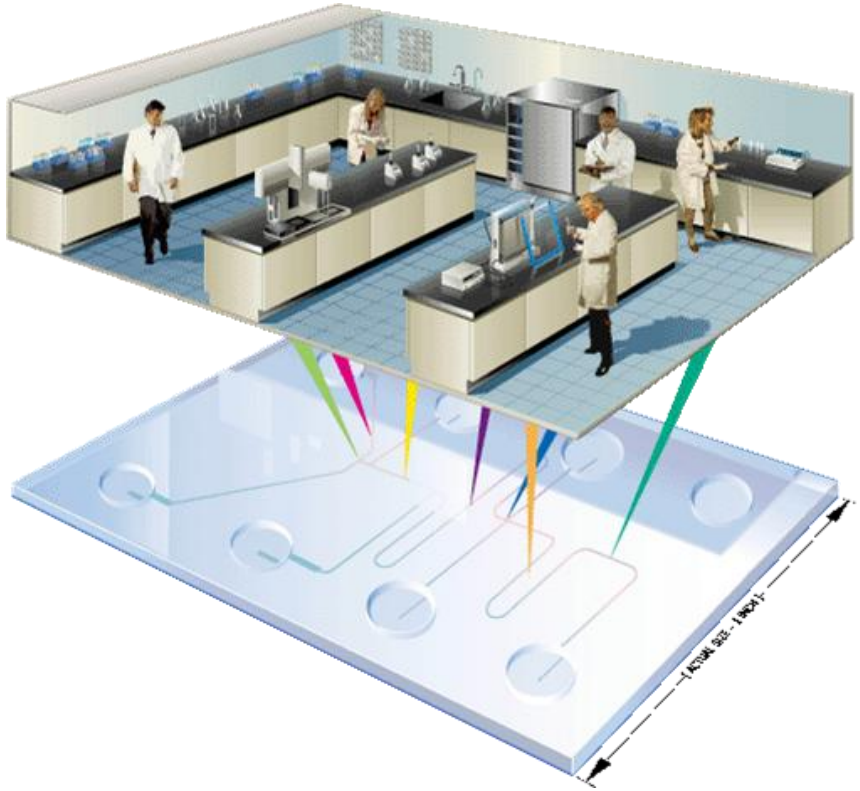


Denovix Nanodrop DS11 - 2017

Miniaturization – Who needs a laboratory?

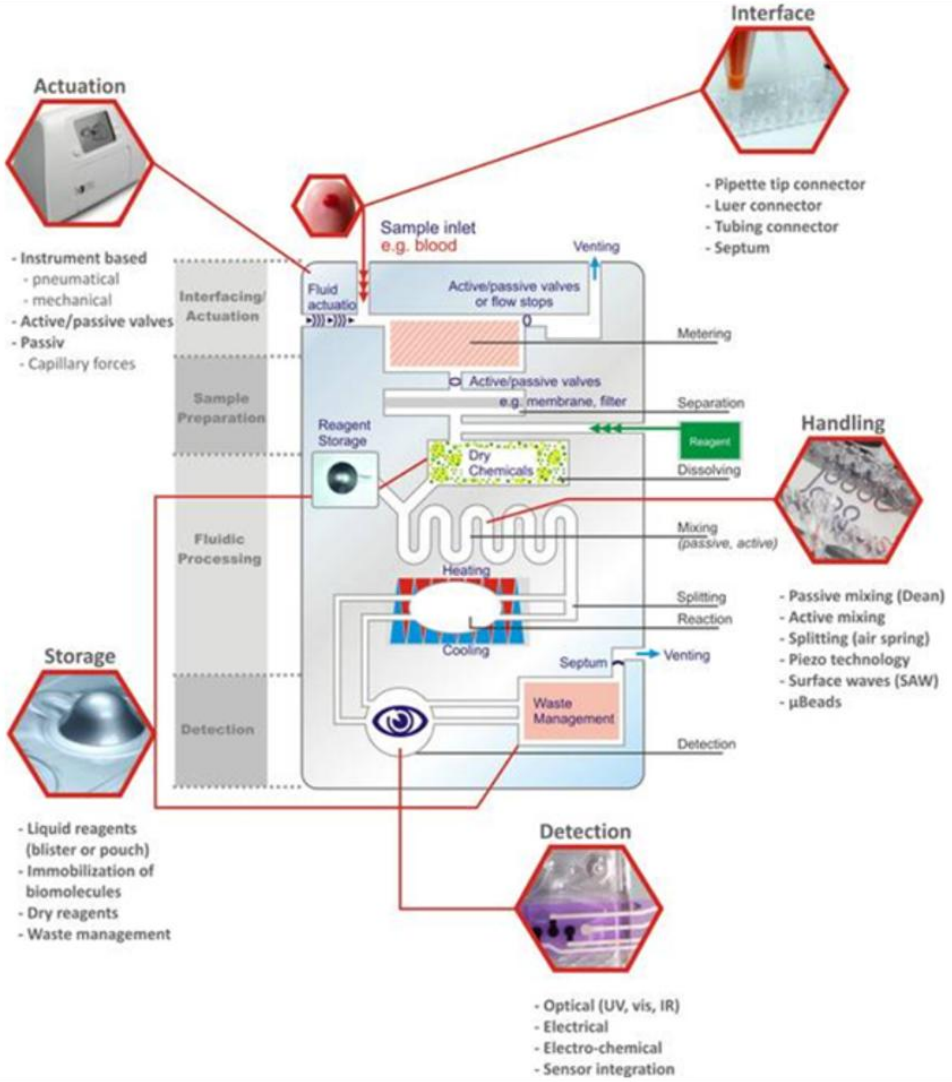
Lab-on-a-chip = Miniaturization of chemical and biological processes

- Microfluidic chip
- Non-fluidic miniaturized systems (e.g. sensors)



https://www.gene-quantification.de/lab-on-chip-index.html (accessed: 09.10.2023)

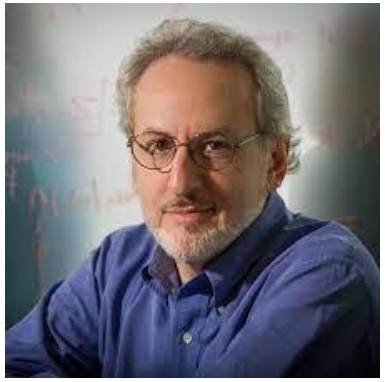
Integration of different functional units (heater, mixer, …)



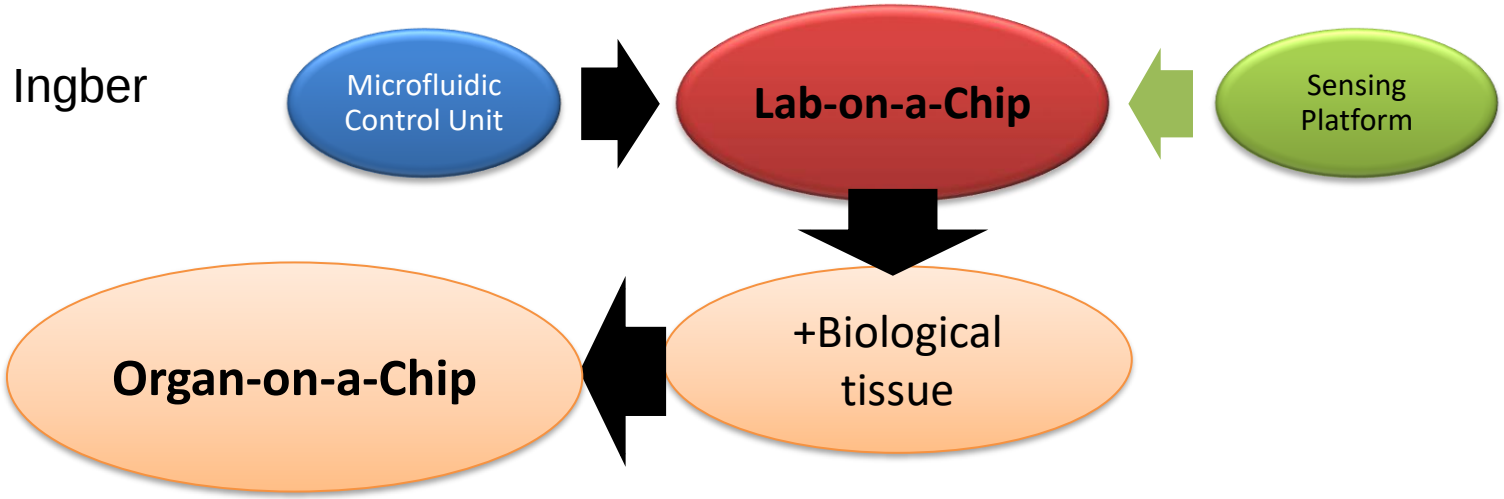
https://www.laserfocusworld.com/optics/article/16569535/idex-buys-microfluidics-maker-thinxxs-microtechnology (accessed: 06.10.2023)

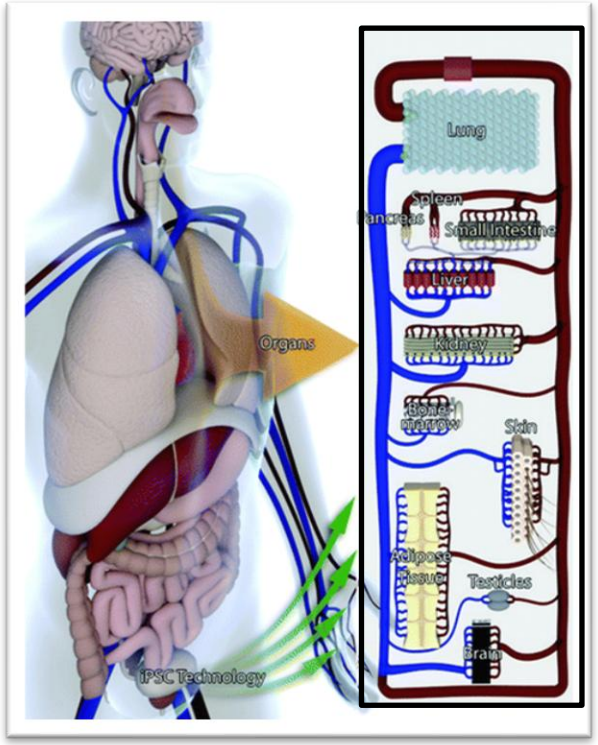
Advancing Drug and Tox Studies: Organ-on-a-Chip

???



Donald E. Ingber



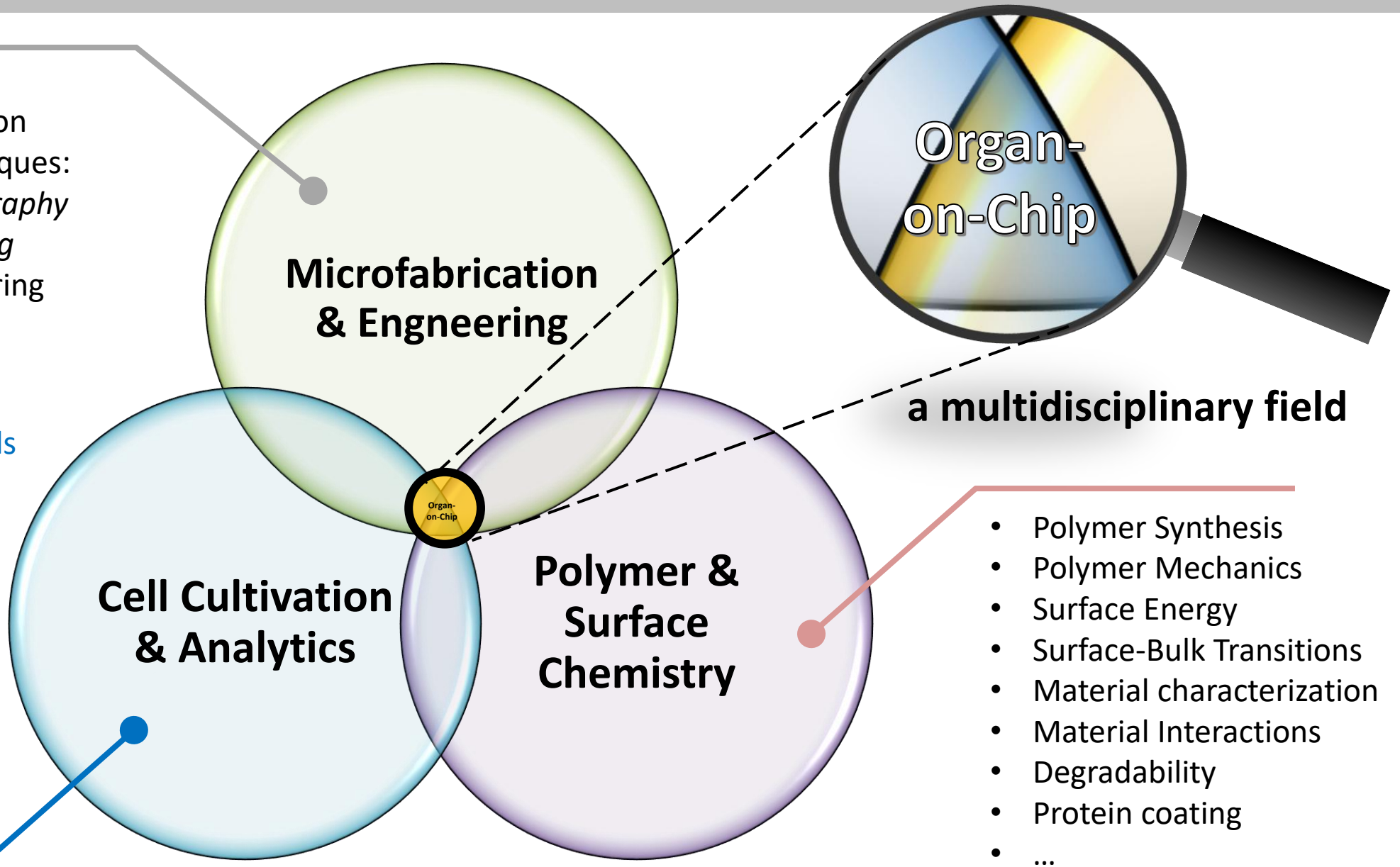


Features to look for in an organ-on-a-chip system:

1. Exhibit **multicellular architecture** that represents characteristics of native tissue
2. **Functional** representation of native tissue (primary cells, h. stem cells, iPSC)
3. Represent **normal and disease** phenotypes

Advancing Drug and Tox Studies: Organ-on-a-Chip

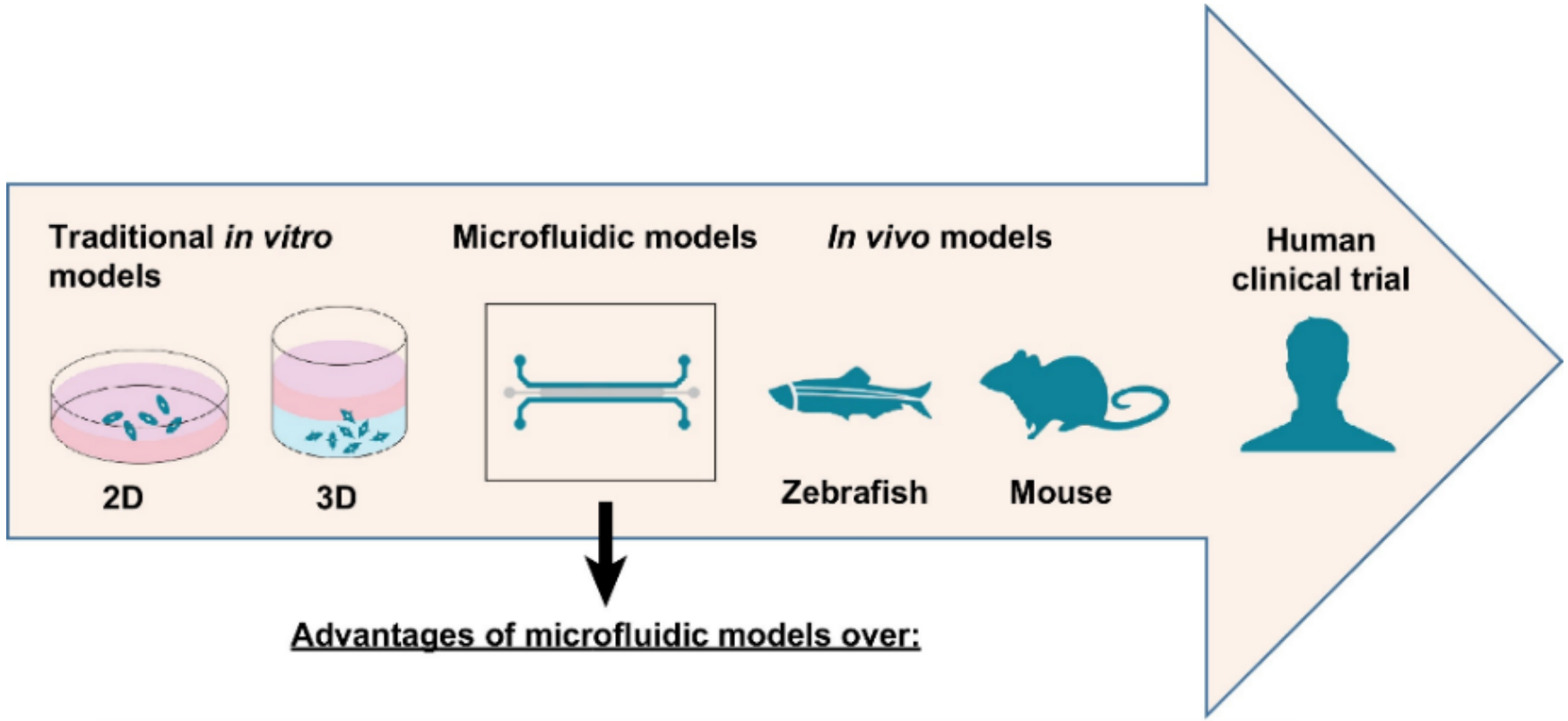
- Fluid Dynamics
- Design & Simulation
- Fabrication techniques:
  - *Soft Lithography*
  - *Micromilling*
- Electrical Engineering
- …



- Isolation of primary cells
- Maintenance:
  - *2D / 3D*
  - *Spheroid*
  - *Organoid*
- Cell Differentiation
- Analytics:
  - *FACS, ELISA*
  - *Western blot*
  - *PCR, Sequencing*
- …

- Polymer Synthesis
- Polymer Mechanics
- Surface Energy
- Surface-Bulk Transitions
- Material characterization
- Material Interactions
- Degradability
- Protein coating
- …

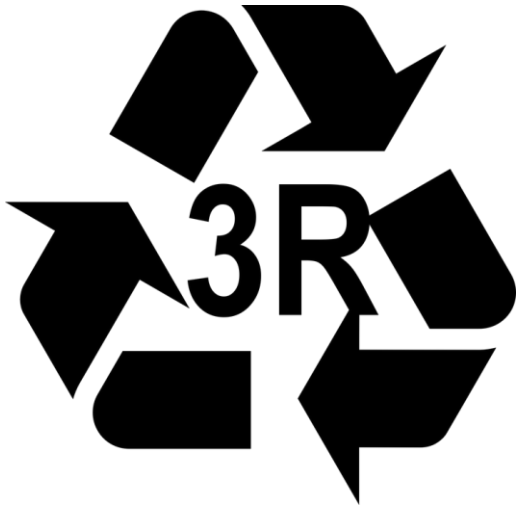
Advancing Drug and Tox studies: Organ-on-a-Chip



Advantages of microfluidic models over:

Traditional *in vitro*	Traditional *in vitro* and *in vivo* models	*In vivo* models
-Ability to directly perfuse vascularized structures	-Increased control of microenvironment -Improved imaging capabilities -Fewer cells and less drug needed	-Use of cells exclusively of human origin

Tissue engineering to **reduce** the quantity of ***in vivo*** models used

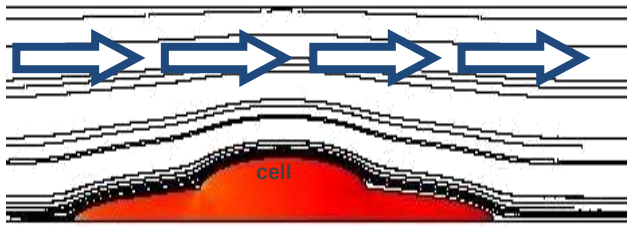


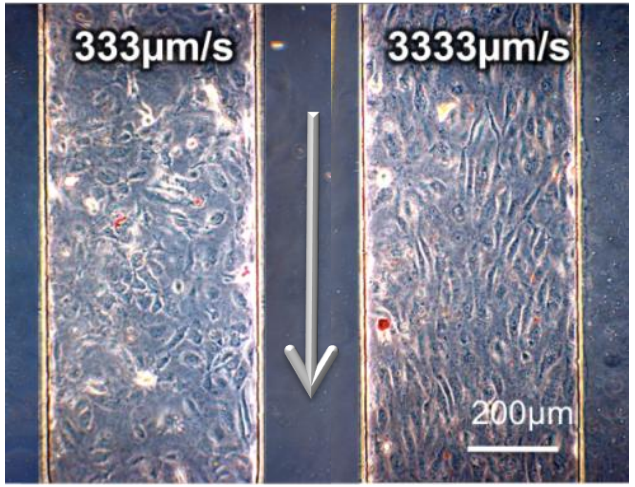
Reduce, **R**ecycle, **R**euse

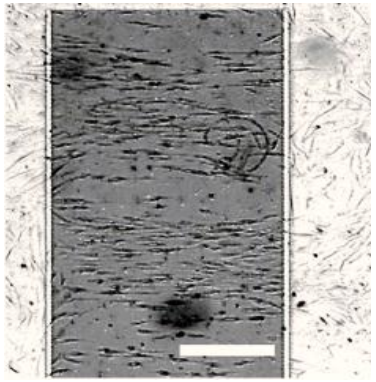
*Organs-on-chips at the frontiers of drug discovery Eric W. Esch, Anthony Bahinski & Dongeun Huh Nature Reviews Drug Discovery volume 14, pages 248–260 (2015)

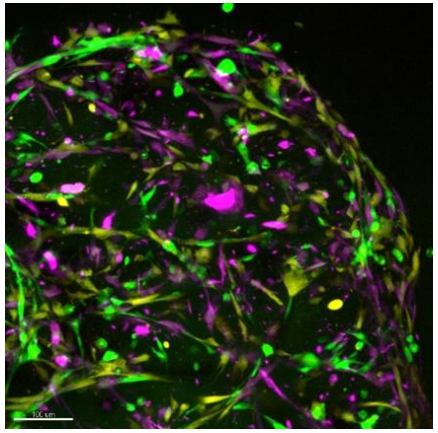
Organ-on-a-Chip: Biological relevance

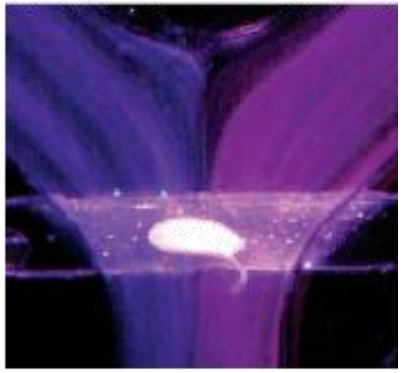
- **Mechanical forces**
  - Shear effects
- **Transport phenomena**
  - Cell treatment with laminar flow
  - Diffusional mixing
  - Surface area to volume ratio
  - Effective culture volume
- **Temperature effects**
- **Material biointerfaces**
  - Surface adsorption
  - Cell adhesion & repulsion
  - Biocompatibility
  - Surface patterning

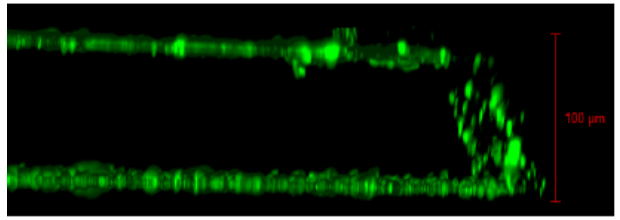








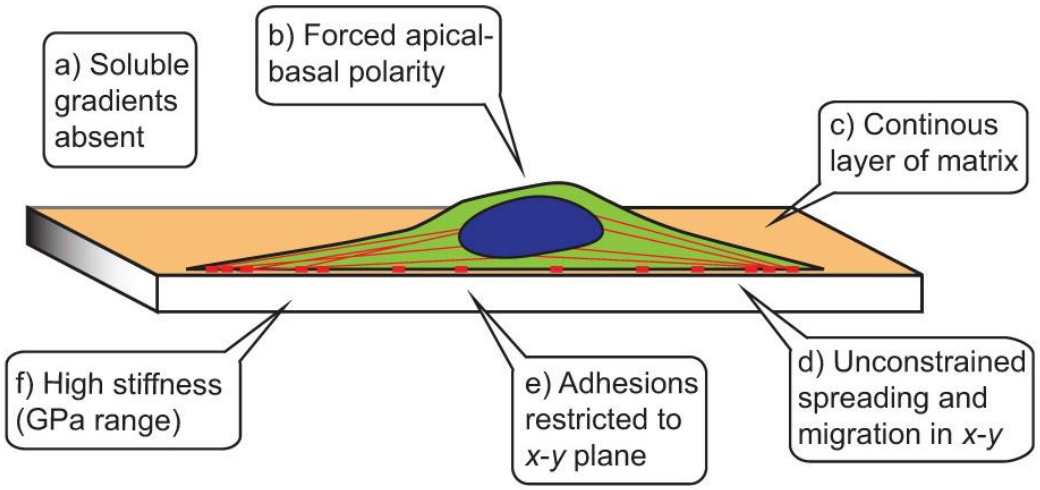




Organ-on-a-Chip: Biological relevance

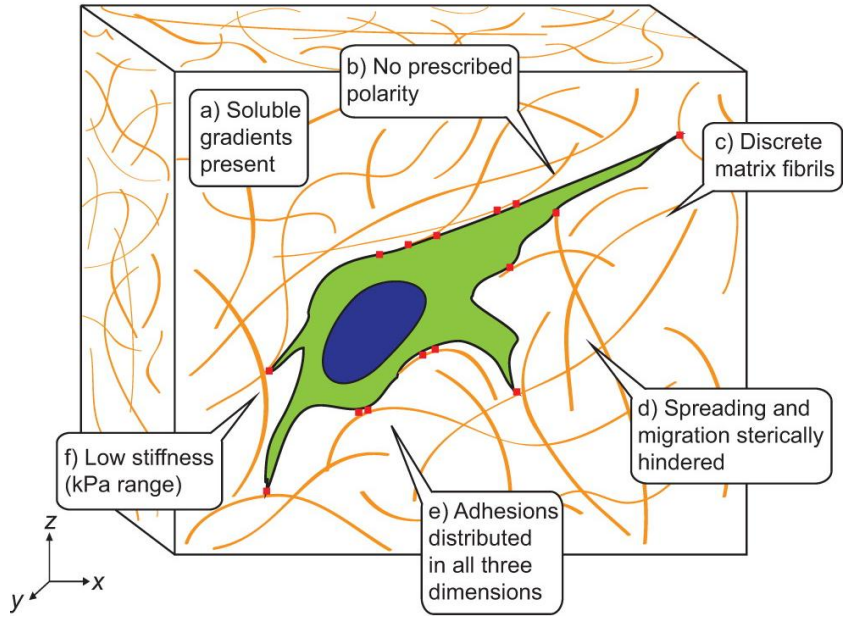
Standard *in vitro* cultures

- 2D environment
- Plastic dishes (GPa)
- Monoculture
- Cell lines (immortalized)
- No mechanical stimuli
- 21% O_2



In vivo environment

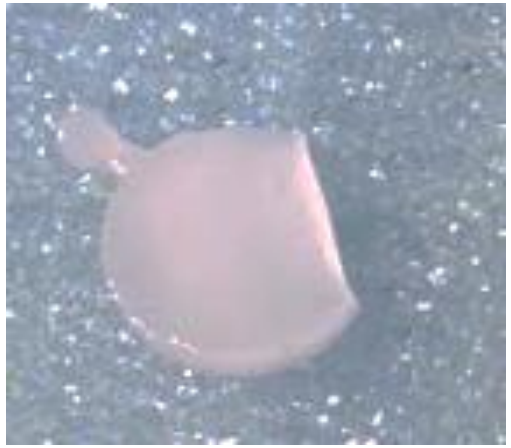
- 3D environment
- Complex matrices (Pa - MPa)
- Cellular heterogeneity
- Primary cells
- Various mechanical stimuli
- 0.1 – 21% O_2



Baker BM, Chen CS. 2012. Deconstructing the third dimension: how 3D culture microenvironments alter cellular cues. J Cell Sci. 2012 Jul 1;125(Pt 13):3015-24. doi: 10.1242/jcs.079509. Epub 2012 Jul 13.

Emulating the cellular microenvironment

- Hydrogels
  - Natural (collagen, fibrin, matrigel, silk..)
  - Synthetic (PEG, PLA, PVA, PMMA…)
  - Stiffness tunable in Pa – kPa range
  - Variable pore size
  - Injectable

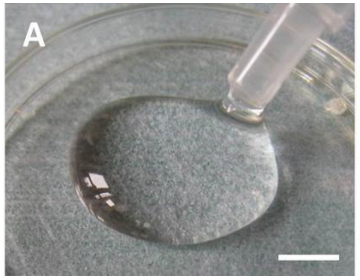


In vivo microenvironment

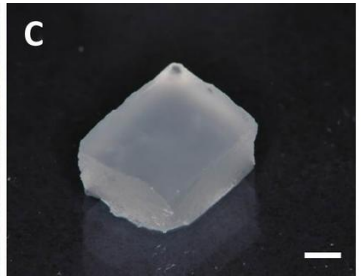
- **3D environment**
- **Complex matrices (Pa - MPa)**
- Cellular heterogeneity
- Primary cells
- Various mechanical stimuli
- 0.1 – 21% O_2

- Degradability (MMP-2)
- Cell adhesion (RGD-sequence, surface charge)

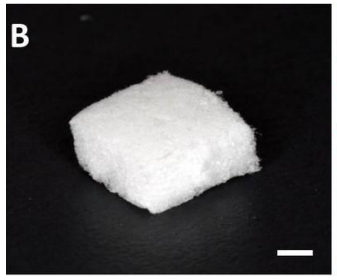
- Natural (collagen, hydroxyapatite,…)
- Synthetic (Bioglass, nanofibers,..)
- Stiffness tunable in MPa – GPa range



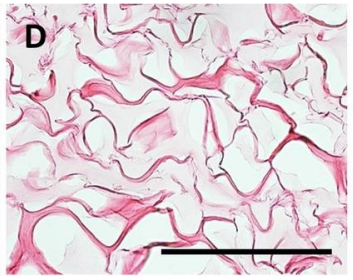
Collagen hydrogel



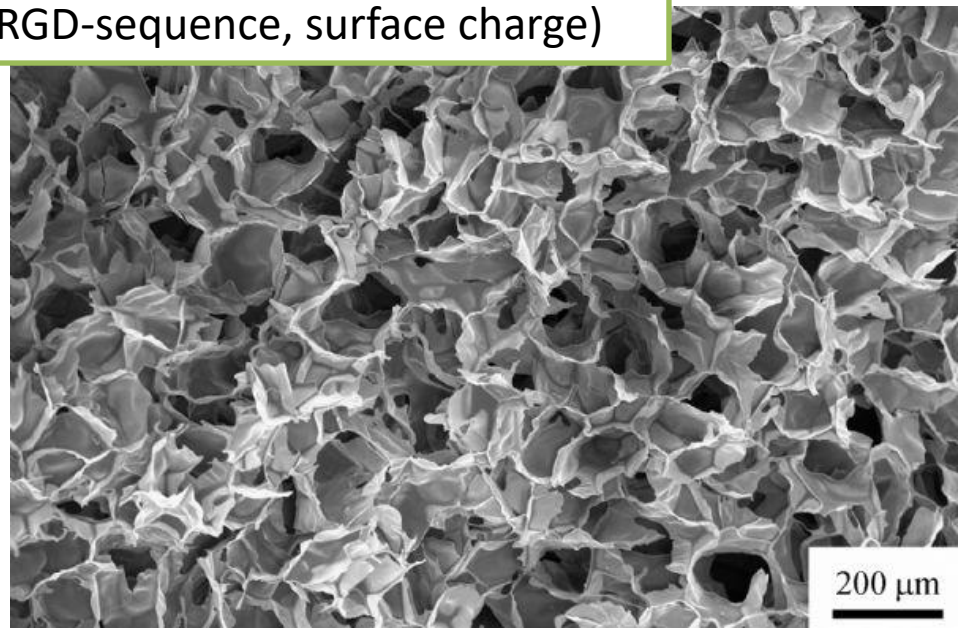
Collagen hydrogel scaffold



Collagen sponge



Structure of collagen hydrogel scaffold



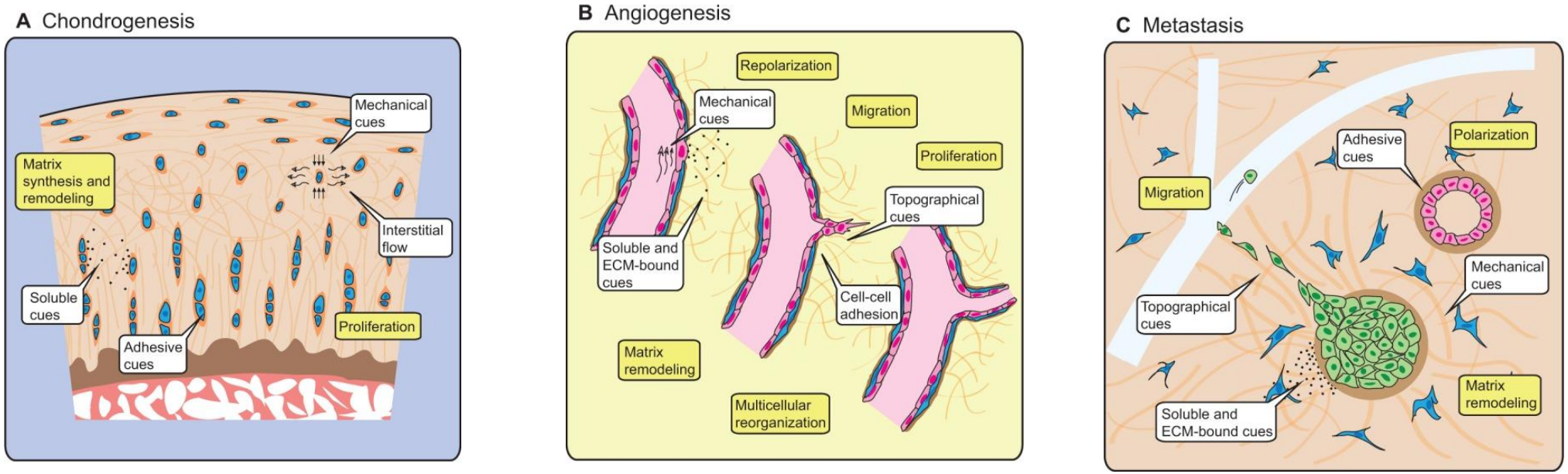
Kato A et al. 2015. Combination of Root Surface Modification with BMP-2 and Collagen Hydrogel Scaffold Implantation for Periodontal Healing in Beagle Dogs. Open Dent J. 2015 Jan 30;9:52-9. doi: 10.2174/1874210601509010052. eCollection 2015.

Emulating the cellular microenvironment

- Complexity
  - Heterogenous cell types (Cell-cell interaction, reciprocal signalling)
  - Single cell type
- Choice of cell type
  - Cell lines (Cancer cells, immortalized primary cells)
  - Primary cells (Isolated from traget tissue)
  - iPSCs and stem cells (Personalized medicine)

***In vivo* microenvironment**

- 3D environment
- Complex matrices (Pa - MPa)
- **Cellular heterogeneity**
- **Primary cells**
- Various mechanical stimuli
- 0.1 – 21% O_2

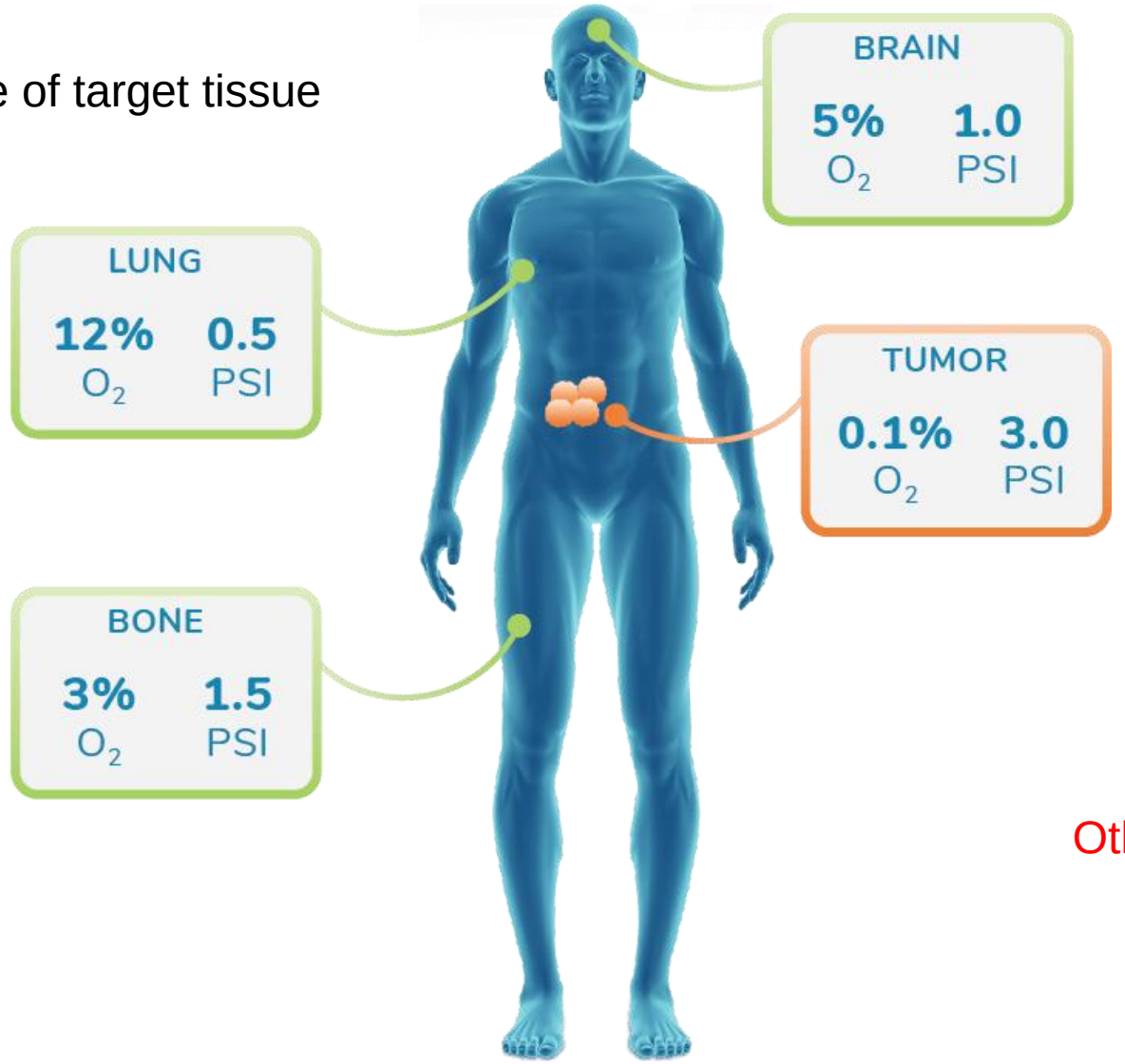


Baker BM, Chen CS. 2012. Deconstructing the third dimension: how 3D culture microenvironments alter cellular cues. J Cell Sci. 2012 Jul 1;125(Pt 13):3015-24. doi: 10.1242/jcs.079509. Epub 2012 Jul 13.

Emulating the cellular microenvironment

Oxygen tension

- Respective of target tissue



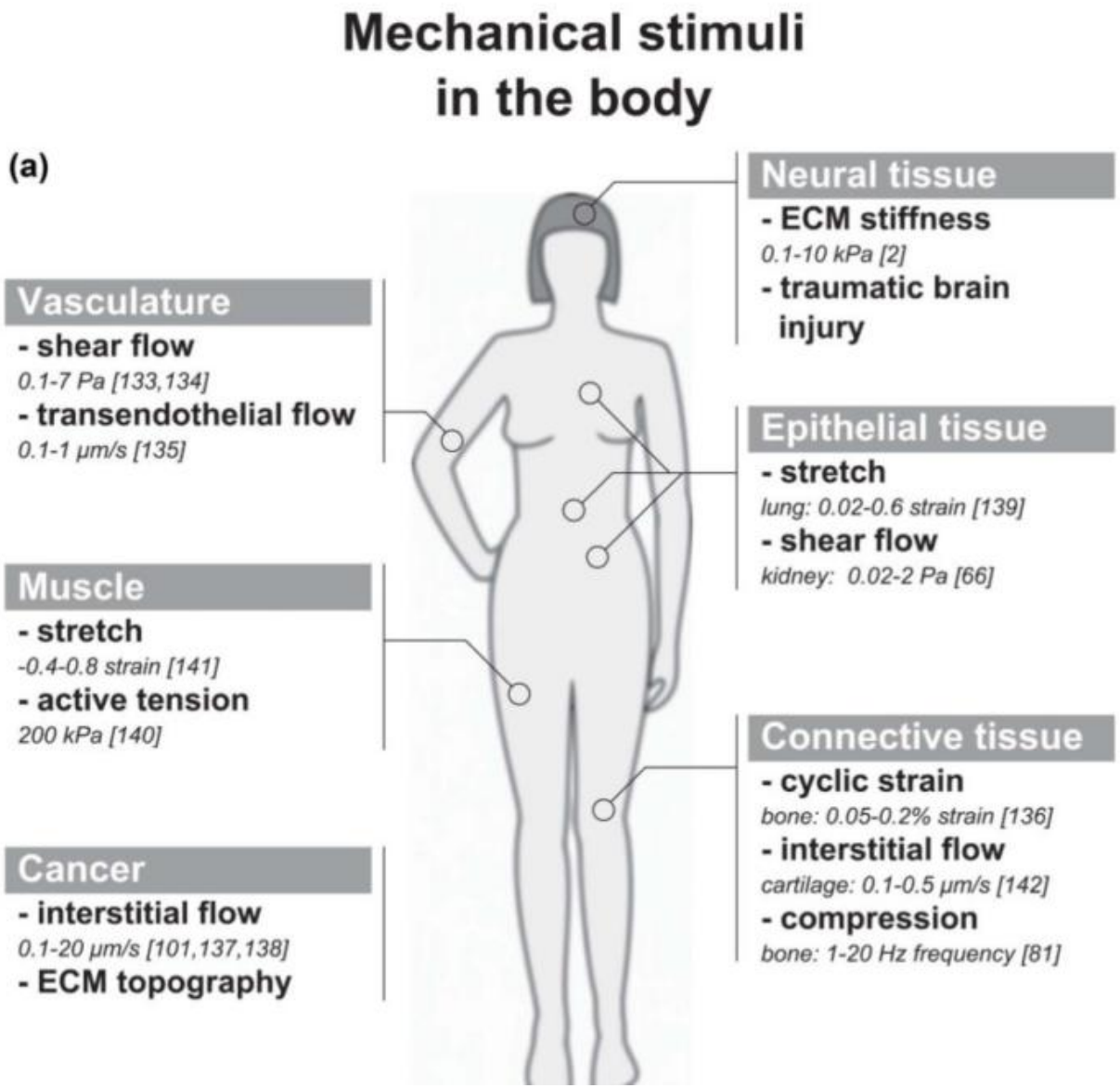
https://www.xcellbio.com/avatar/

In vivo microenvironment

- 3D environment
- Complex matrices (Pa - MPa)
- Cellular heterogeneity
- Primary cells
- **0.1 – 21% O_2**
- Various mechanical stimuli

Other gaso-transmitters?

Emulating the cellular microenvironment



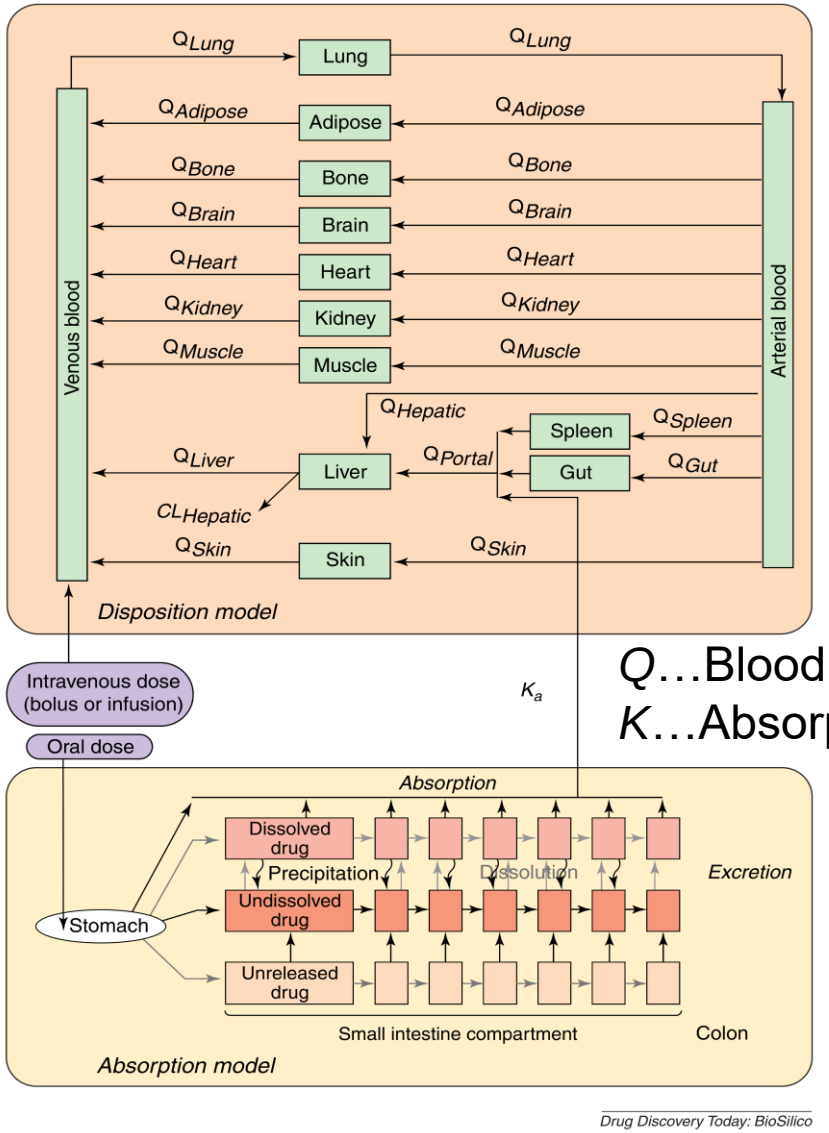
Polacheck et al. 2012. Microfluidic platforms for mechanobiology. Lab Chip. 2013 Jun 21; 13(12): 2252–2267.

In vivo microenvironment

- 3D environment
- Complex matrices (Pa - MPa)
- Cellular heterogeneity
- Primary cells
- 0.1 – 21% O2
- **Various mechanical stimuli**

- Mechanical properties
  - ECM stiffness
  - Topology
  - Curvature
- Mechanical deformation
  - Shear stress/Interstitial flow
  - (Cylic) stretching
  - Compression
  - Strain-stiffening

Pharmacokinetics – model-based strategies



Drug Discovery Today: BioSilico

Figure 2. Conceptual PBPK model structure linked to an absorption model [23]. Blood flows are indicated as Q_{organ}, whereas K_a is the rate of absorption.

Q…Blood flow
K…Absorption

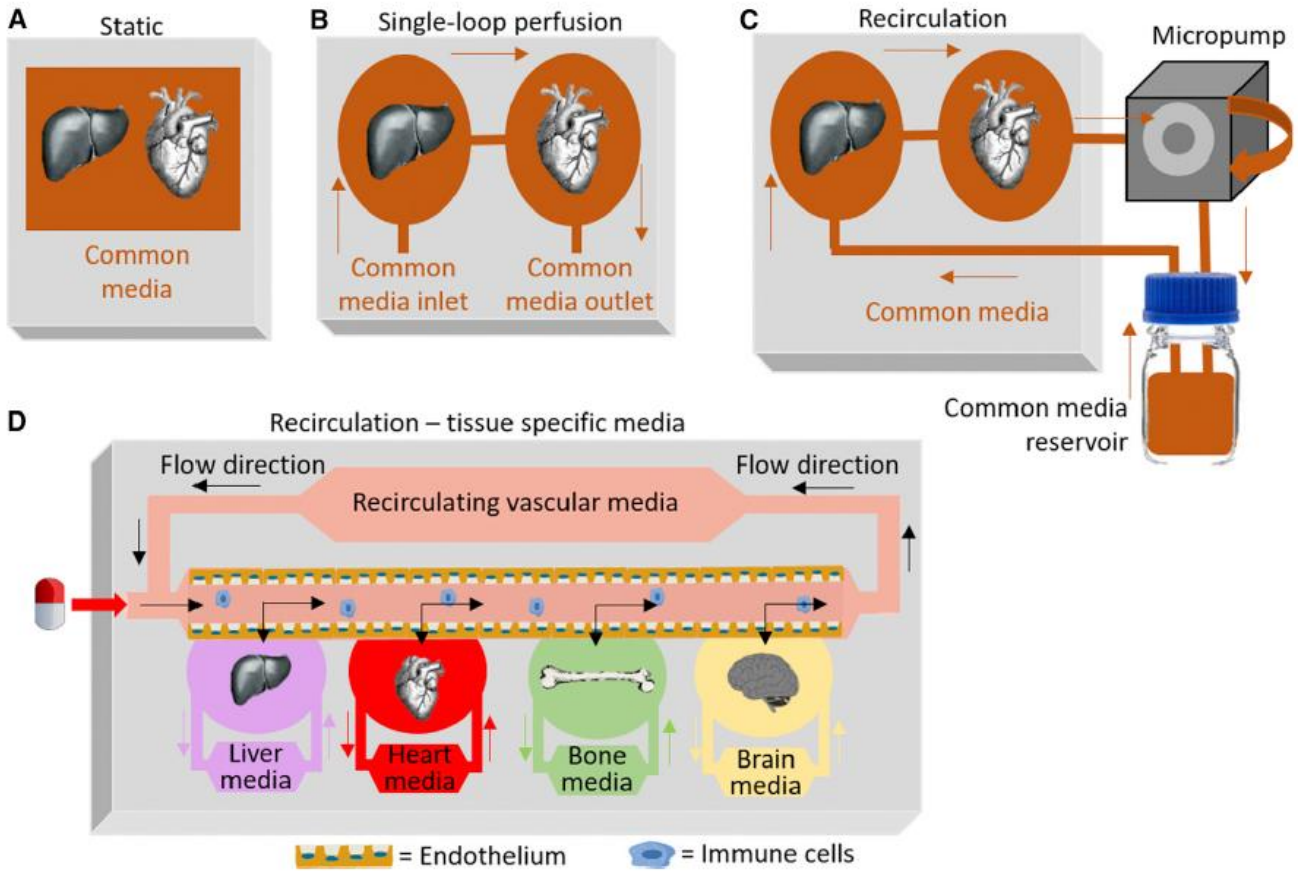
Physiologically **B**ased **P**harmaco**k**inetic

- PBPK model-based approaches for ADME characteristics of a drug → complex model approaches (especially **Metabolism** where most important enzymes are **cytochromes**)

- Important to know key parameters for PBPK modeling

Replace animal testing by
Organ and human-on-a-chip aided modeling!

Body-on-a-Chip Concepts



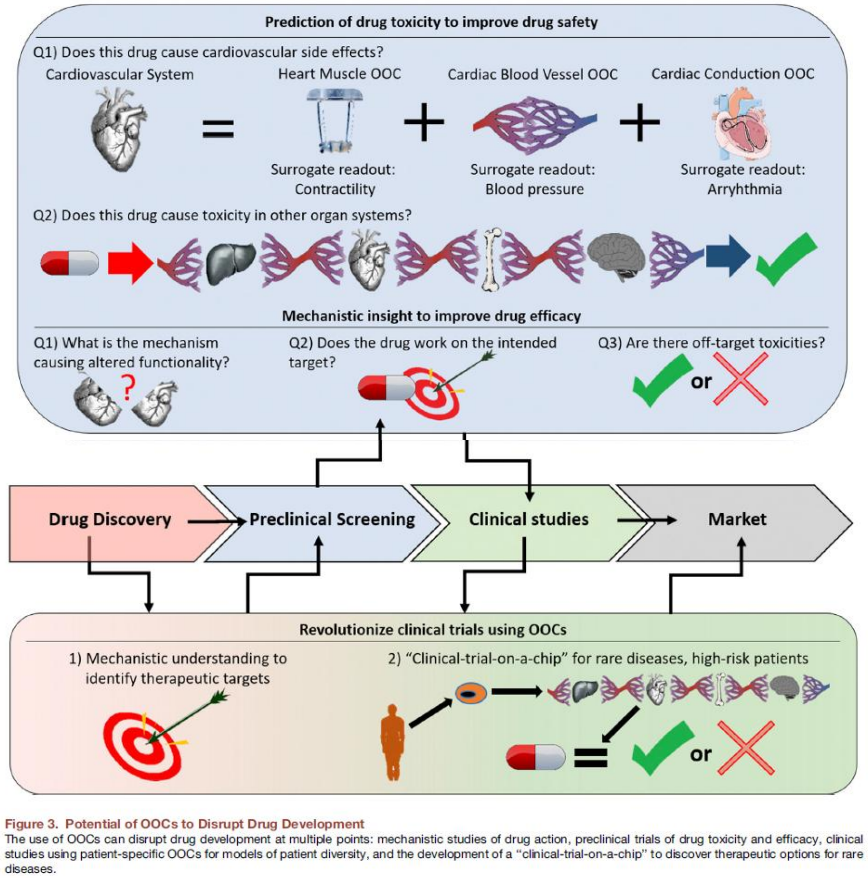


Figure 3. Potential of OOCs to Disrupt Drug Development
The use of OOCs can disrupt drug development at multiple points: mechanistic studies of drug action, preclinical trials of drug toxicity and efficacy, clinical studies using patient-specific OOCs for models of patient diversity, and the development of a "clinical-trial-on-a-chip" to discover therapeutic options for rare diseases.

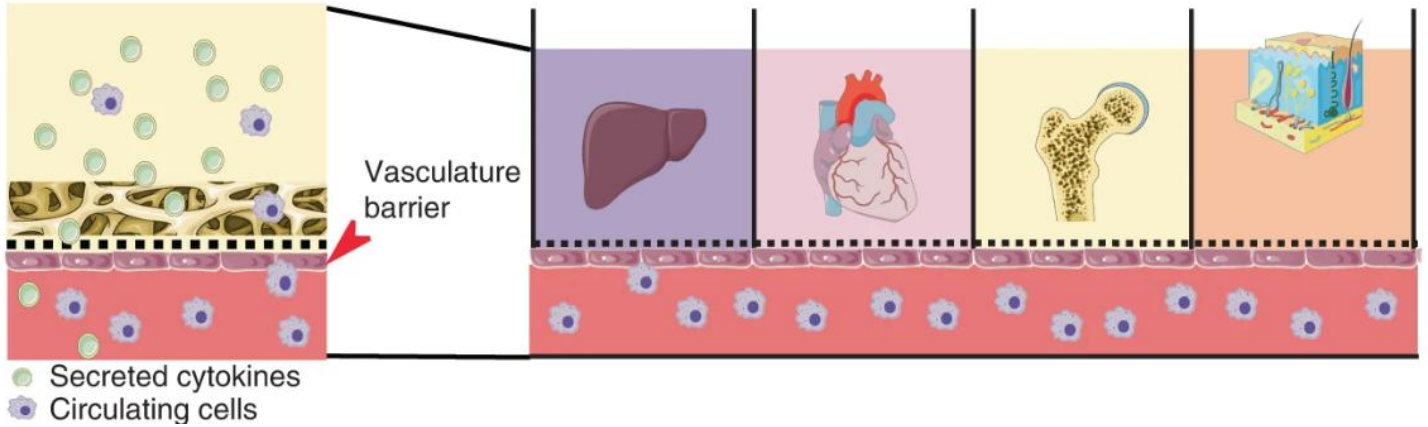
Integrating Multiple OOCs toward a Body-on-a-Chip (A–C) Methods to integrate multiple OOC systems include (A) static culture, (B) single-loop perfusion, or (C) recirculation of a common media capable of supporting all organ systems. (D) The development of individual OOCs connected to a selective membrane barrier, such as an endothelial layer, would enable integration of OOCs with perfusion that connects all OOCs while preserving the tissue-specific media composition for each OOC. The recirculating media can include more biomimetic components, such as circulating immune cells.

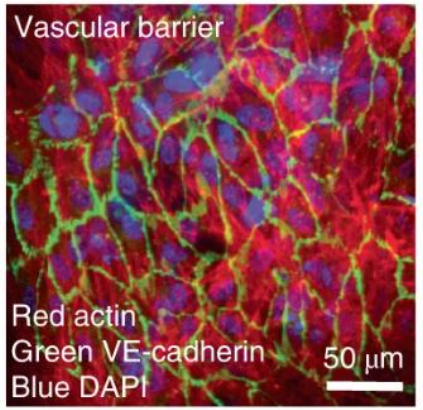
Body-on-a-Chip: State-of-the-art

nature › nature biomedical engineering › articles › article
https://doi.org/10.1038/s41551-022-00882-6
Article | Published: 27 April 2022

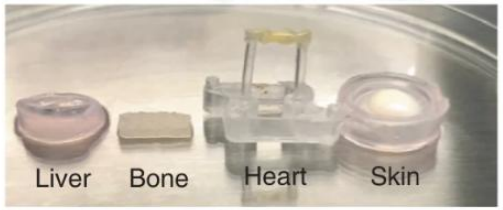
A multi-organ chip with matured tissue niches linked by vascular flow

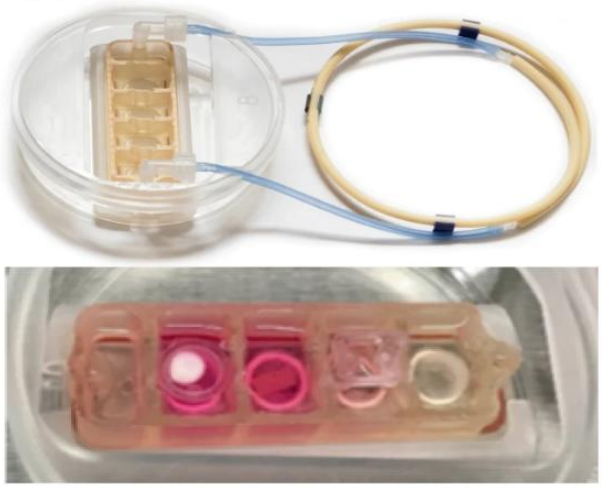
Multi-organ system: tissue-specific niches maintained by vascular barrier separation





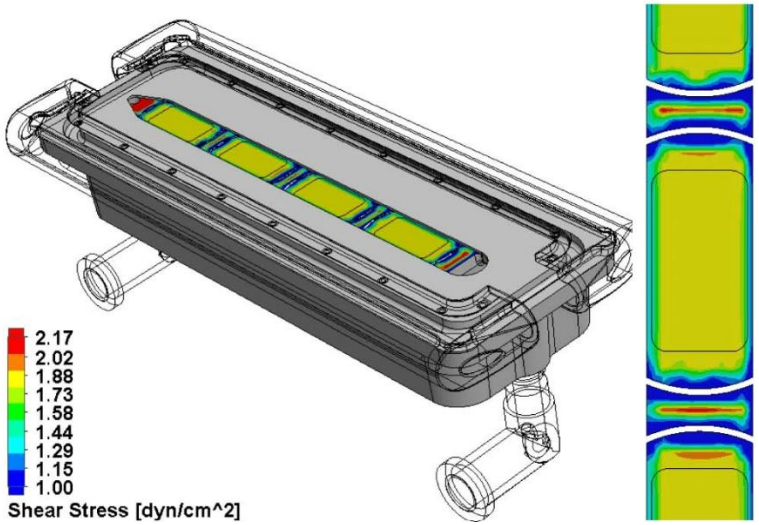
Modular, multi-tissue platform components, assembly and use



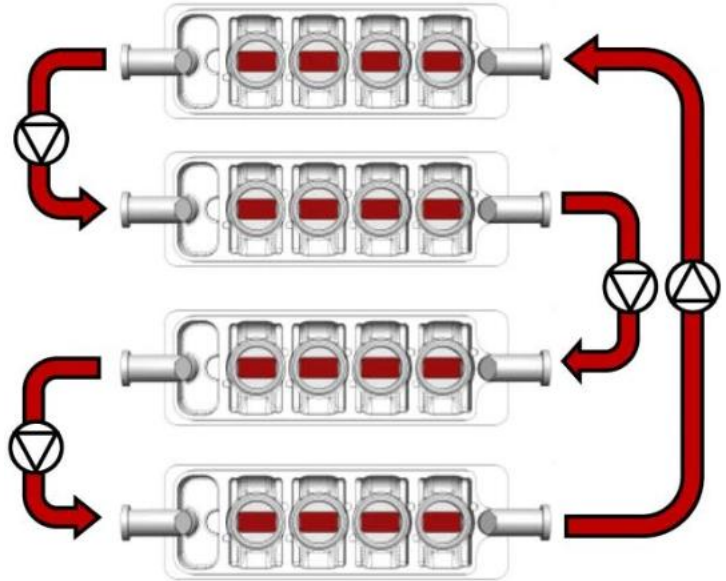


Body-on-a-Chip: State-of-the-art

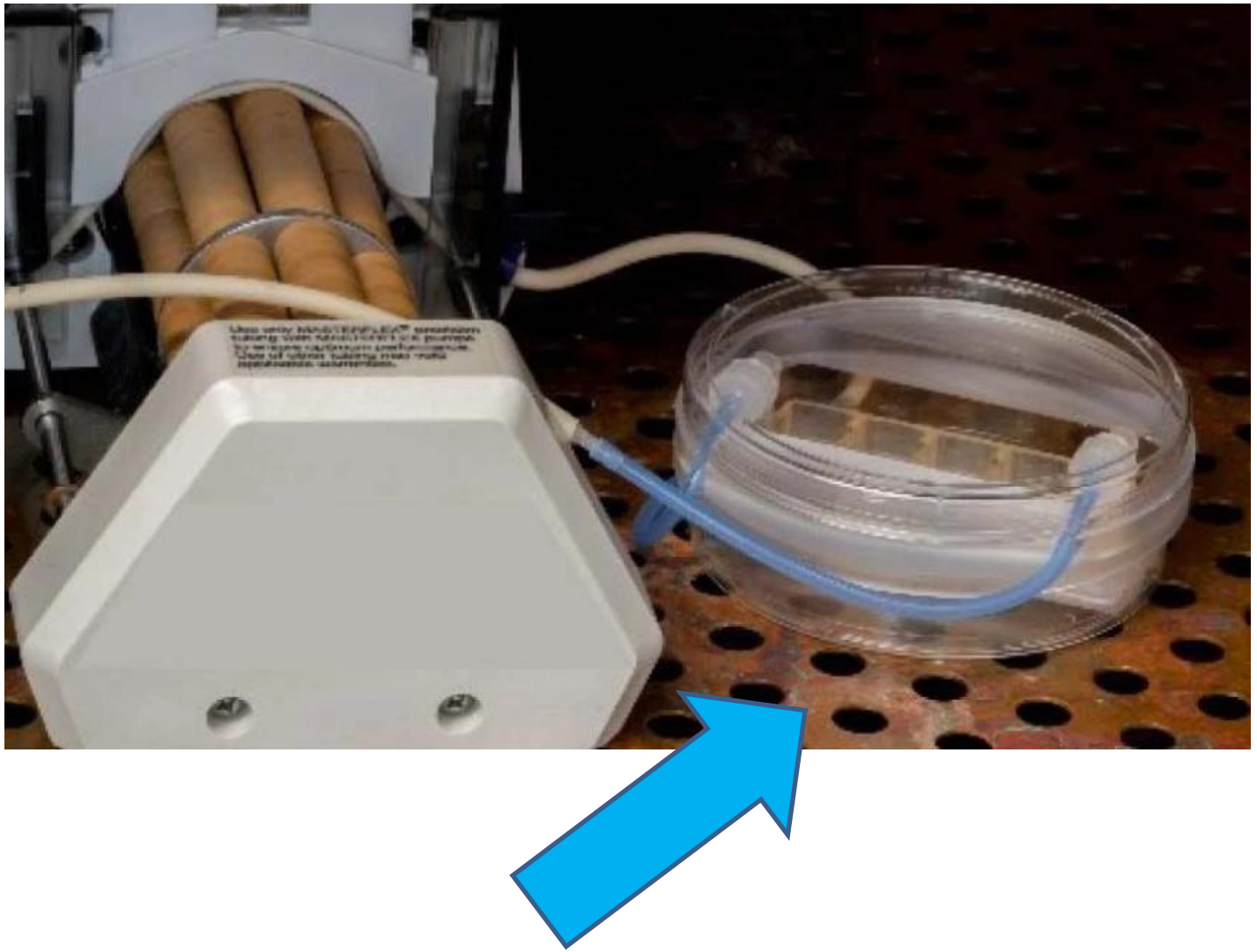
Simulation



Distribution



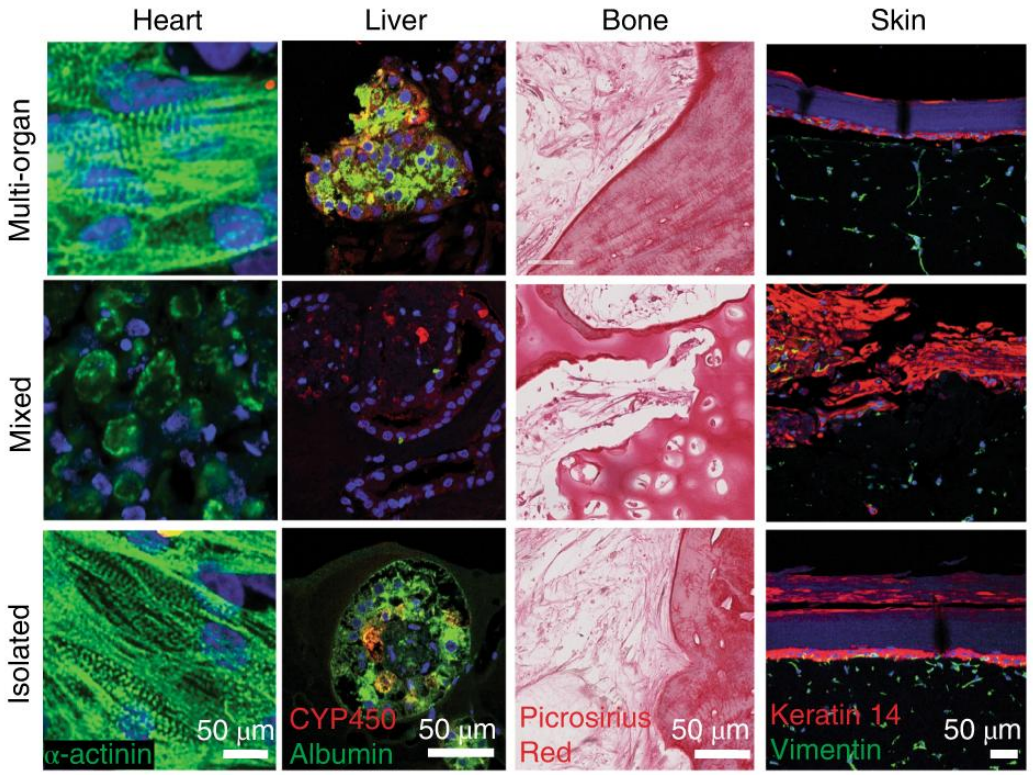
Actual setup



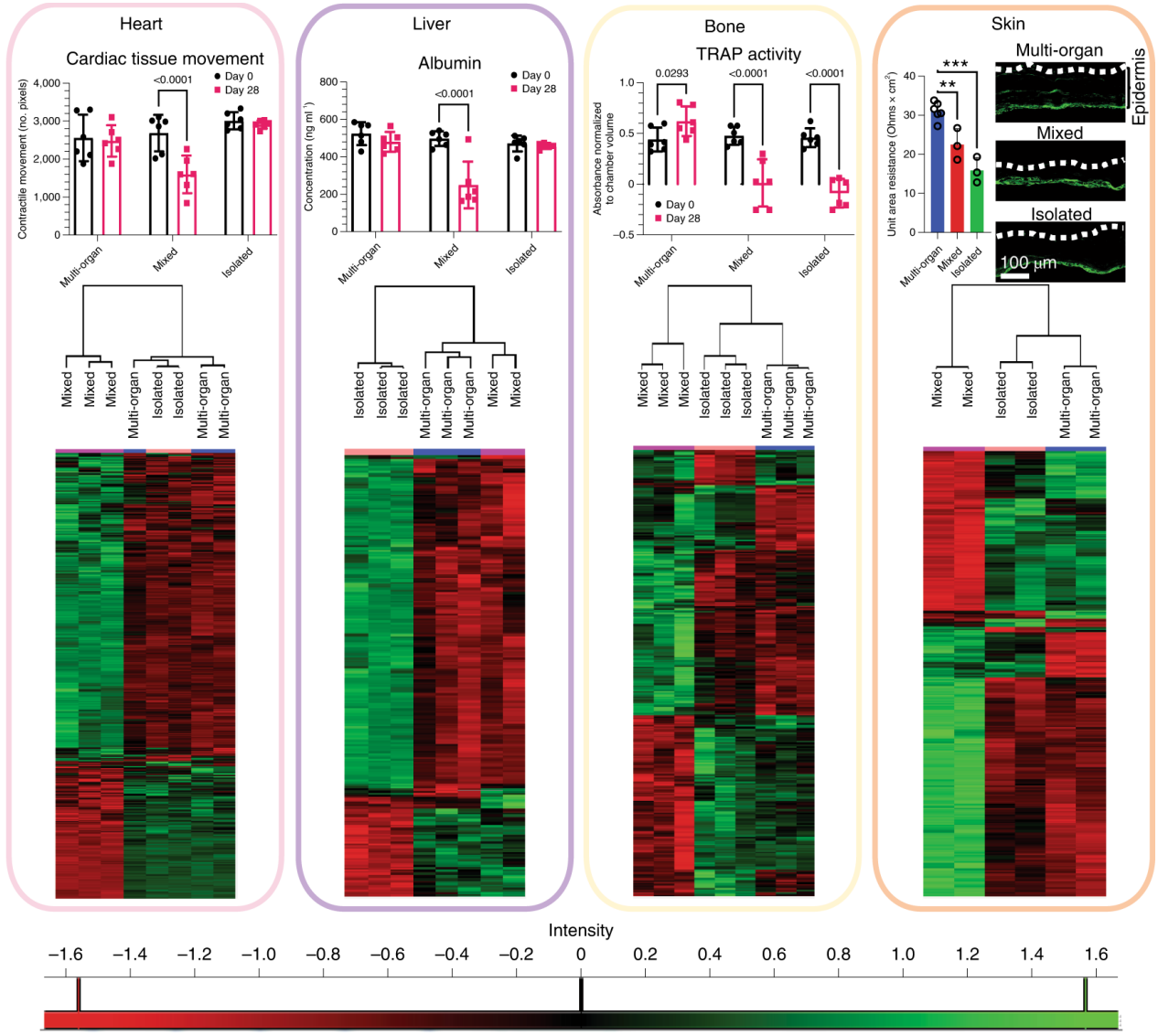
Body-on-a-Chip: State-of-the-art

Characterization: Incredible amount of data

Immunofluorescence staining



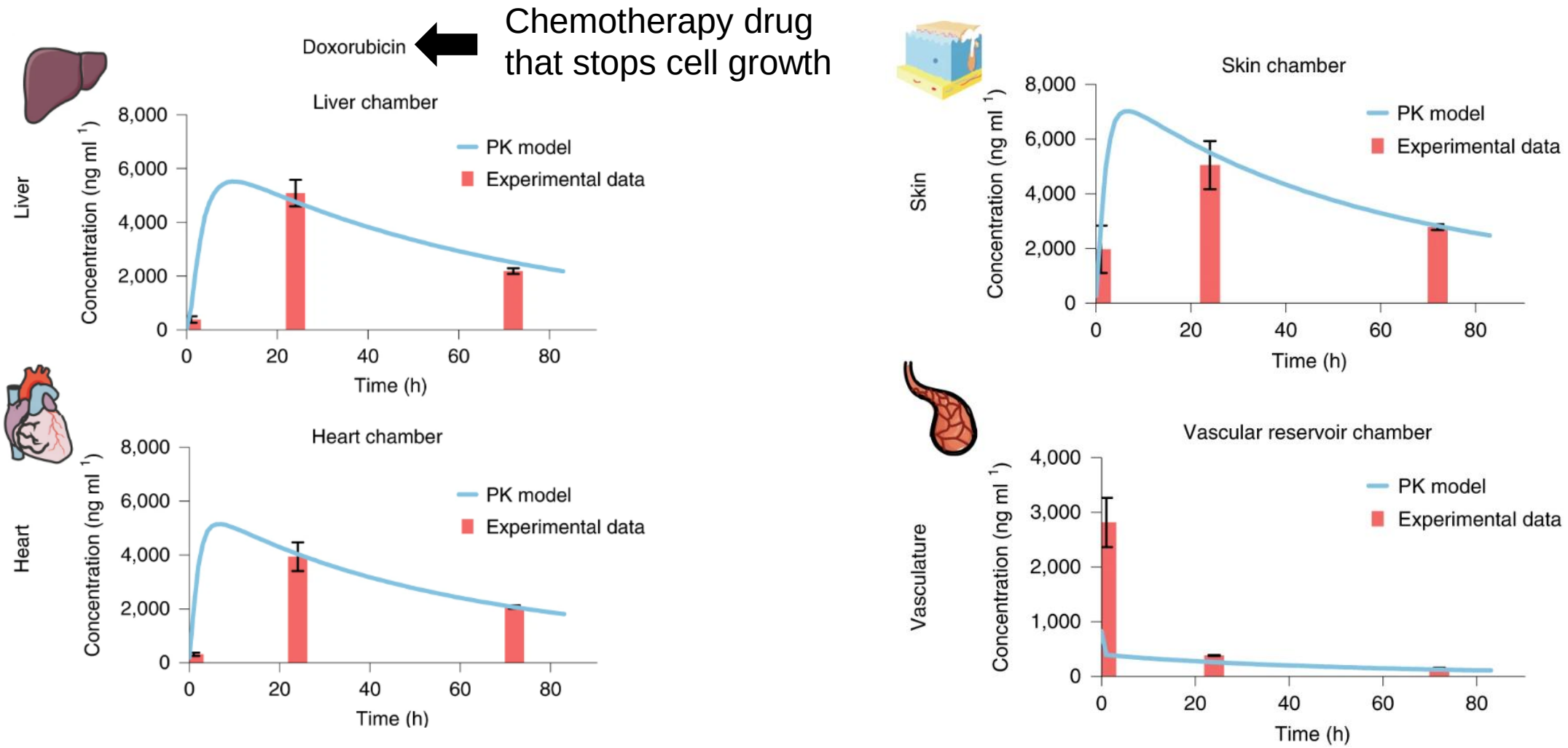
Proteomic analysis



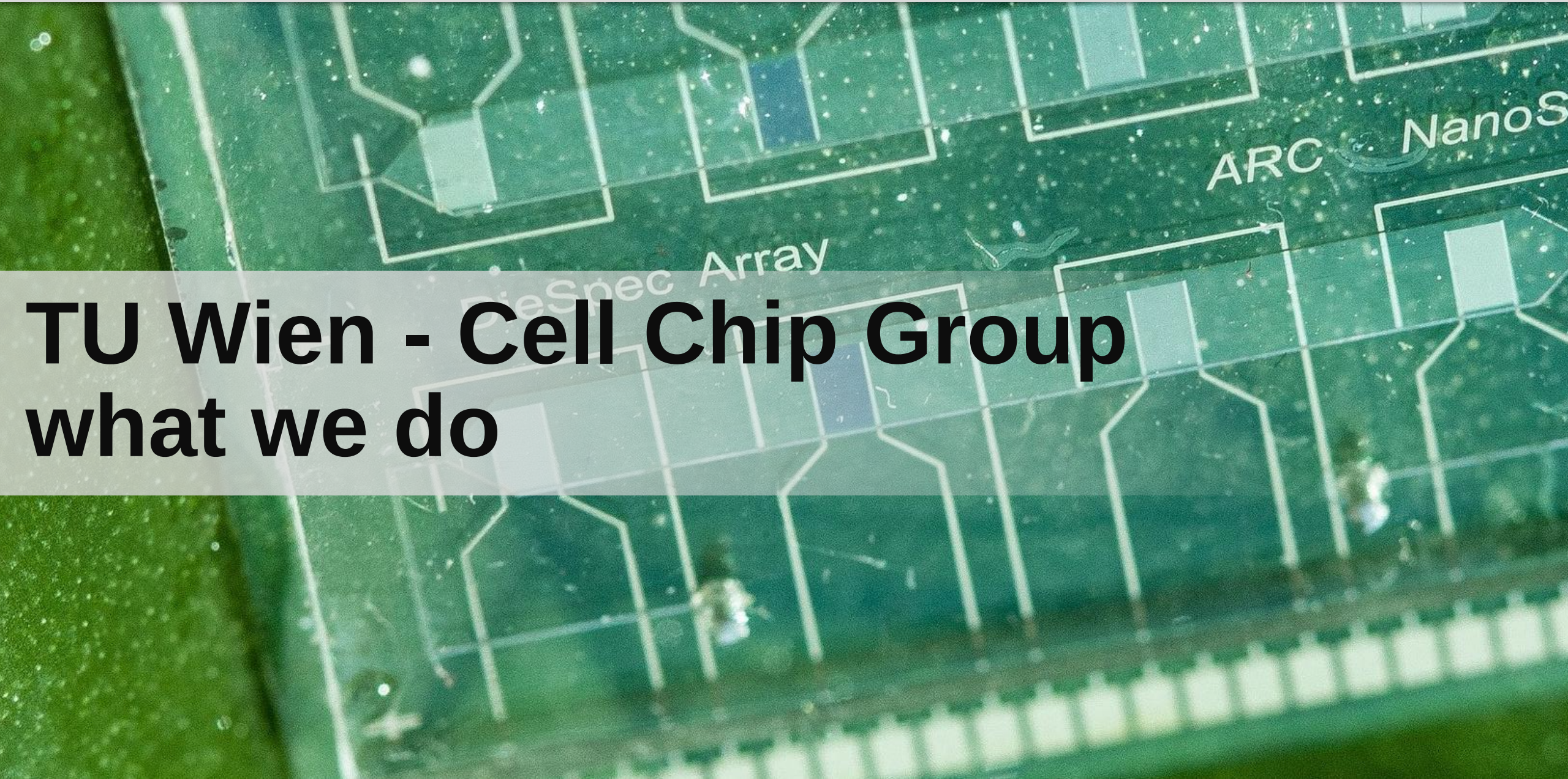
Experimental data form **day 0** and **day 24**

Body-on-a-Chip: State-of-the-art

Experimental data and PK model of doxorubicin treatment in the Multi-organ tissue chip.

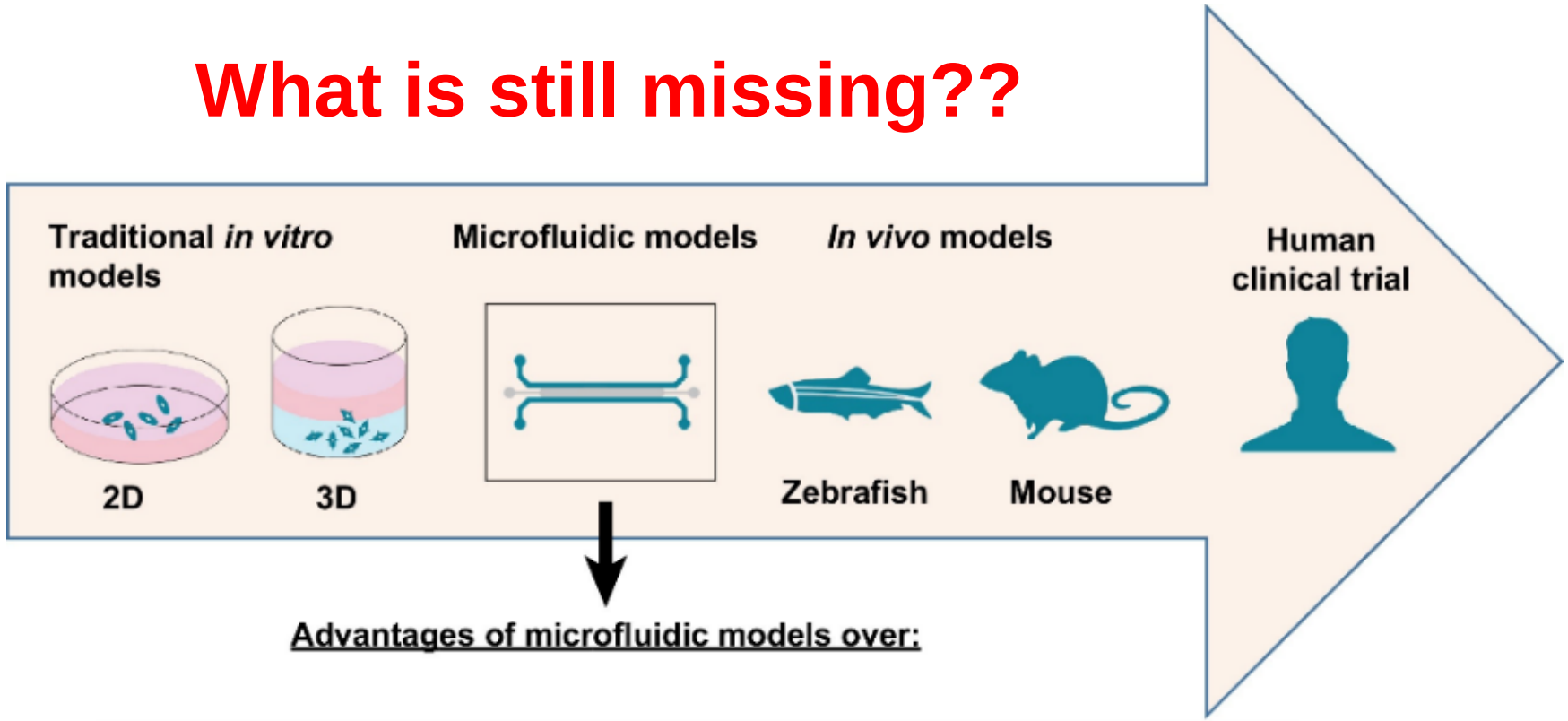


Experimental data form **hours 0, 24** and **72**



TU Wien - Cell Chip Group
what we do

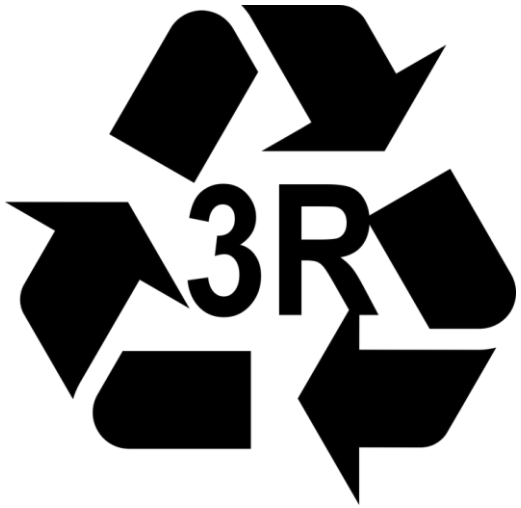
What is still missing??



Advantages of microfluidic models over:

Traditional *in vitro*	Traditional *in vitro* and *in vivo* models	*In vivo* models
-Ability to directly perfuse vascularized structures	-Increased control of microenvironment -Improved imaging capabilities -Fewer cells and less drug needed	-Use of cells exclusively of human origin

Tissue engineering to **reduce** the quantity of ***in vivo*** models used



Reduce, **R**ecycle, **R**euse

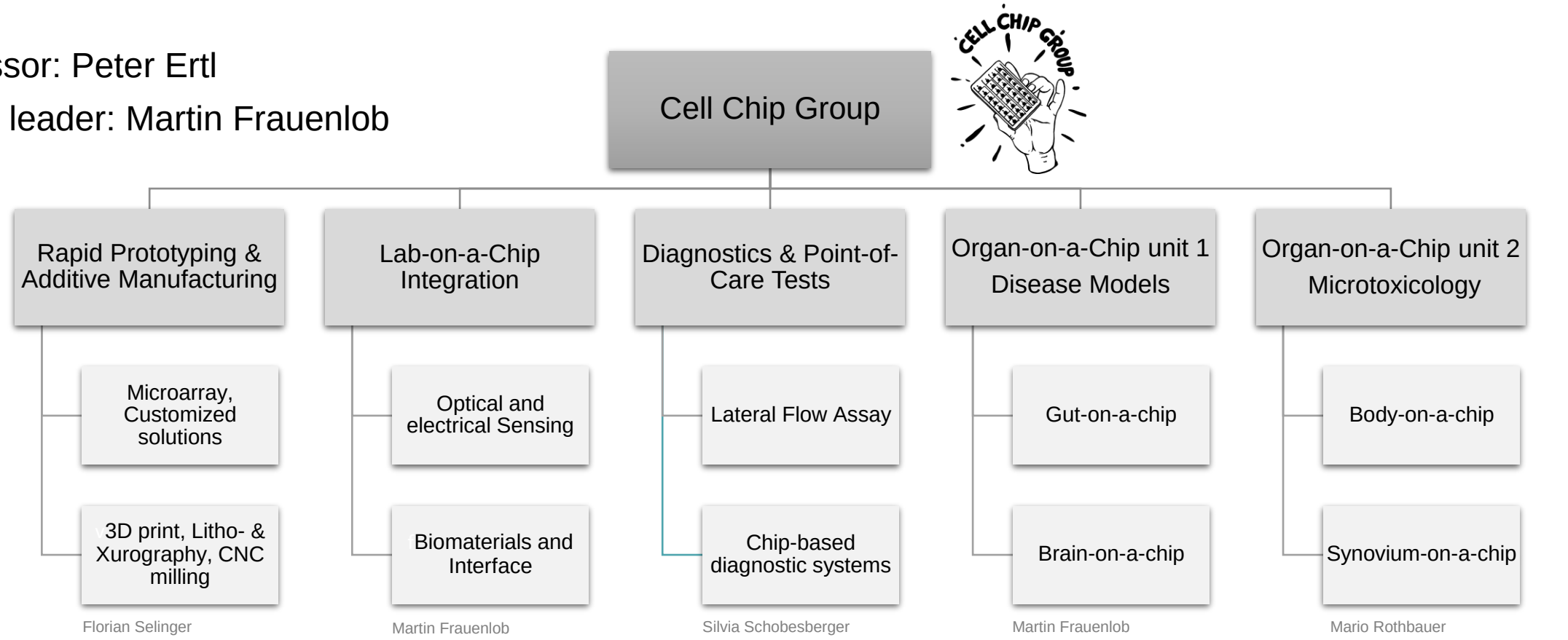
Time-resolved dataset

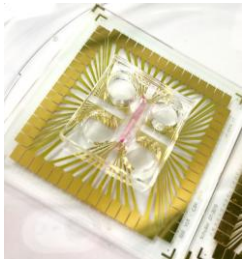
*Organs-on-chips at the frontiers of drug discovery Eric W. Esch, Anthony Bahinski & Dongeun Huh Nature Reviews Drug Discovery volume 14, pages 248–260 (2015)

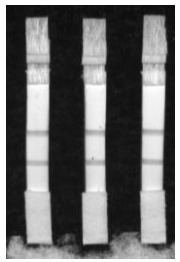
Cell Chip Group

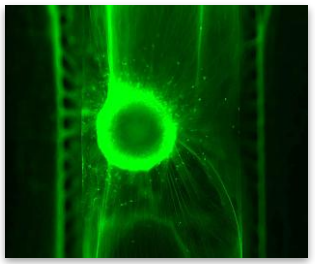
Professor: Peter Ertl

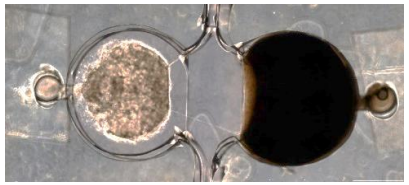
Group leader: Martin Frauenlob







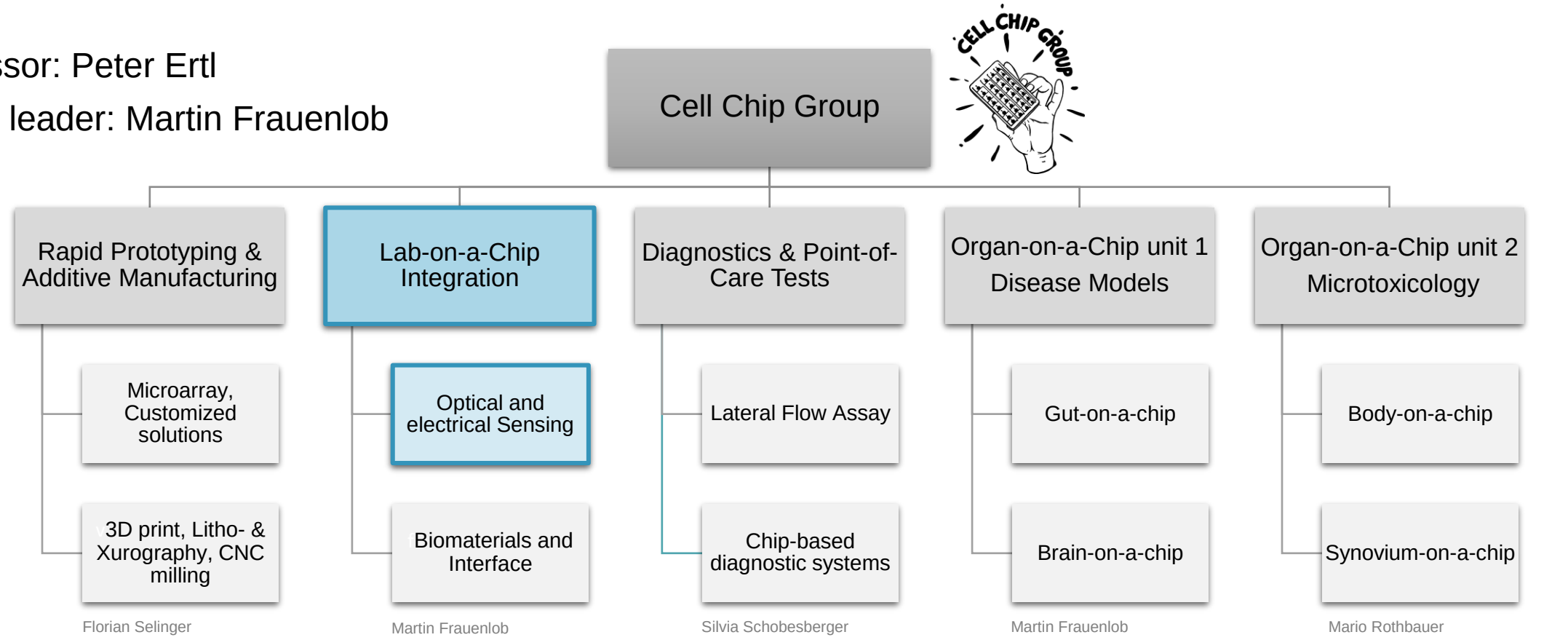


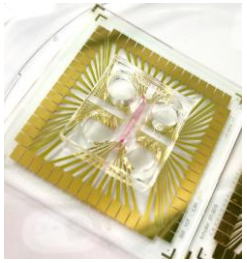


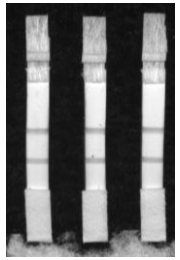
Cell Chip Group

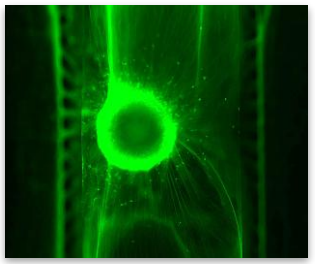
Professor: Peter Ertl

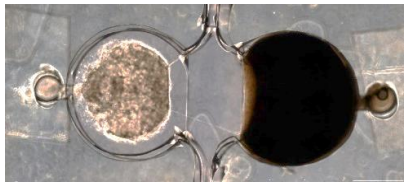
Group leader: Martin Frauenlob









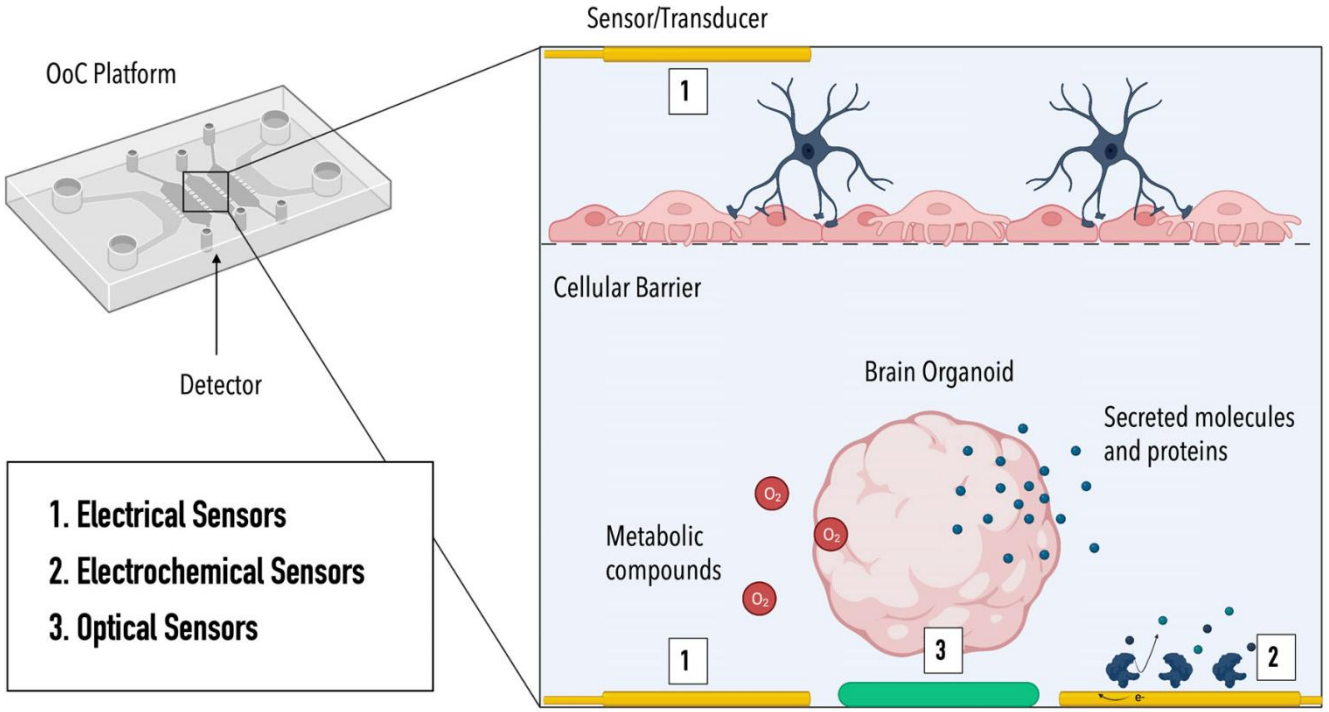


Pharmacokinetic live monitoring

Microenvionmental Parameters
- Oxygen
- pH
- Shear Stress
- Temperature

Tissue Functionality
- Barrier Integrity
- Electrophysiolgical Activity

Pathological Alterations
- Inflammation (cytokine release)
- Metabolic Dysfunction (glucose, lactate)
- Overexpression

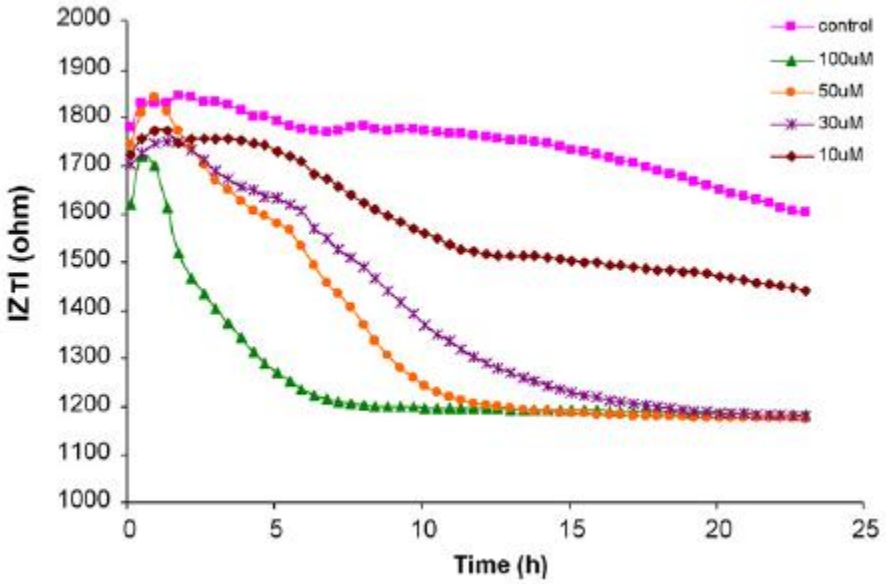


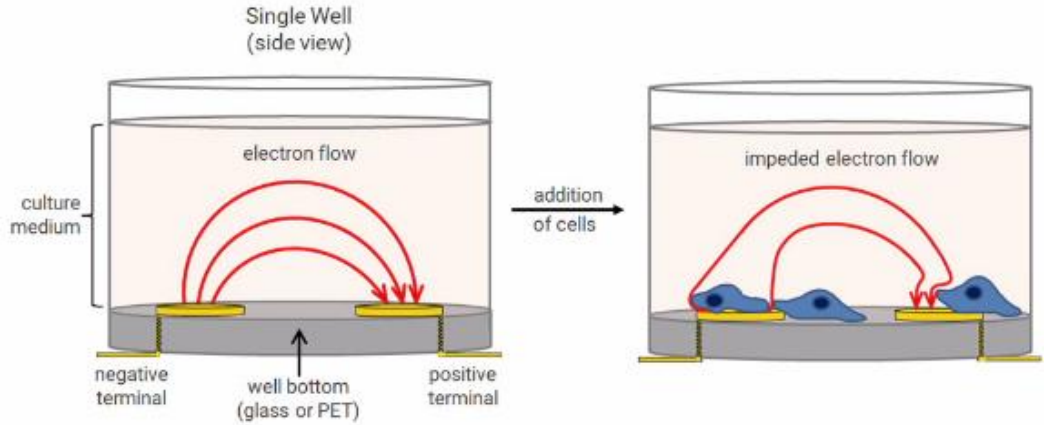
Installing lab equipment: Sensor integration

Impedance

Impedance is the electrical resistance in **alternating current** (AC).
Can be used to detect resistance changes in the because of particles in the electron flow field.
It has a **real part** (resistor, capacitor, inductor) and an **imaginary part** (reactance).
At high frequencies >1MHz can polarize particle in the field leading to a deformation of the field.

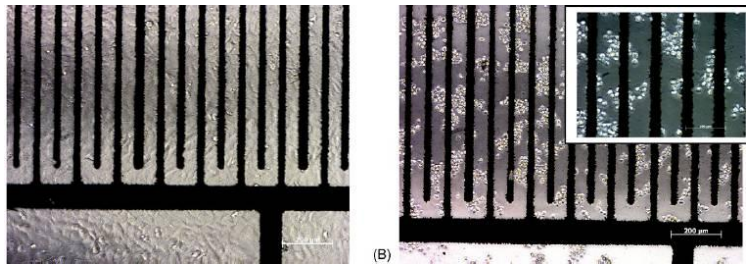
Sodium arsenite exposure





To evaluate density of a cellular membrane

Cells in the system deform the electro magnetic field at a certain flow frequency and that can be measured.



Readout is very complex because of frequency and phase shift dependence

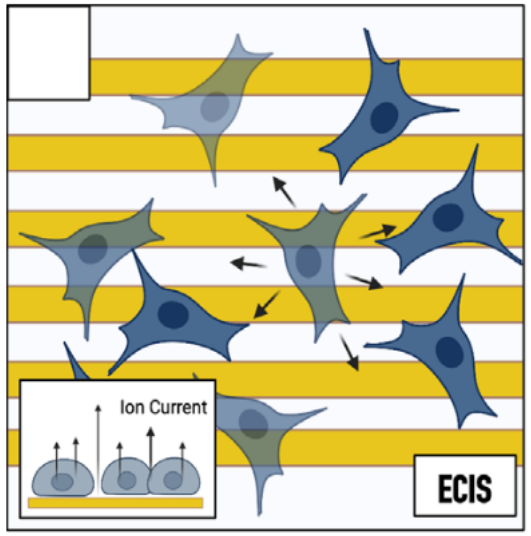
Ceriotti, L et.al. *Biosensors and Bioelectronics* 22 (2007) 3057-3063

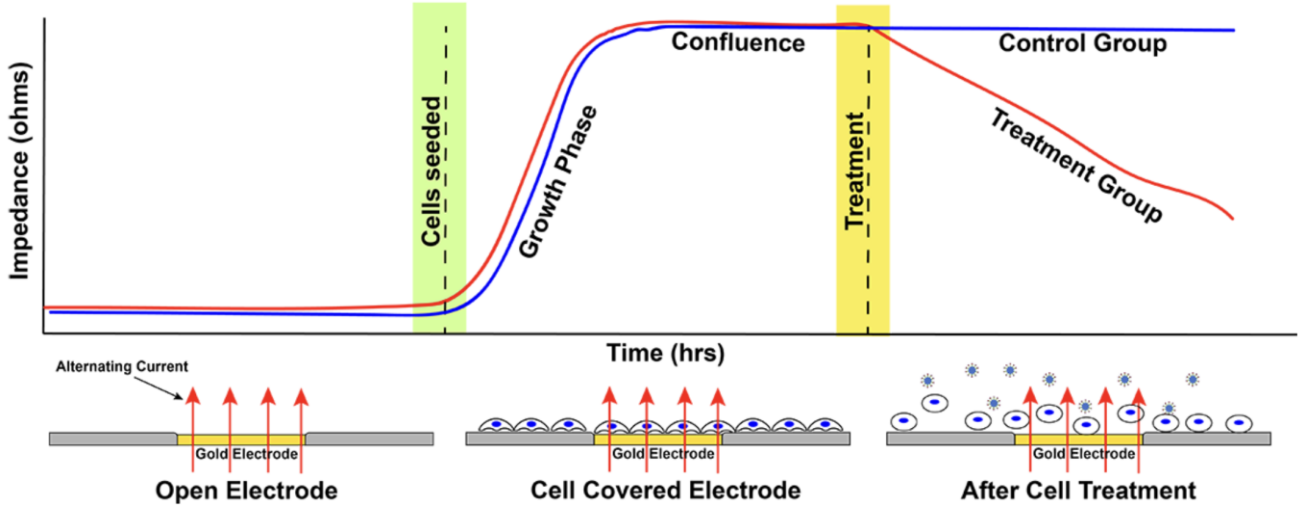
Installing lab equipment: Sensor integration

Impedance

ECIS = electrical cell–substrate impedance sensing

- Localized measurement
- Array of small working electrodes combined with a large common counter electrode
- Cell attachment, morphology, function, motility
- Planar



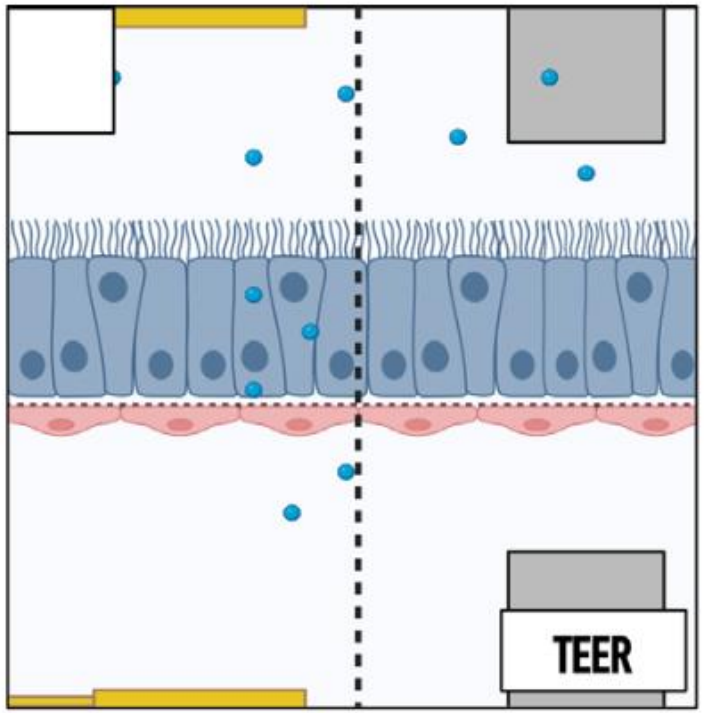


https://www.biophysics.com/whatIsECIS.php

https://doi.org/10.1021/acsbiomaterials.0c01110

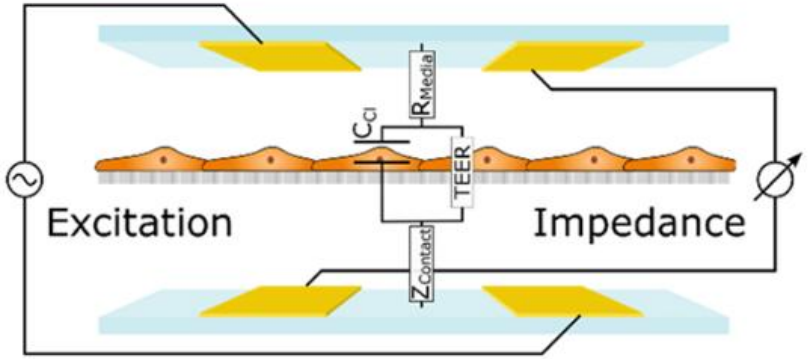
Installing lab equipment: Sensor integration

Impedance



TEER = trans-epithelial/endothelial electrical resistance

- Resistance of cell cultured on membrane to monitor biological barrier formation
- Barrier integrity
- Normalized to the membrane area Ω cm^2
- Planar or chopstick

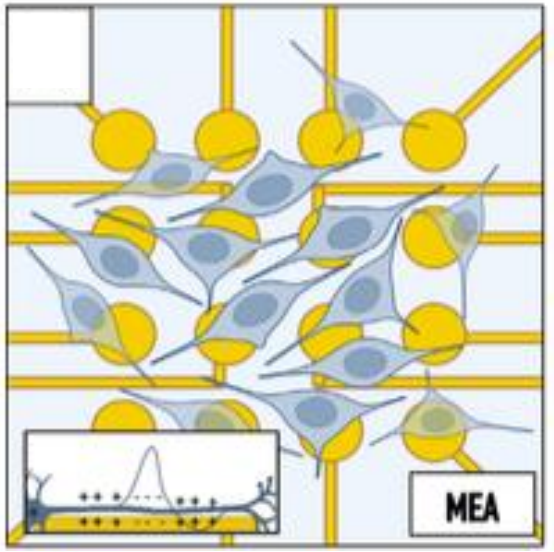


https://doi.org/10.1021/acsbiomaterials.0c01110

Installing lab equipment: Sensor integration

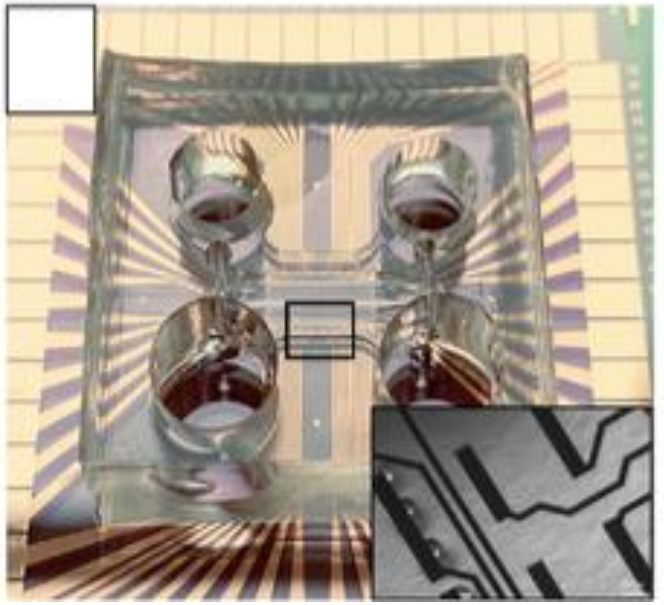
Multielectrode Array Potentiometer

- Assessing cerebral tissue (dys-)function since changes in neuronal activity patterns (e.g. variations in the firing rate) are believed to reflect underlying alterations in cellular structure and functionality.
- Tool for in Situ Monitoring of Drug Effects on Neurotransmitter Release from Neural Cells



→ **Imbalances in extracellular ion concentrations or transmembrane potentials**, which occur during de- and repolarization events of **electrically active cells**, can be readily detected using **voltage-sensitive** electrodes, such as multi-electrode arrays (MEAs).

→ Consist of hundreds of microelectrodes that enable the **spatiotemporal mapping** of electrophysiological events



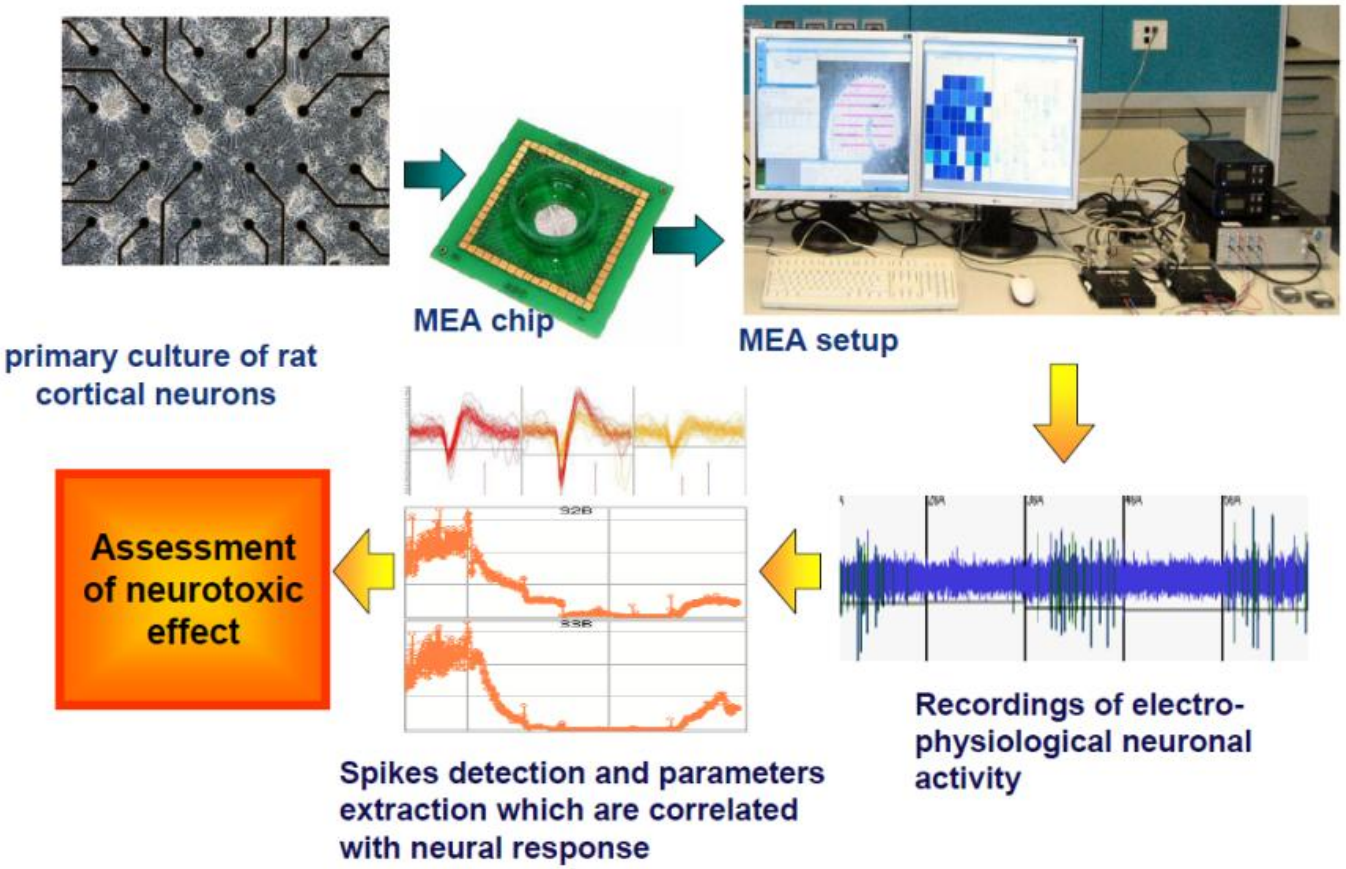
No current applied (MEA passively records natural signals)

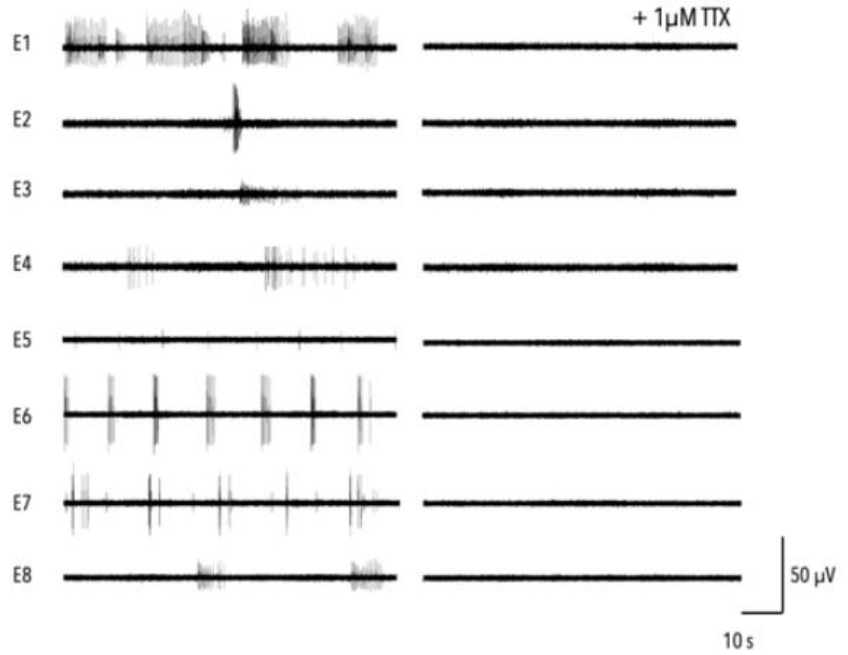
Voltage fluctuations due to neuronal activity

https://doi.org/10.1002/btm2.10604

Installing lab equipment: Sensor integration

Multielectrode arrays





TTX (= tetrodotoxin): sodium channel blocker that **inhibits the firing of action potentials** in neurons by binding to the voltage-gated sodium channels in nerve cell membranes and blocking the passage of sodium ions (responsible for the rising phase of an action potential) into the neuron

https://doi.org/10.1101/2022.08.19.504522

Installing lab equipment: Sensor integration

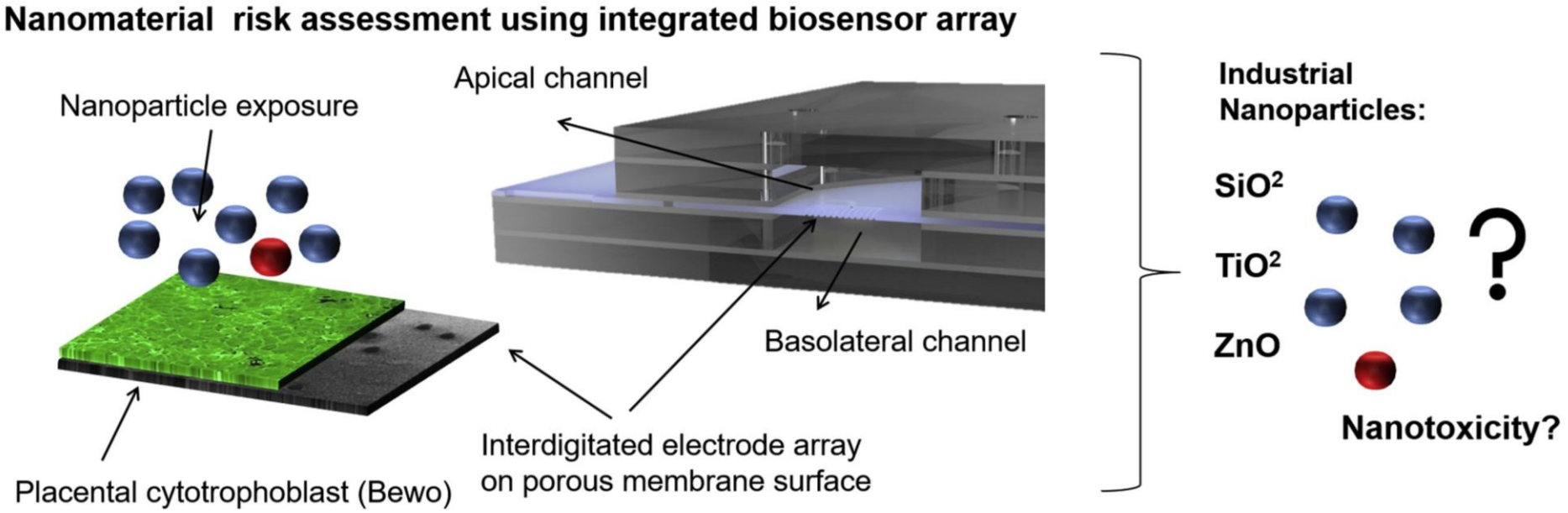
Limitation:
Electrodes mostly printed on glass

Sensor-integrated porous membranes

- The need to bring the electrodes to the cells
- Cells are on the interface between tissue: e.g. Placenta on-a-Chip

What is happening at the interface?
What goes through?

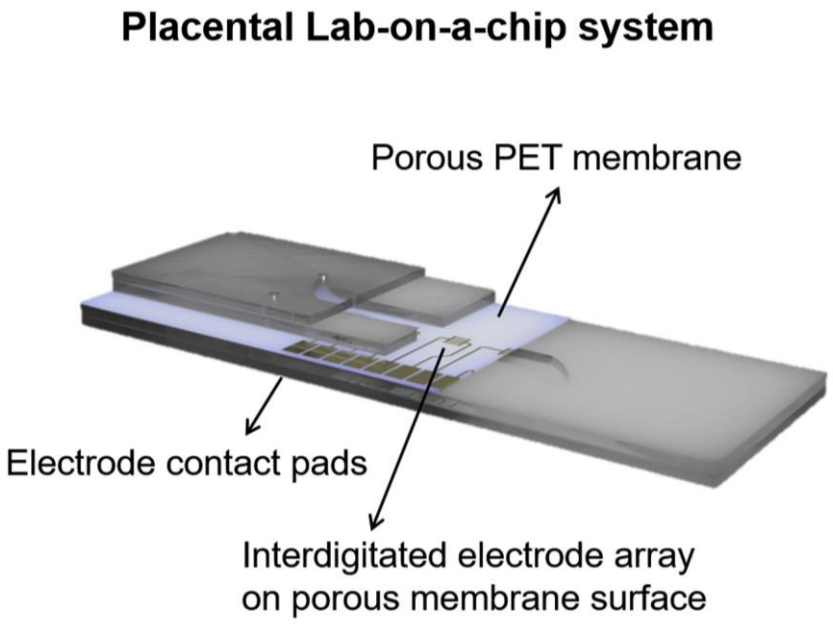
Reproducibility



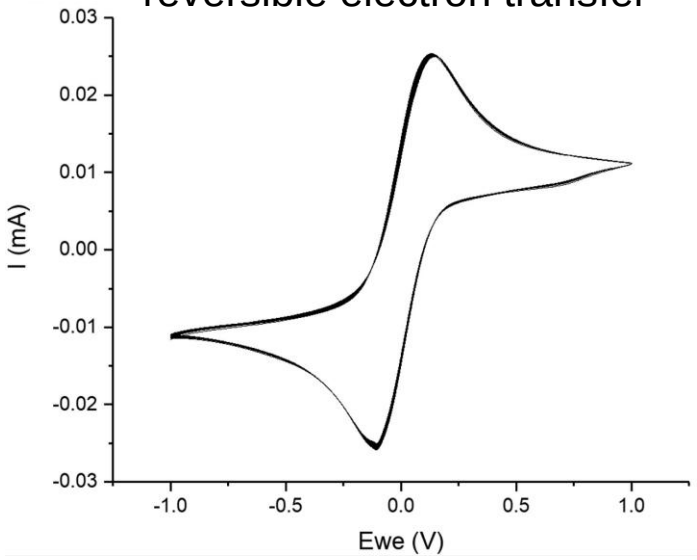
https://doi.org/10.1016/j.snb.2020.127946

Sensor-integrated porous membranes

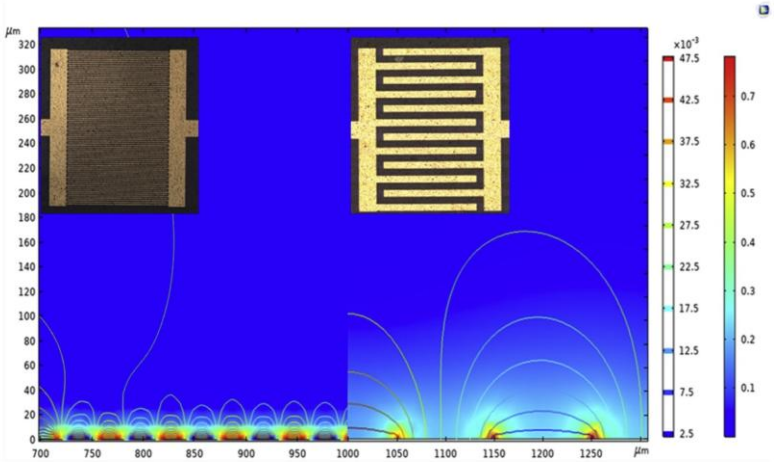
Development of a gold deposition protocol for porous PET-membranes



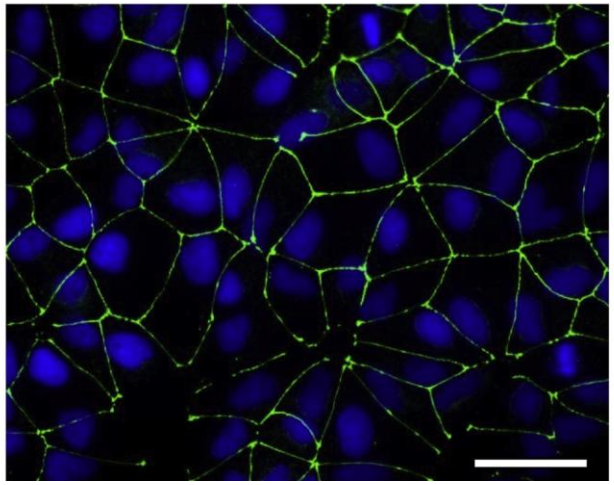
Cyclic voltammogram demonstrates reversible electron transfer



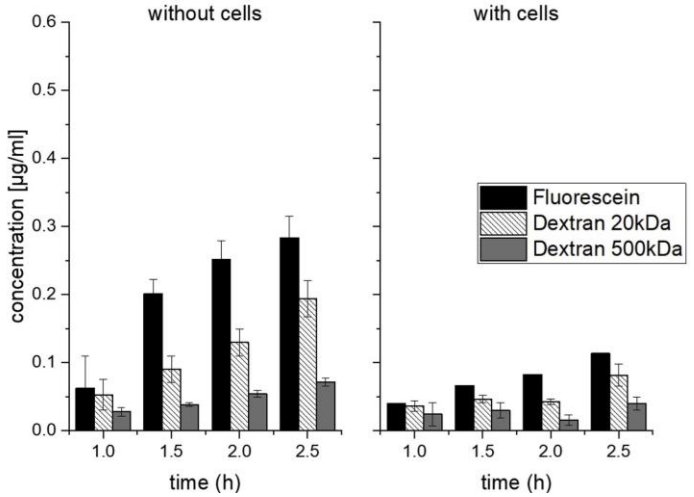
Electric field distribution differs because of electrode distance



Cellular adhesion



Change of molecular transport



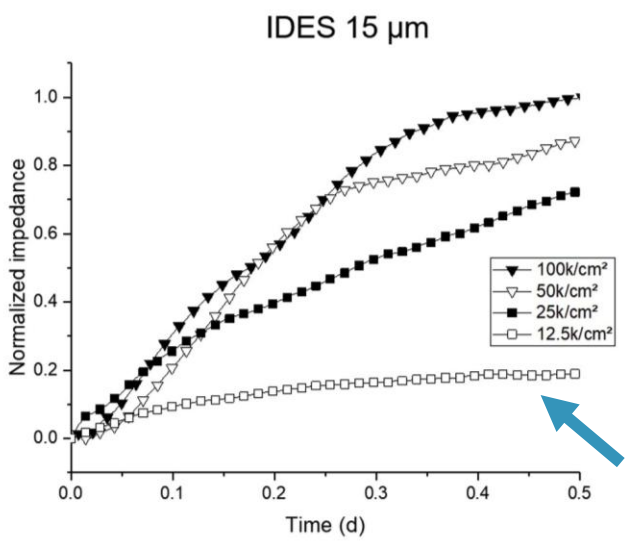
https://doi.org/10.1016/j.mex.2019.10.038

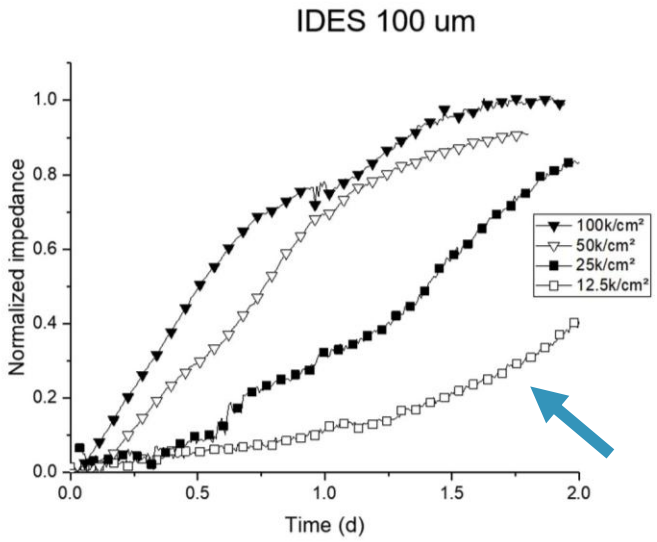
https://doi.org/10.1016/j.snb.2020.127946

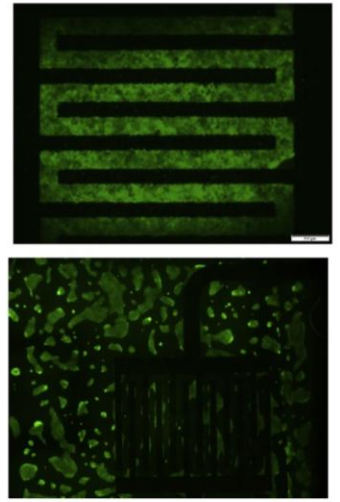
Sensor-integrated porous membranes

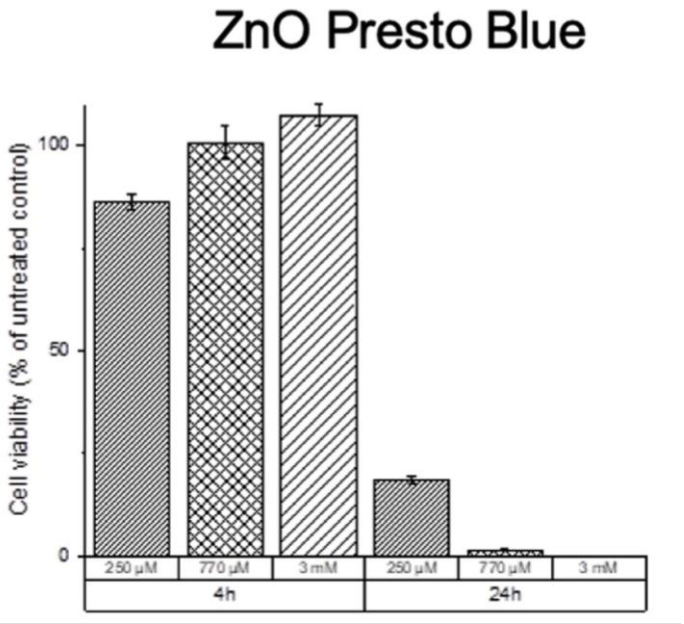
Difference in **sensitivity** based on electrode gap

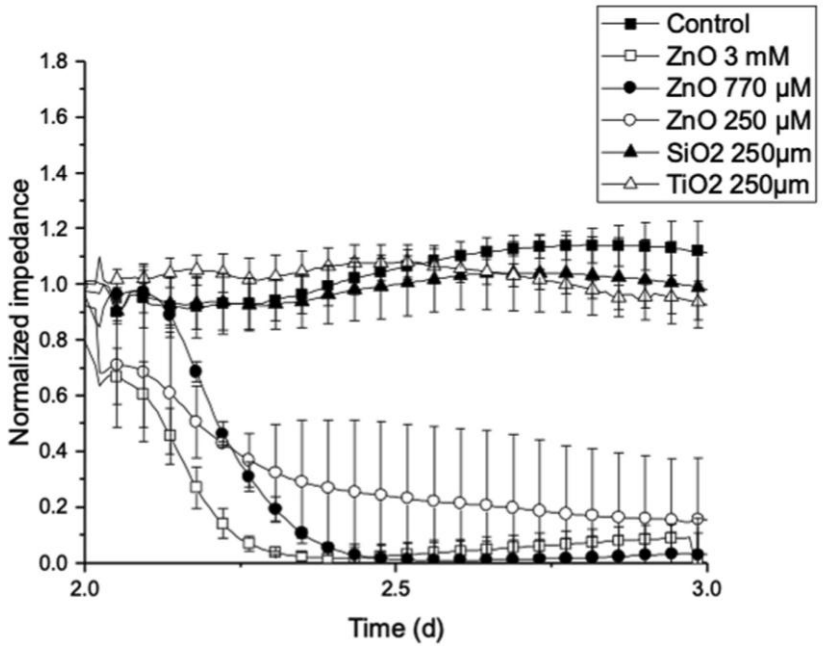
Change of cell concentration in membrane over time











Toxicity study:

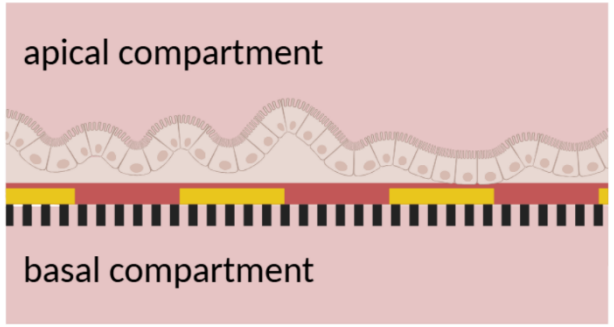
Impedance signal change based on nanoparticle concentration and type

Confirmed with standard method (Presto Blue)

Sensor integration: Biological validation

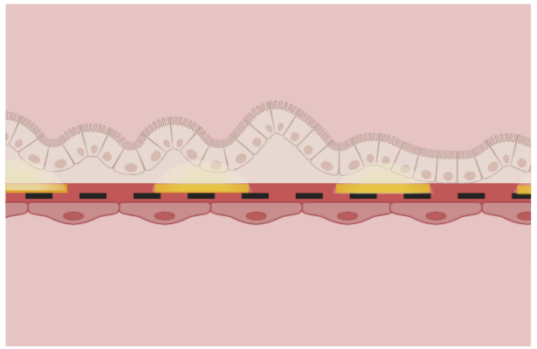
1% collagen
electrode
membrane

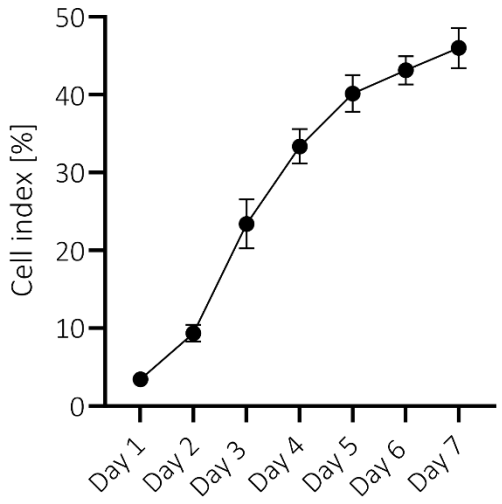
Single culture
Caco-2

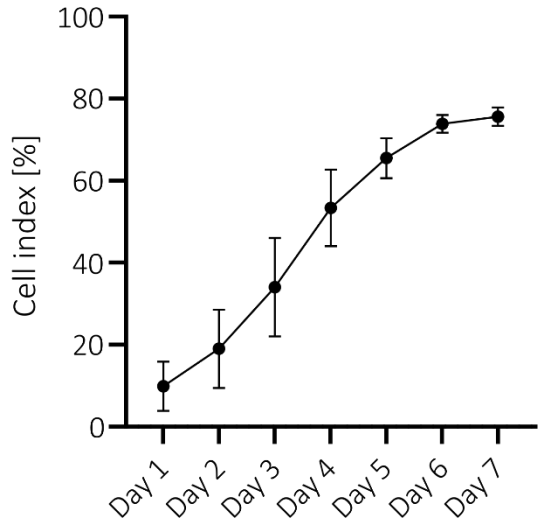


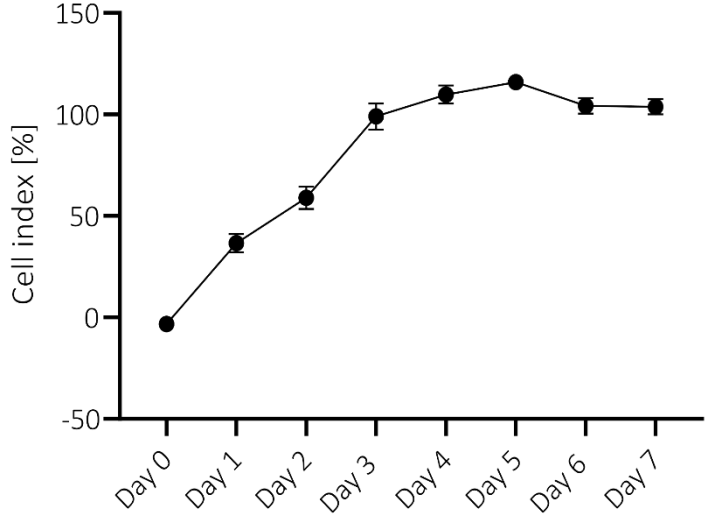
direct co-culture
(Caco-2 & HT29)

indirect co-culture
(Caco-2 & HUVECs)









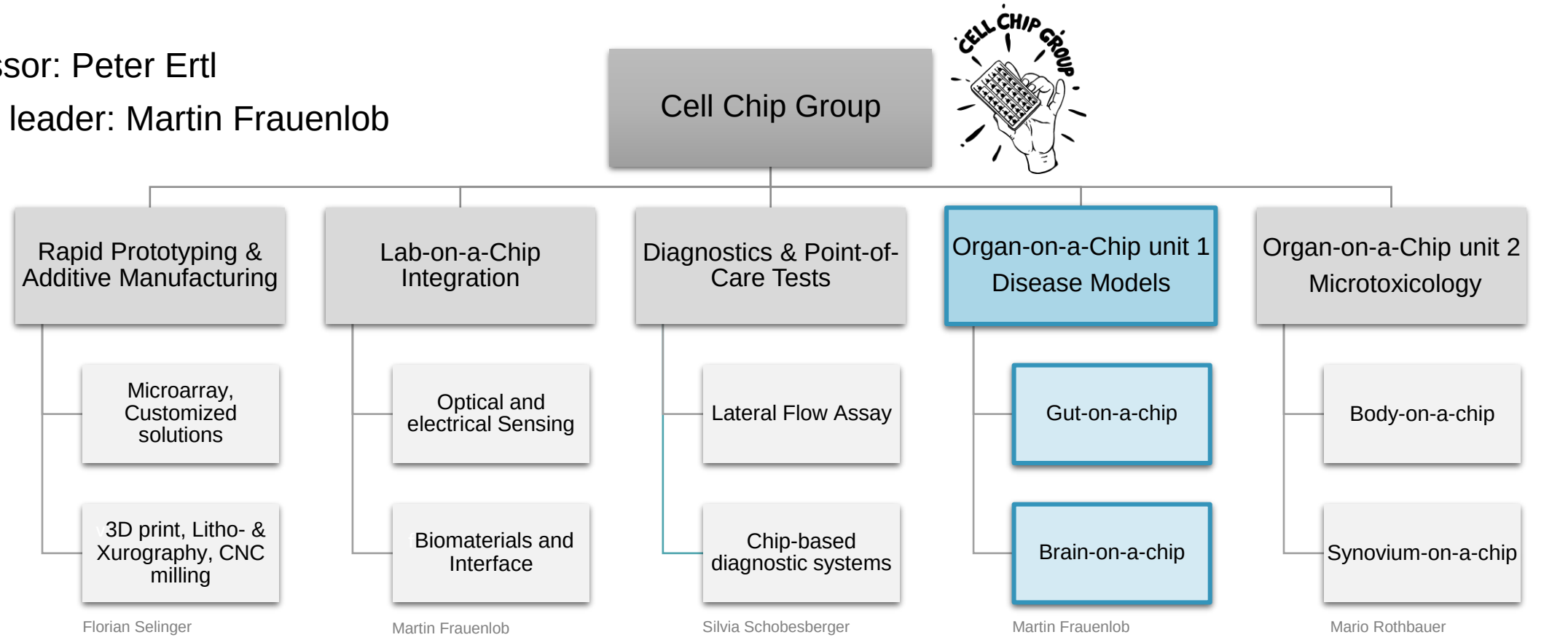
In all cases we can demonstrate the detection of a **time-resolved cell growth or death** at the tissue interface.

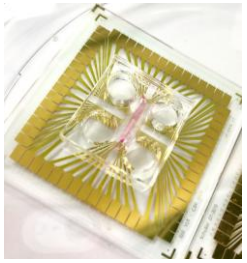
https://doi.org/10.1039/D4LC00896K

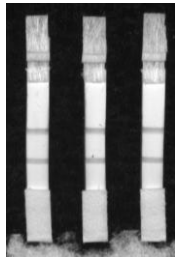
Cell Chip Group

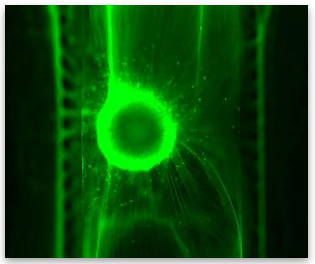
Professor: Peter Ertl

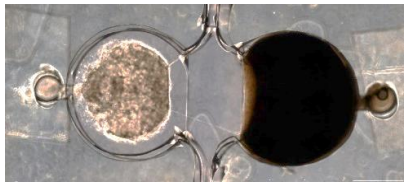
Group leader: Martin Frauenlob





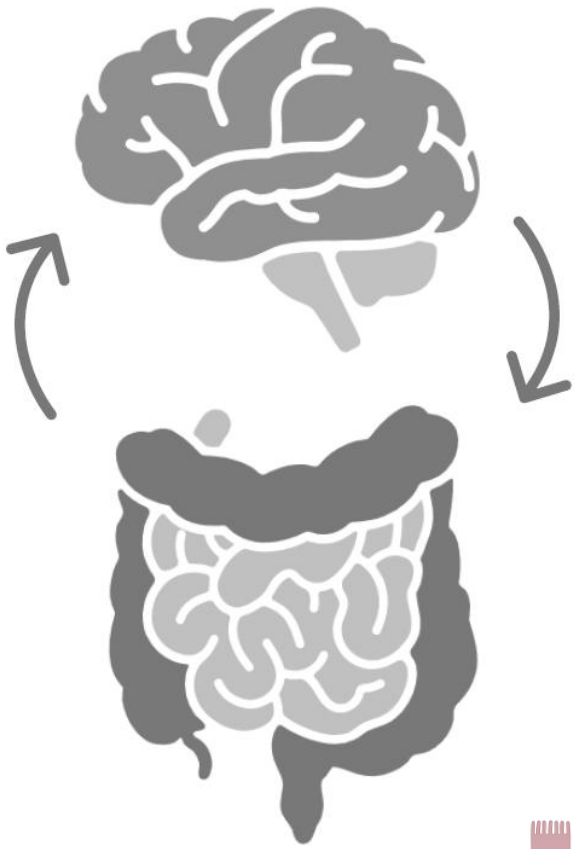






The Gut-Brain Axis

Organ crosstalk

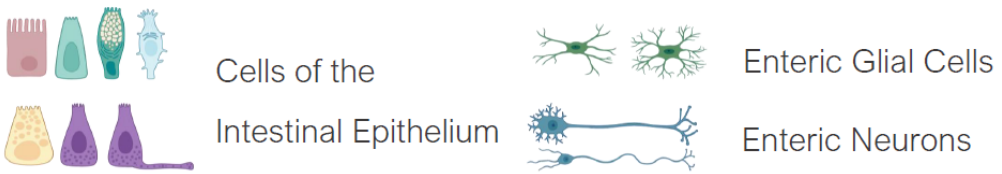


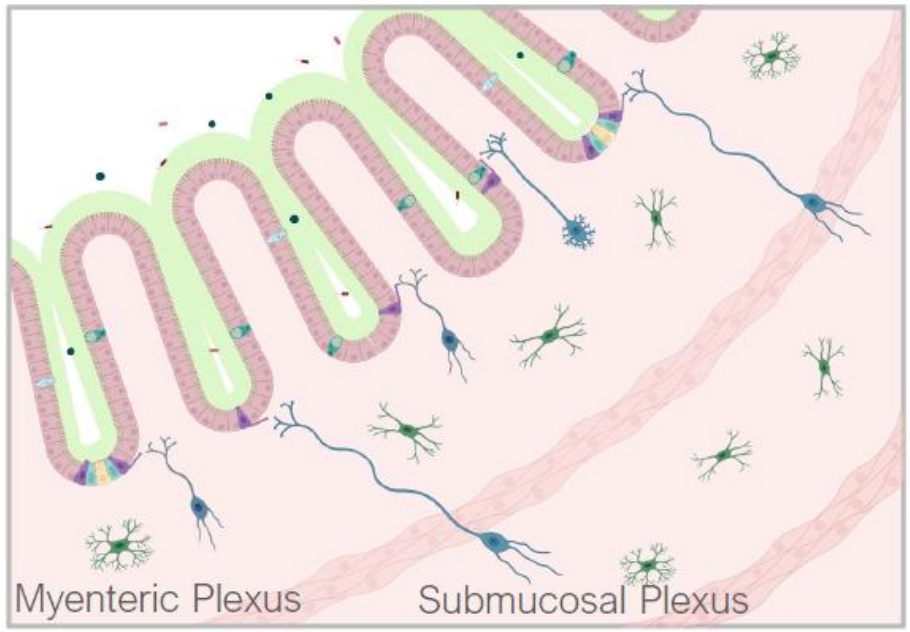
Influence on Mental Health:
Changes in gut microbiota have been linked to mood disorders such as anxiety and depression.
The gut can produce neurotransmitters and metabolites that affect brain function.

Impact on Neurodegenerative Diseases:
Changes in the gut–brain axis crosstalk may play a role in conditions like Parkinson's and Alzheimer's disease.

Interface between the intestine and the nervous system

The enteric nervous system is the connection between the brain and the gut.

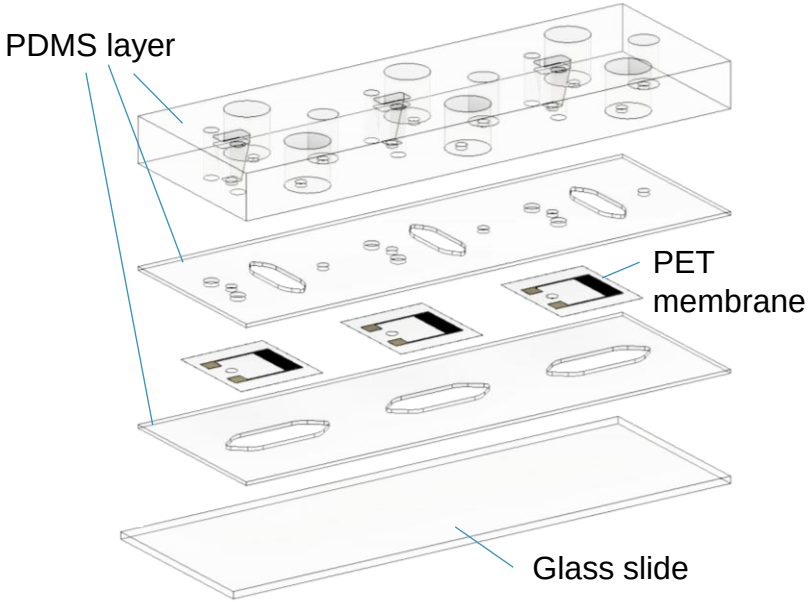




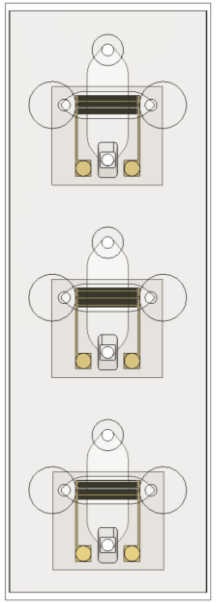
Sensor-integrated Gut-on-a-Chip

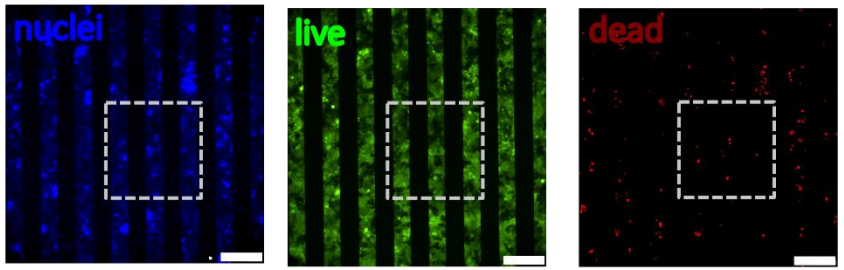
The setup

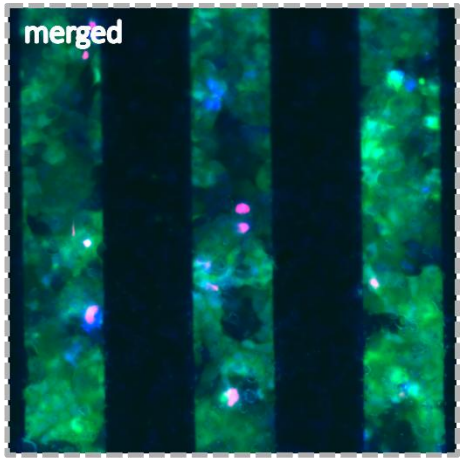
3D extrusion

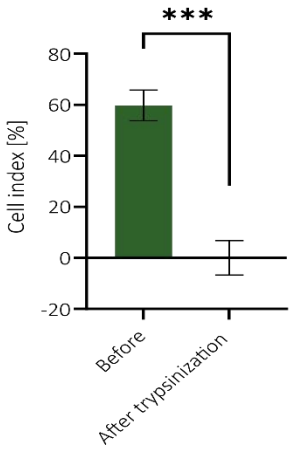


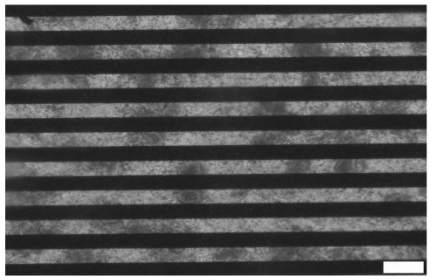
Top view

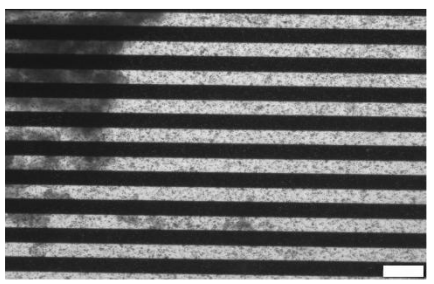












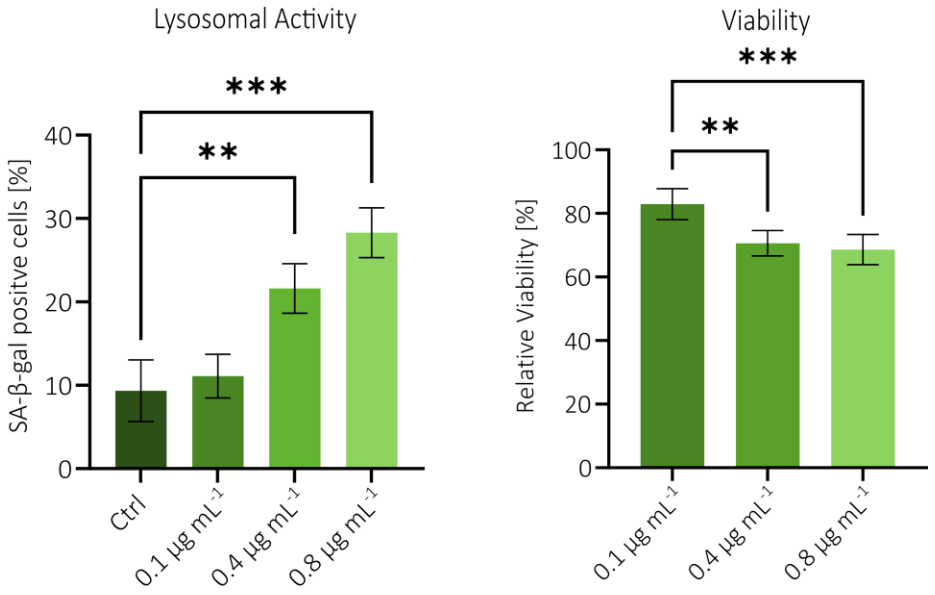
Impact on Neurodegenerative Diseases → elderly patients

Sensor-integrated Gut-on-a-Chip

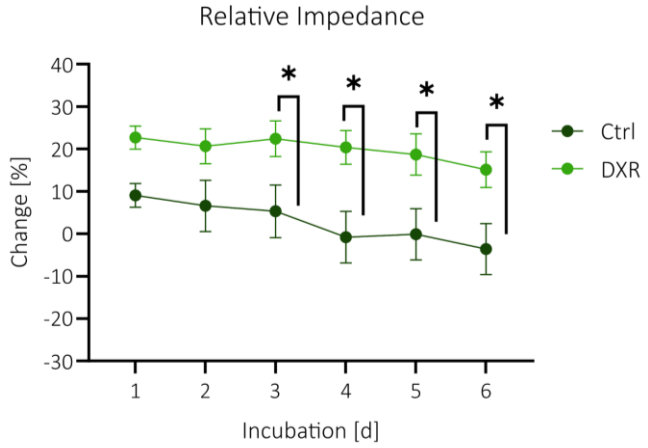
Aging the gut barrier:

Less proliferation → cytostatic agents → Doxorubicin

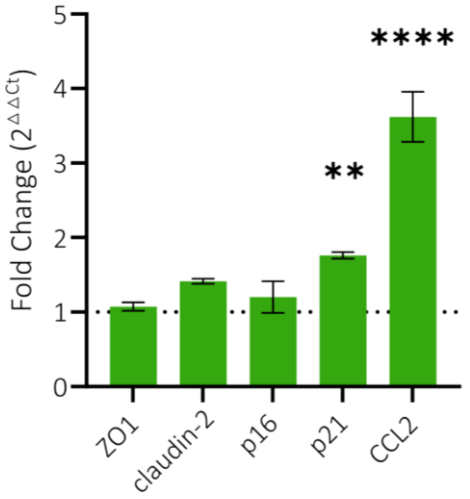
Effect of Doxorubicin on senescence and cell viability:



Impedance measuremnents:
Signal increase unexpected

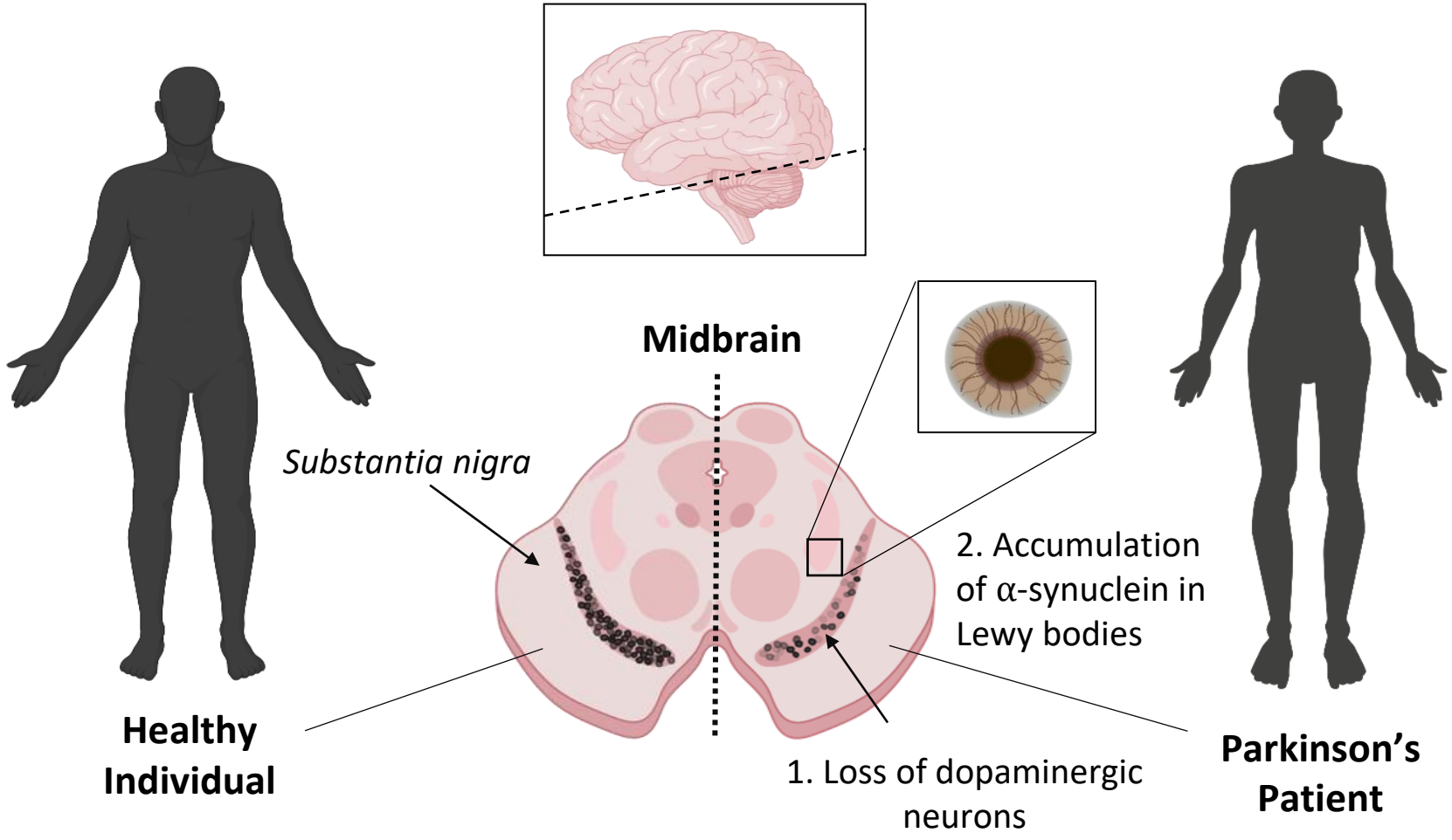


PCR Results:
Significant increase in p21 and CCL2 expression a marker upregulated in aged intestinal cells



The Human Midbrain and Parkinson's Disease

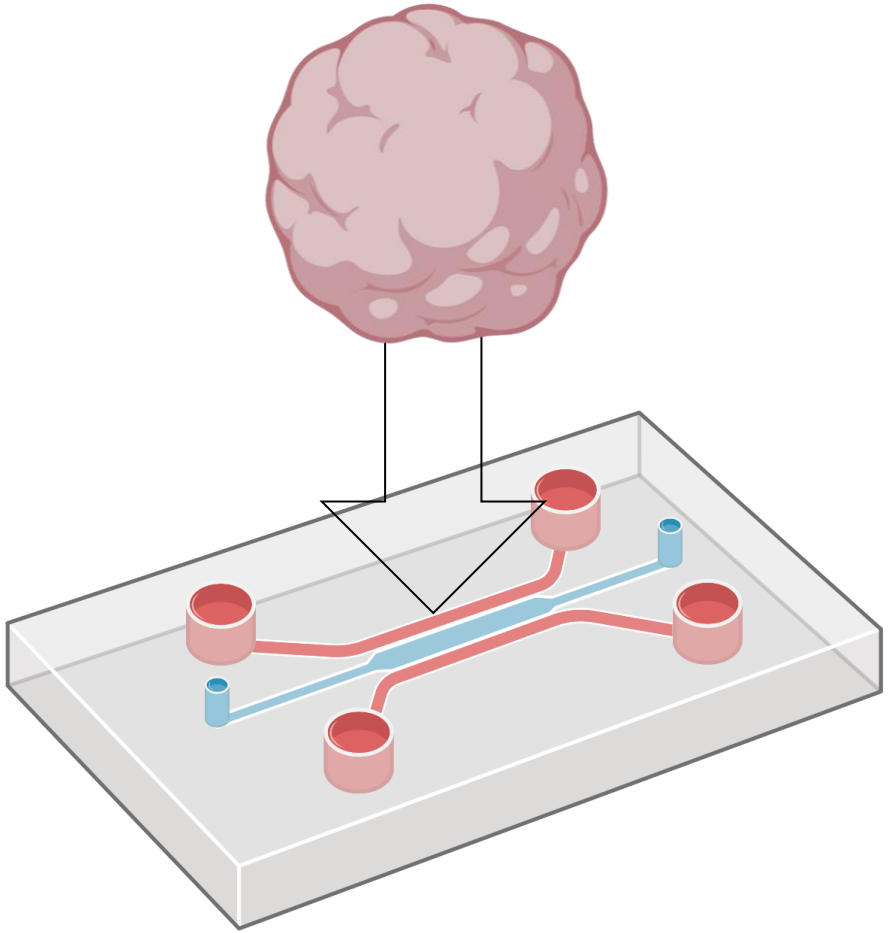
Parkinson's disease is the second most common neurodegenerative disorder worldwide with a prevalence of **9.4 million**.[1]



- **Motor symptoms**
  bradykinesia, akinesia, tremor, rigidity..
- **Non-motor symptoms**
  depression, hallucinations,..

[1] *Maserejian, N., Vinikoor-Imler, L. , Dilley, A. Estimation of the 2020 Global Population of Parkinson's Disease (PD). in (MDS Virtual Congress 2020, 2020)*

Organoid Meets Organ-on-a-Chip Technology



1. Immaturity

Physiologic Microenvironment

2. Insufficient Nutrient Supply

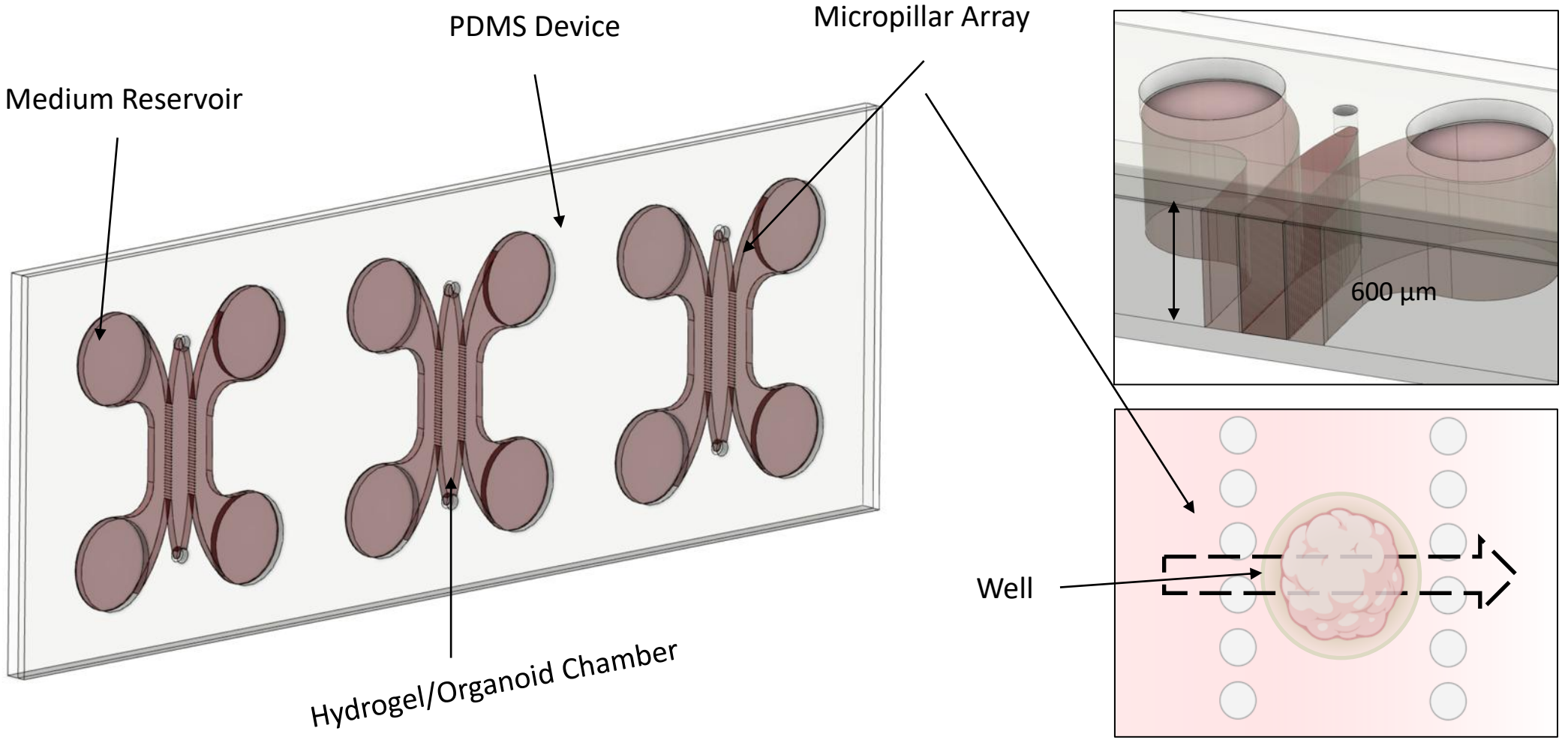
Nutrient Flow

3. Non-Invasive Analysis

Non-invasive monitoring with integrated sensors

- Optical Sensors
- Electrical Sensors

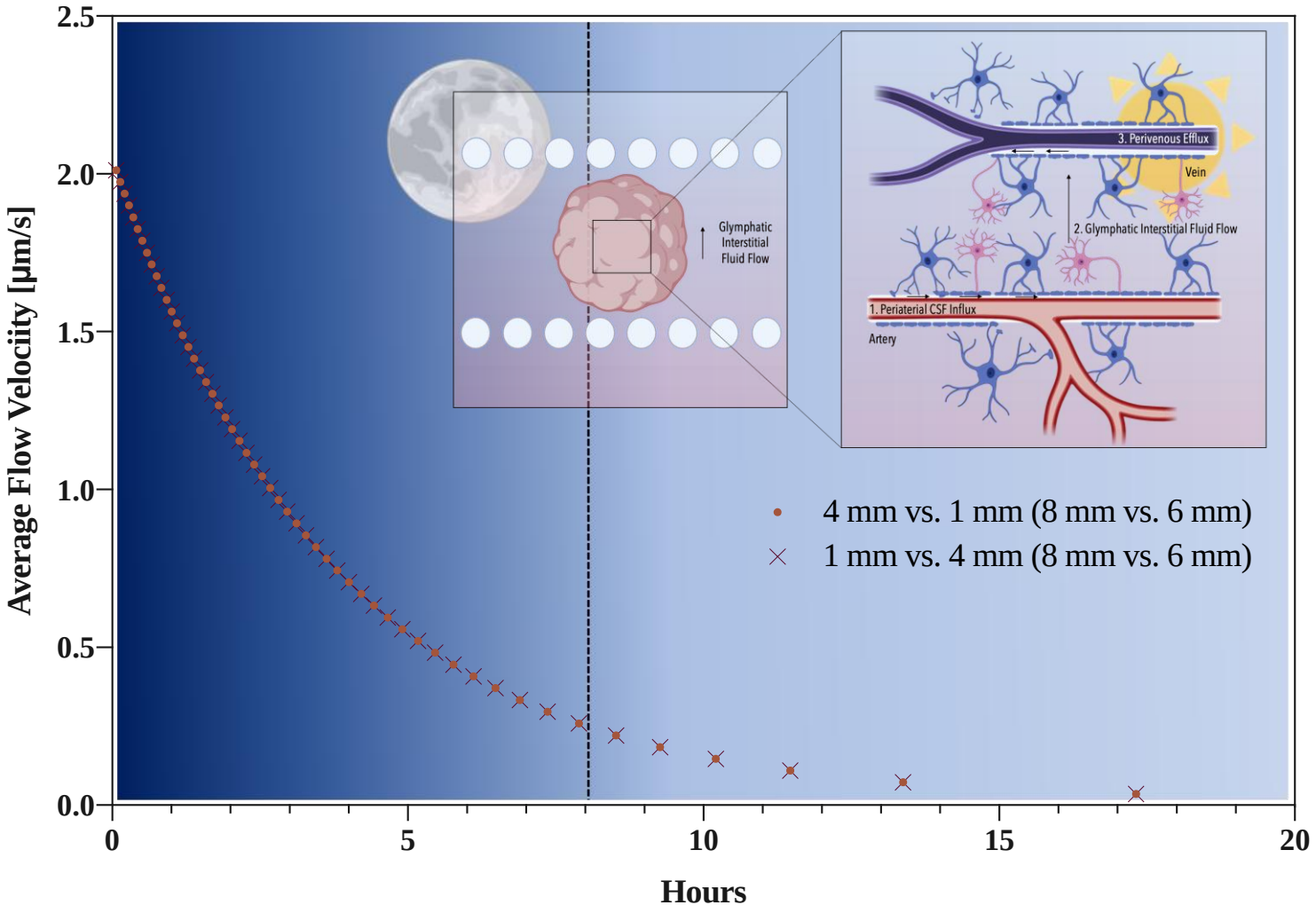
Hydrostatic Pressure Driven Flow Based Approach to Direct Nutrients through the Organoid

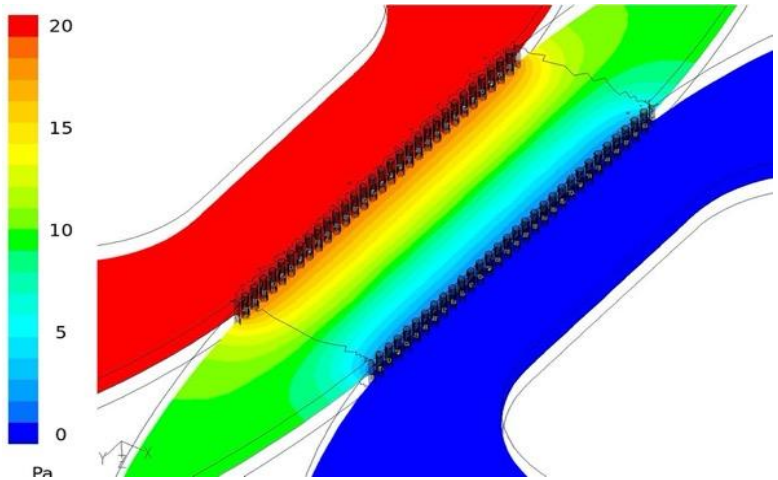


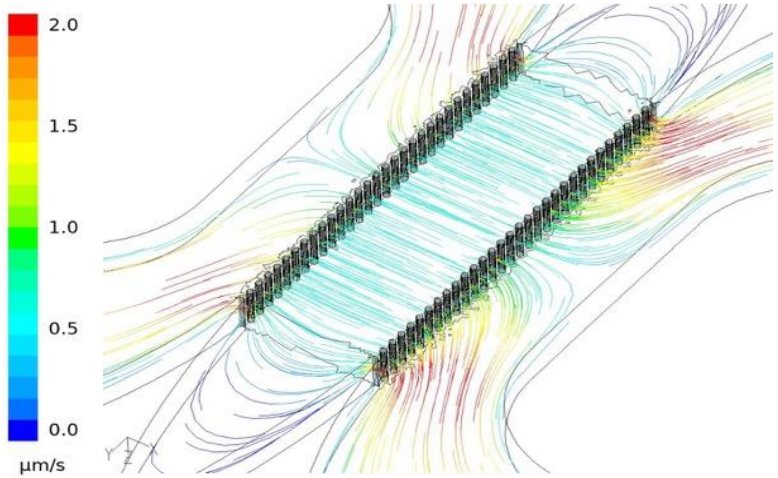
Spitz S., Ertl P., Schwamborn J., Bolognin S., EPO, App.No.20173702.0-1101, Microfluidic Device, patent pending

CFD Simulation of Interstitial Flow Profile on Chip

Flow velocity [µm/s] over Time

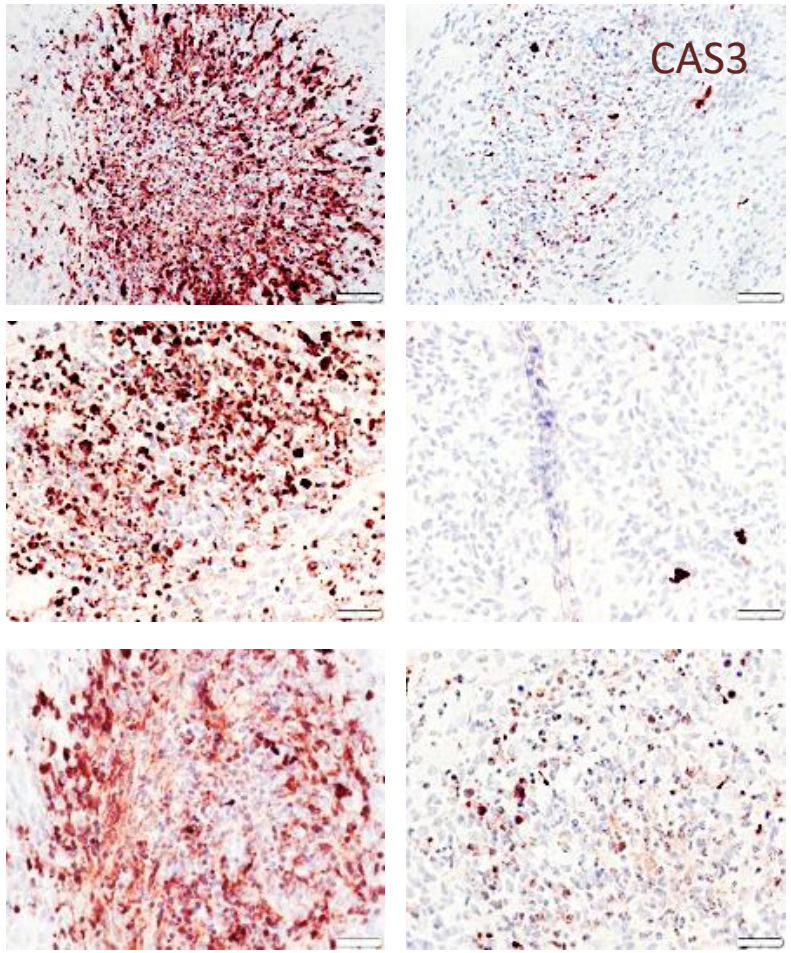






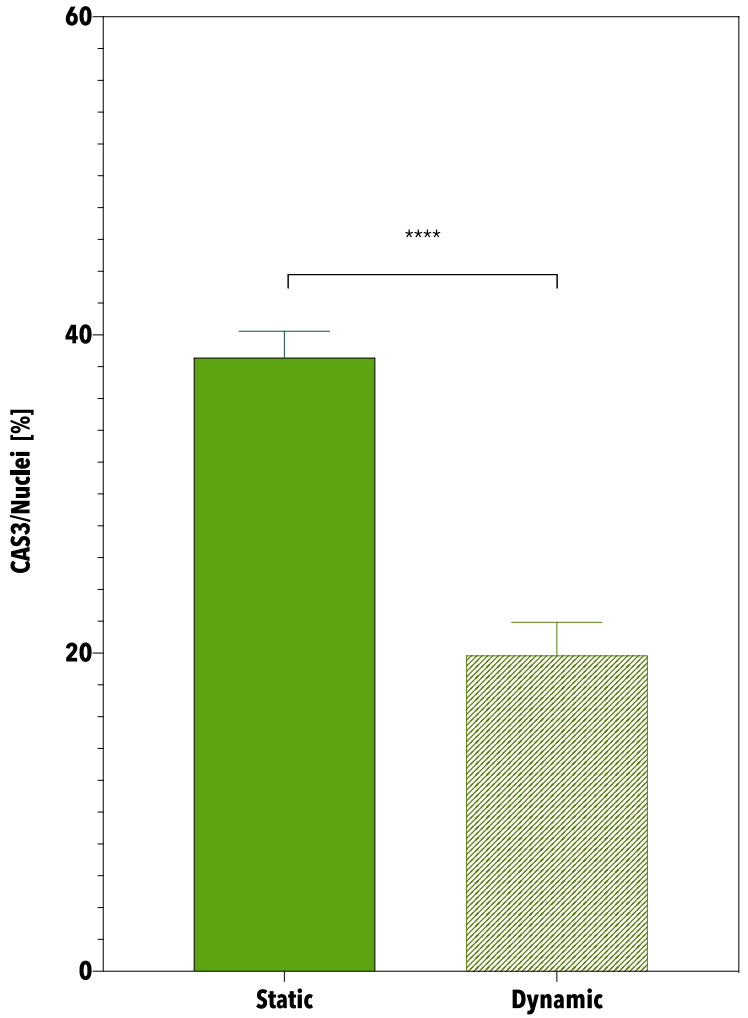
Dynamic Cultivation Reduces Dead Core Formation

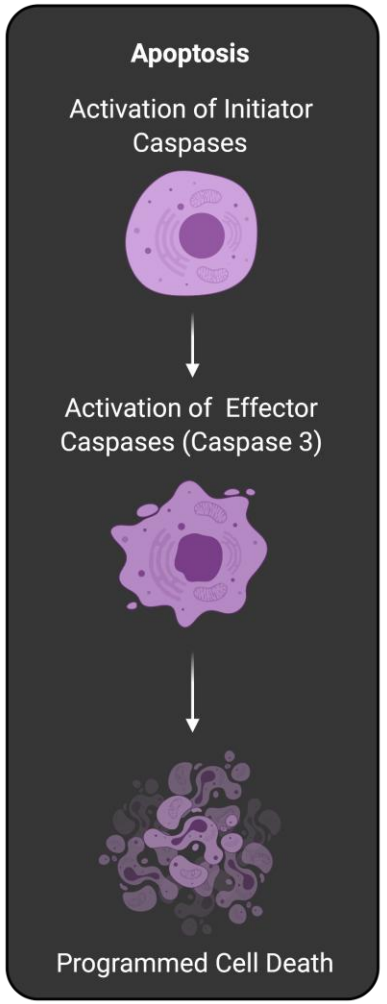
D35 after 25 days on chip



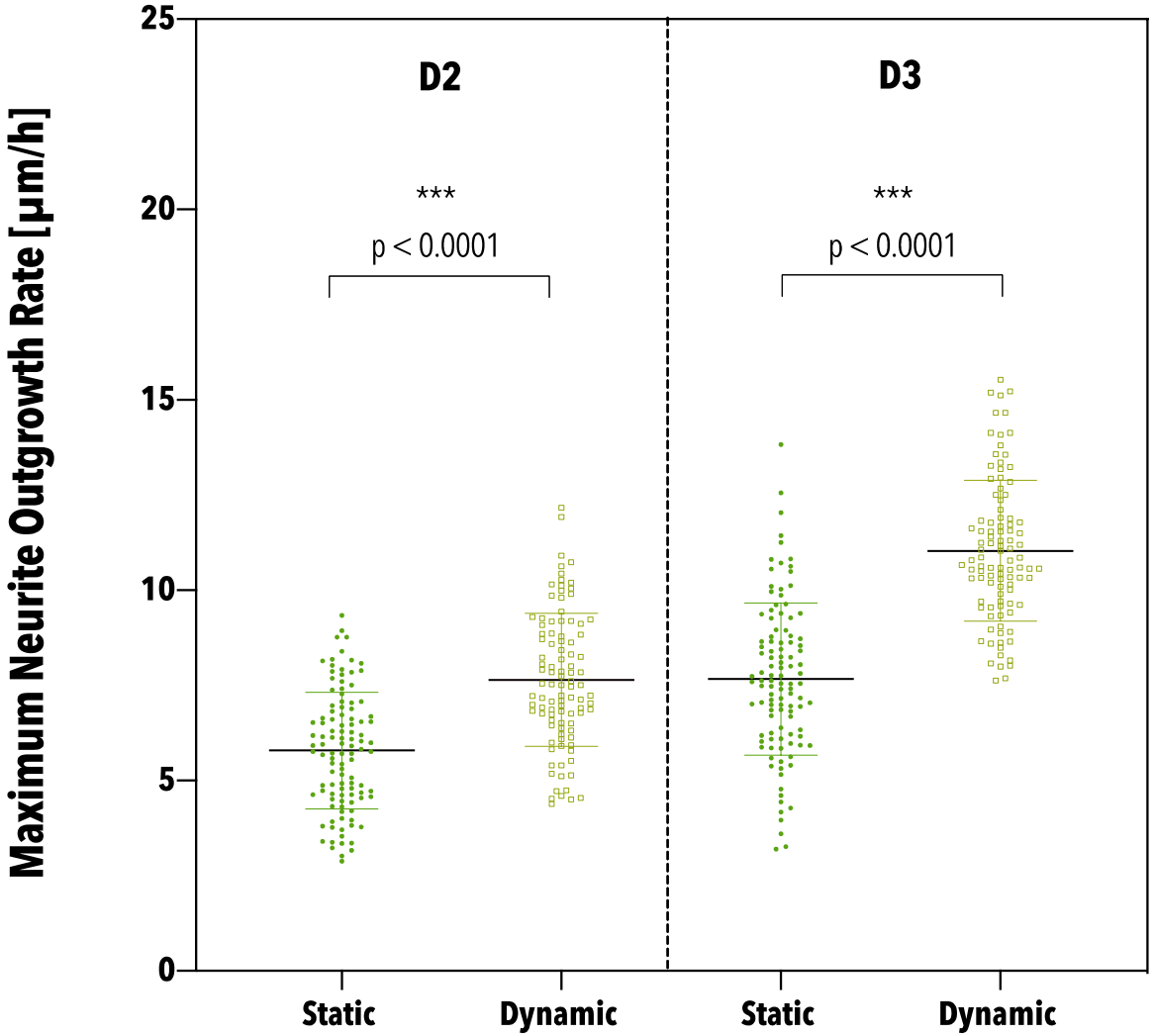
Static Dynamic

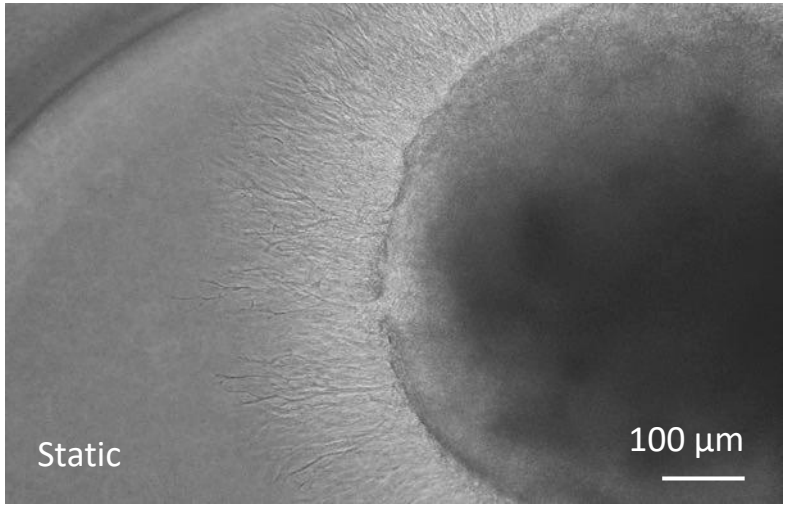
caspase-3 signal … apoptosis marker

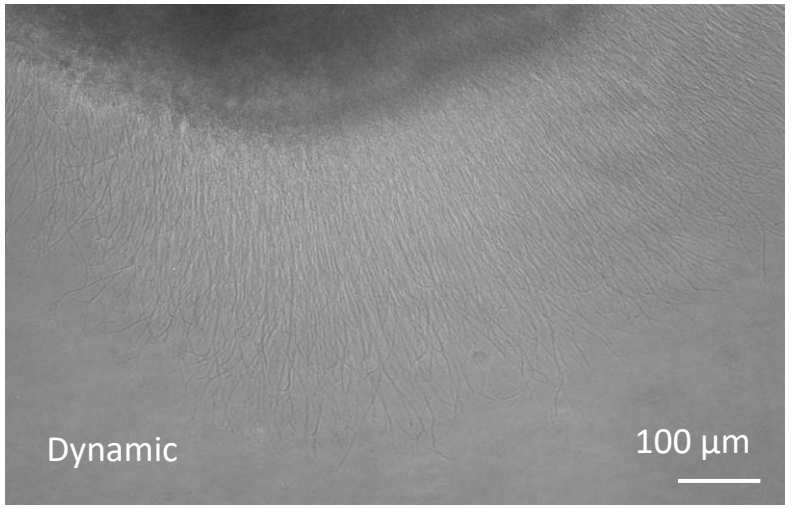




Dynamic Cultivation Enhances Neurite Outgrowth







N= 10

Monitoring Organoid Growth and Viability via Oxygen Consumption

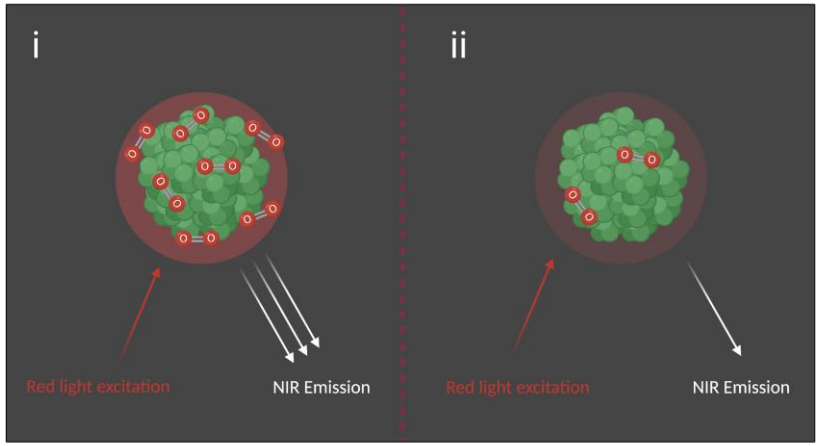
- Non-invasive monitoring of organoid growth and viability
- Integration of an optical oxygen sensor spot
- **Luminescent intensity of REDFLASH** indicator dye is quenched by oxygen

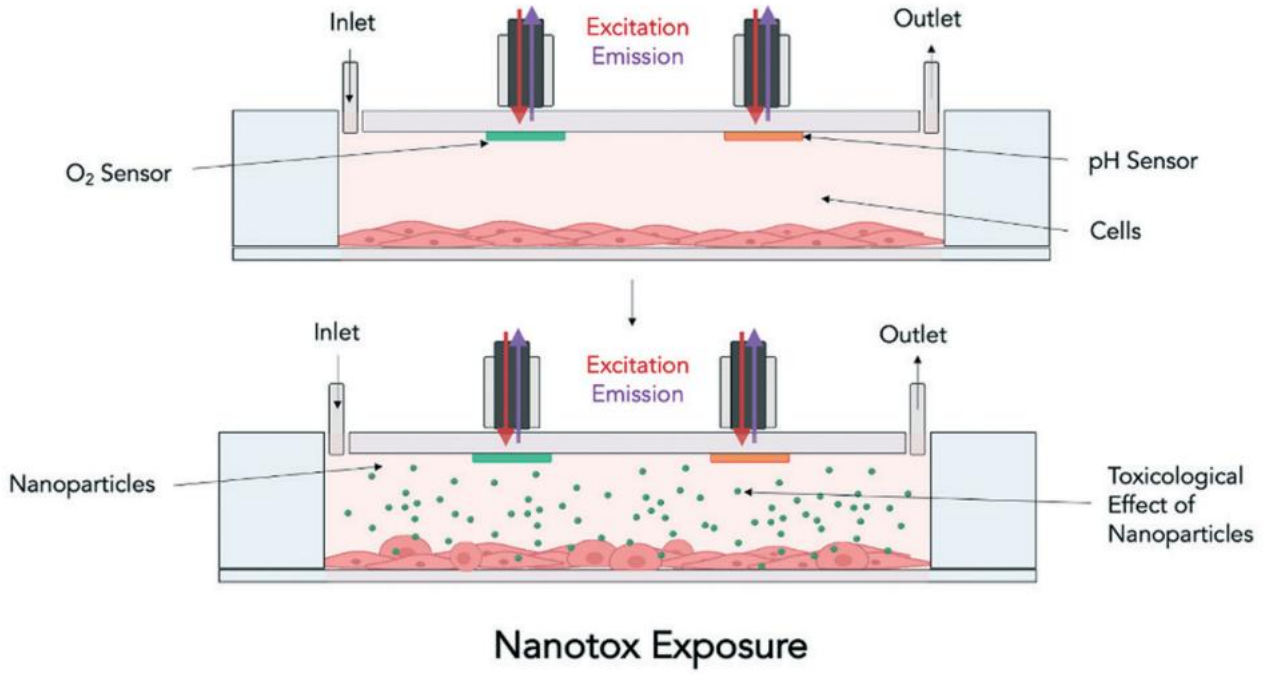
  → information on the local oxygen concentration

Bridging the academic-industrial gap: application of an oxygen and pH sensor-integrated lab-on-a-chip in nanotoxicology

Helene Zirath*[ab†], Sarah Spitz[ab†], Doris Roth[ab], Tobias Schellhorn[a], Mario Rothbauerb[c], Bernhard Müller[d], Manuel Walch[e], Jatinder Kaur[e], Alexander Wörle[e], Yvonne Kohl[f], Torsten Mayr[d], and Peter Ertl *[ab]

Sensing Principle:

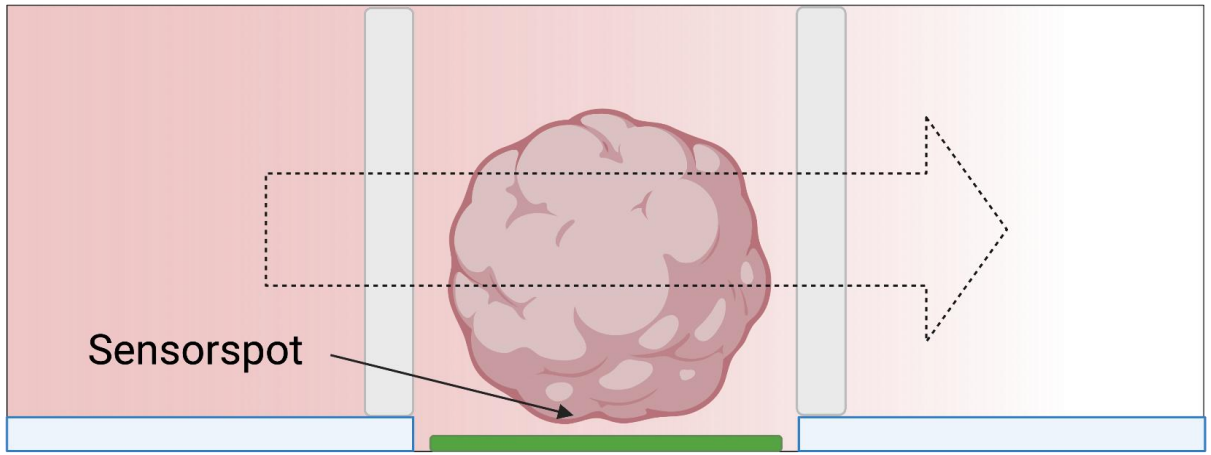


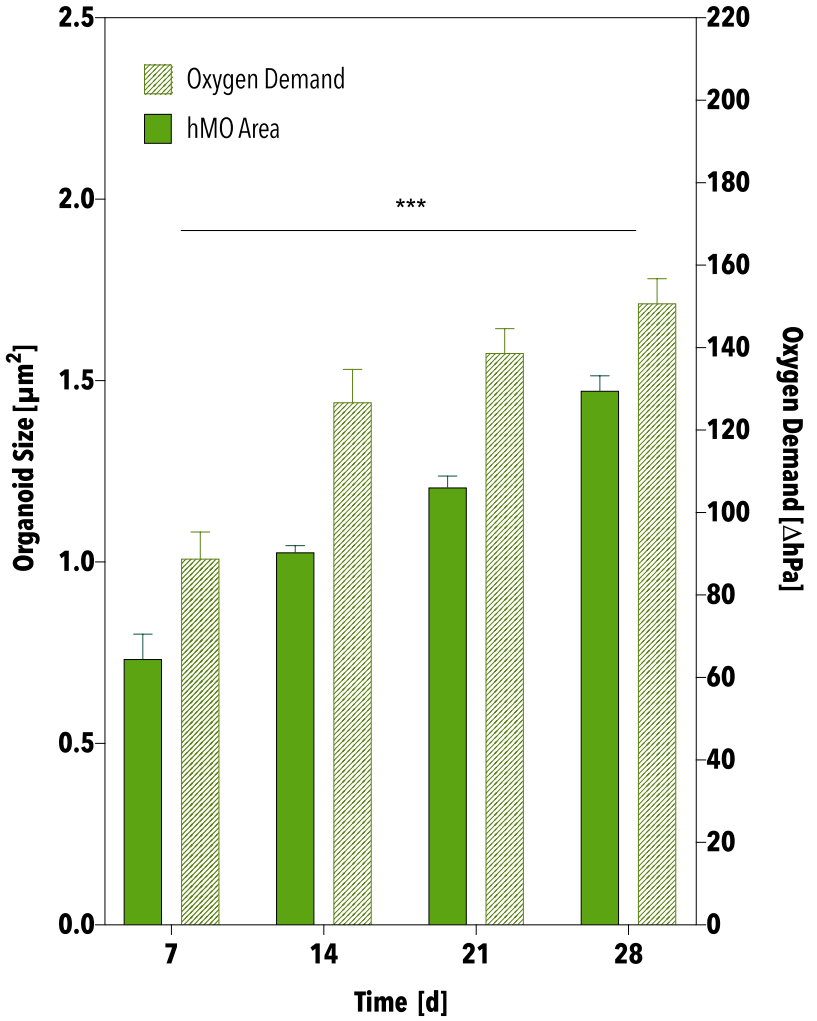


Nanotox Exposure

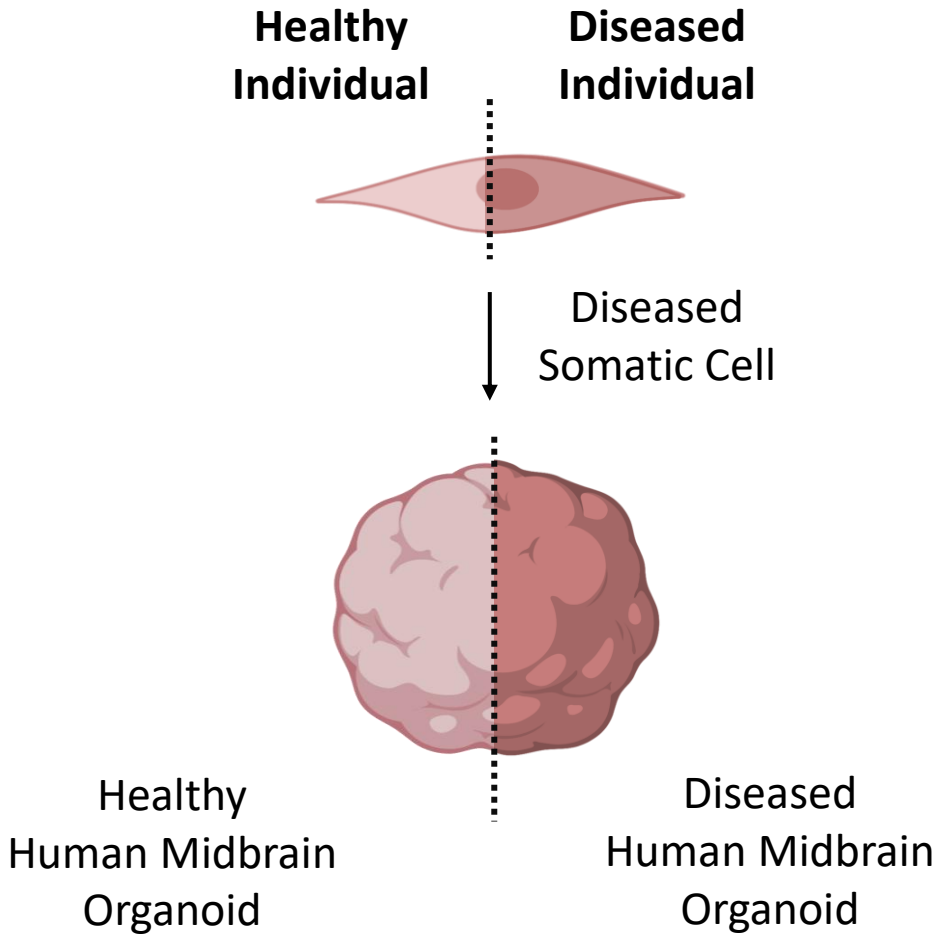
Oxygen Demand Correlates with Organoid Growth

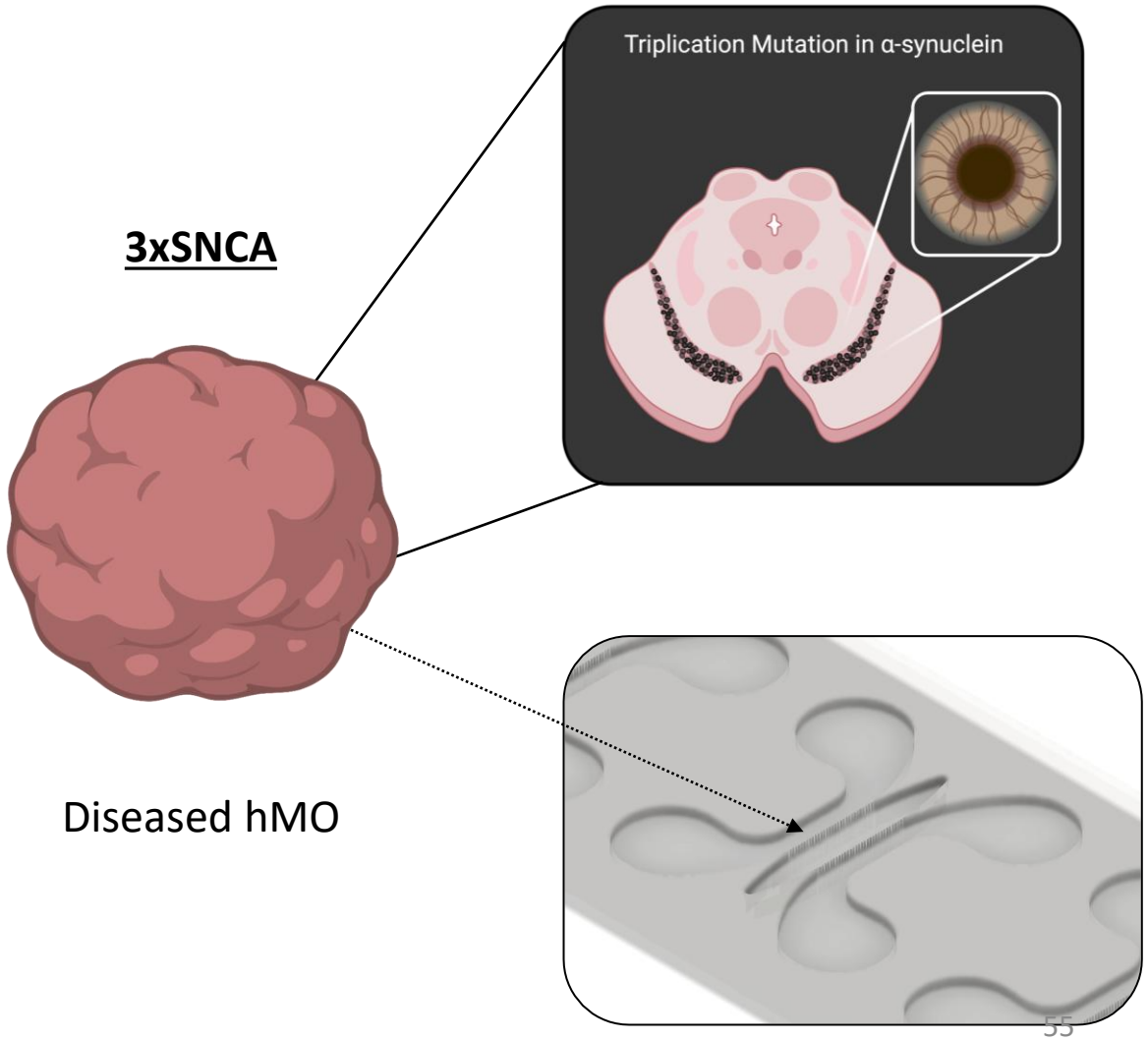
- Significant increase in oxygen demand over time (***)
- Correlation between oxygen demand and hMO growth





Do Sensor Integrated Microfluidic Devices Reveal Phenotypic Differences Between Healthy and Diseased hMOs?



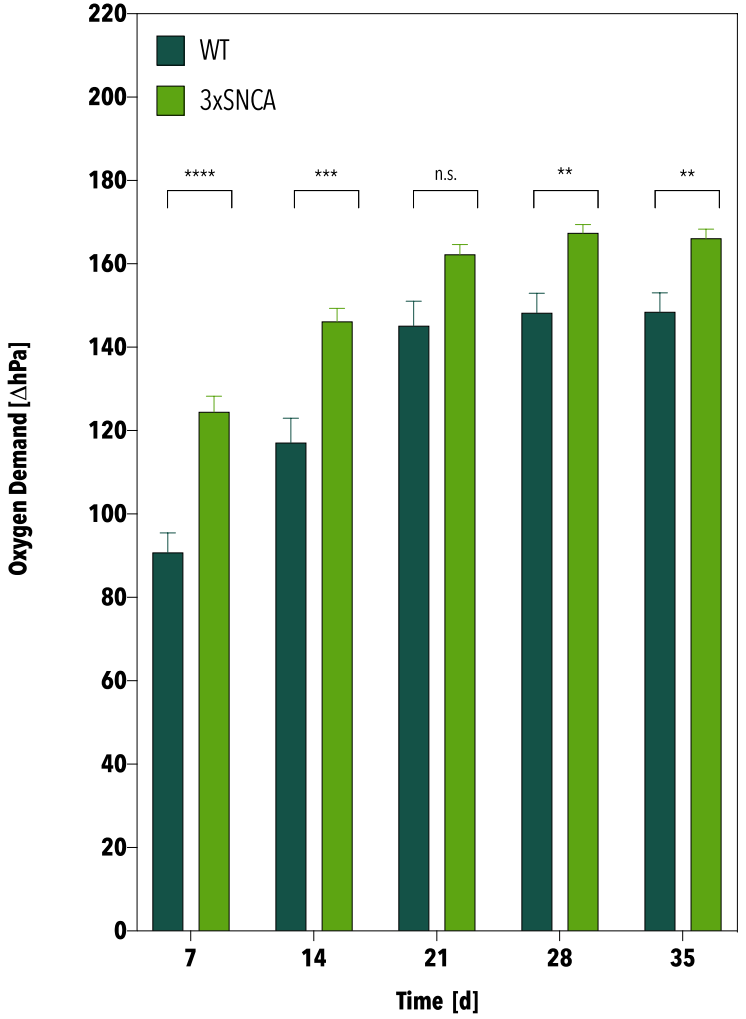


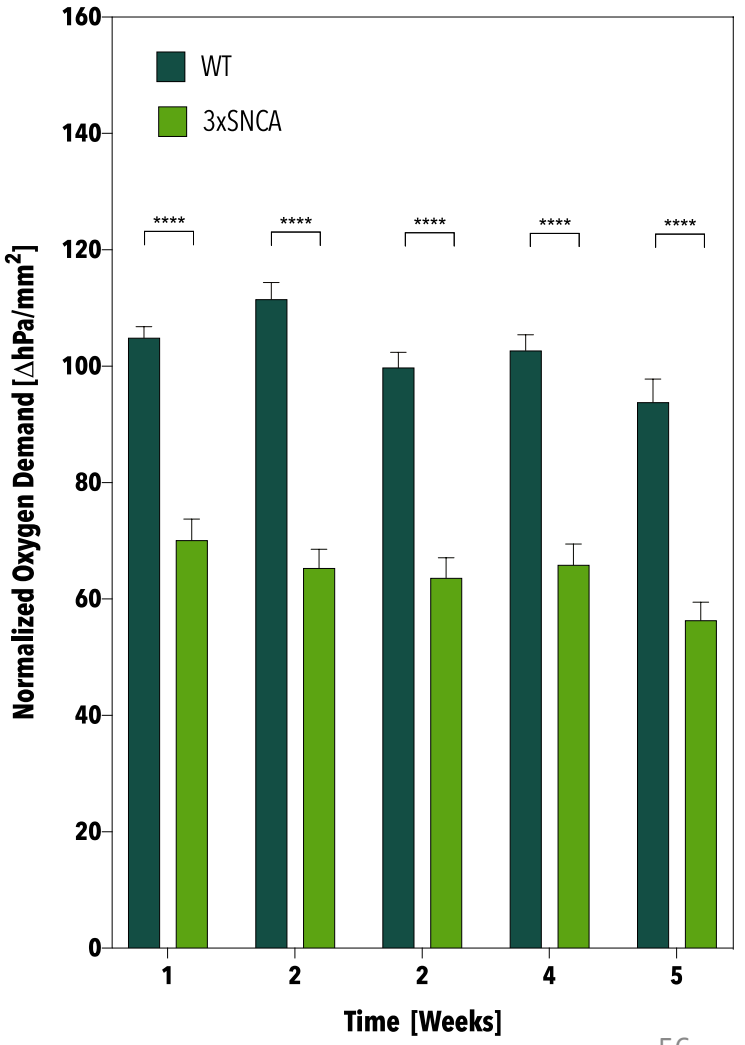
Oxygen Monitoring Reveals Phenotypic Differences

- Significant phenotypic differences between WT and diseased hMOs
- Significantly lower normalized **oxygen demand in diseased hMOs**

  → Pathogenic alpha-synuclein aggregates preferentially bind to mitochondria and affect cellular respiration

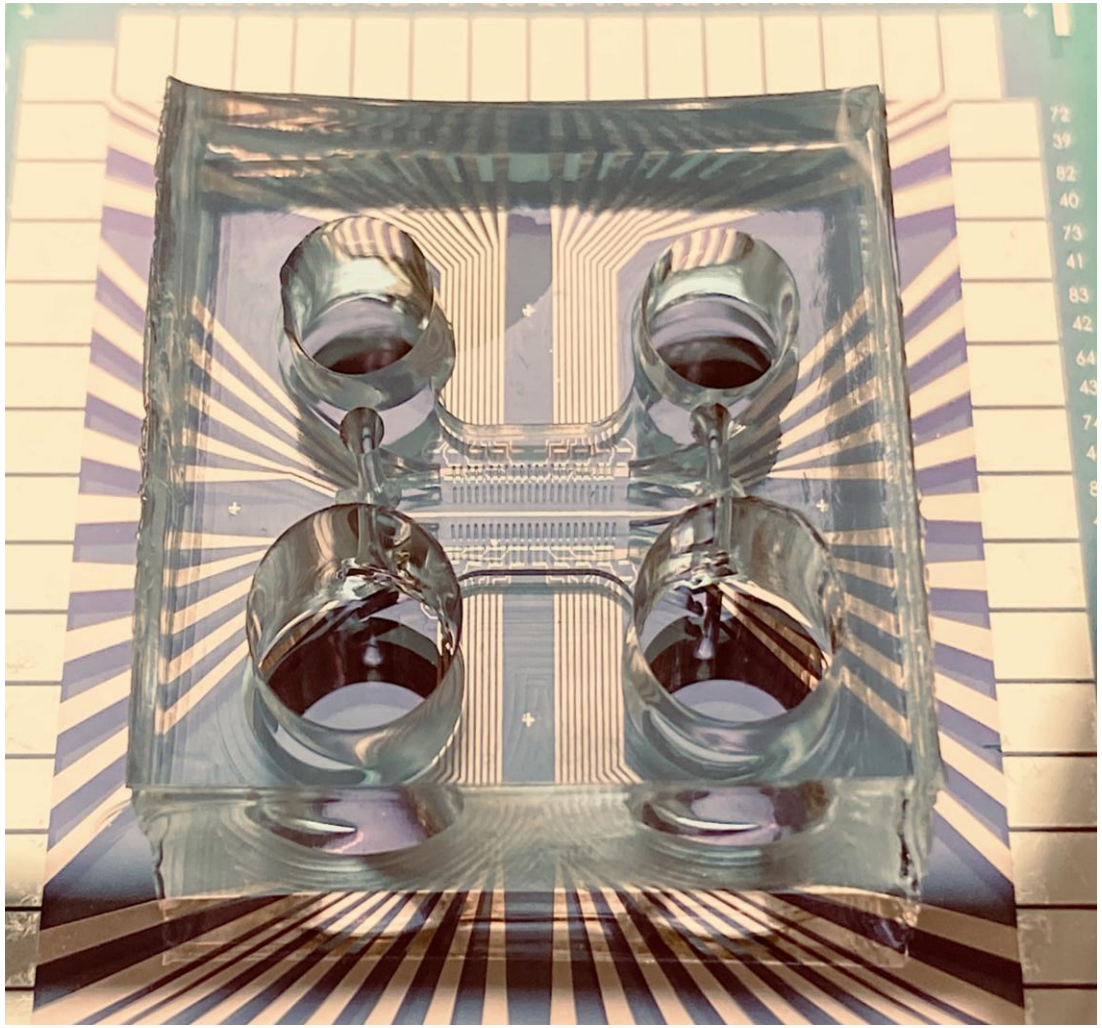
WT… wild type (healthy) 3xSNCA…diseased model

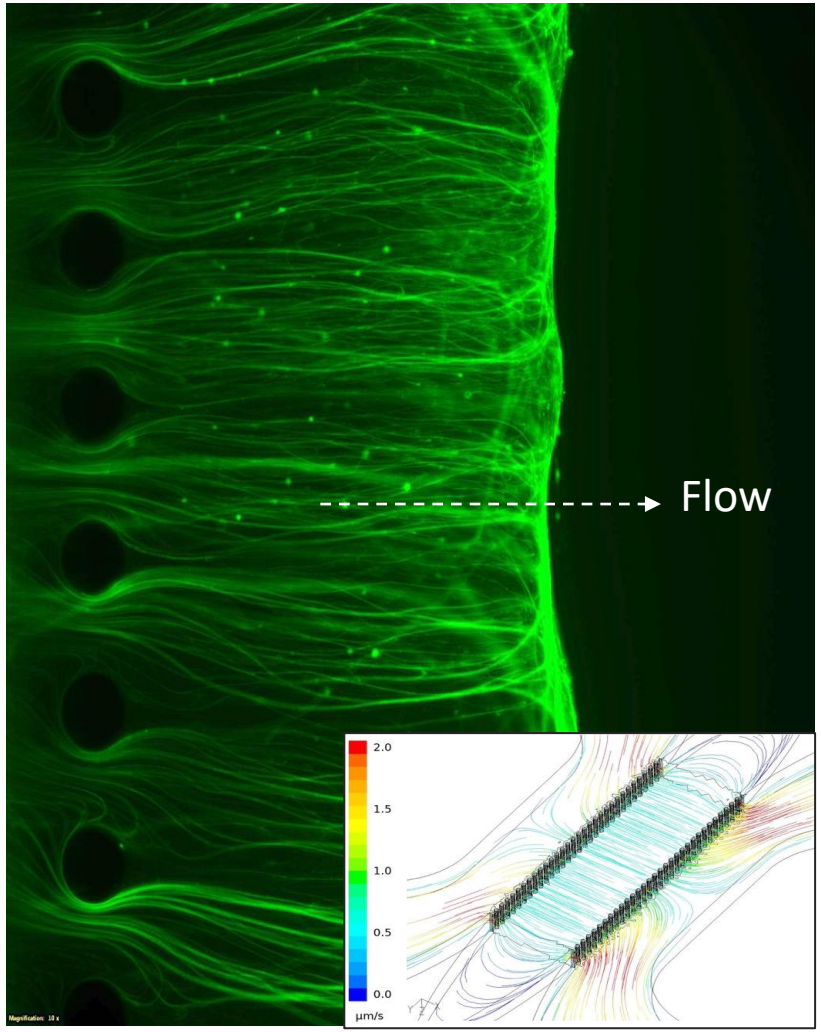


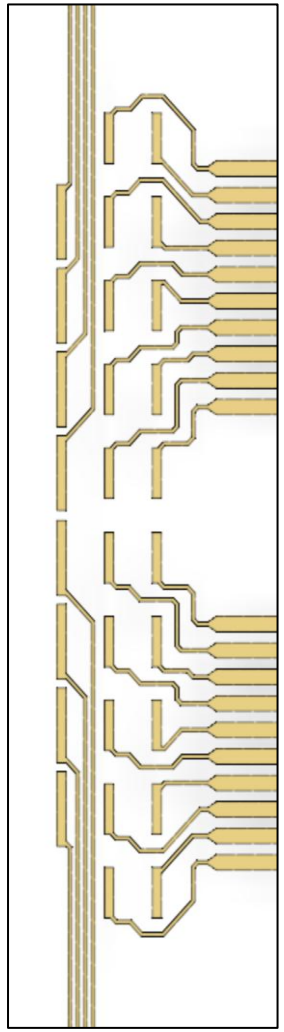


Wang et al. Acta Neuropathologica Communications (2019) 7:41
https://doi.org/10.1186/s40478-019-0696-4

Integration of a 2D MEA Array to Record Electrophysiological Activity of a 3D hMO





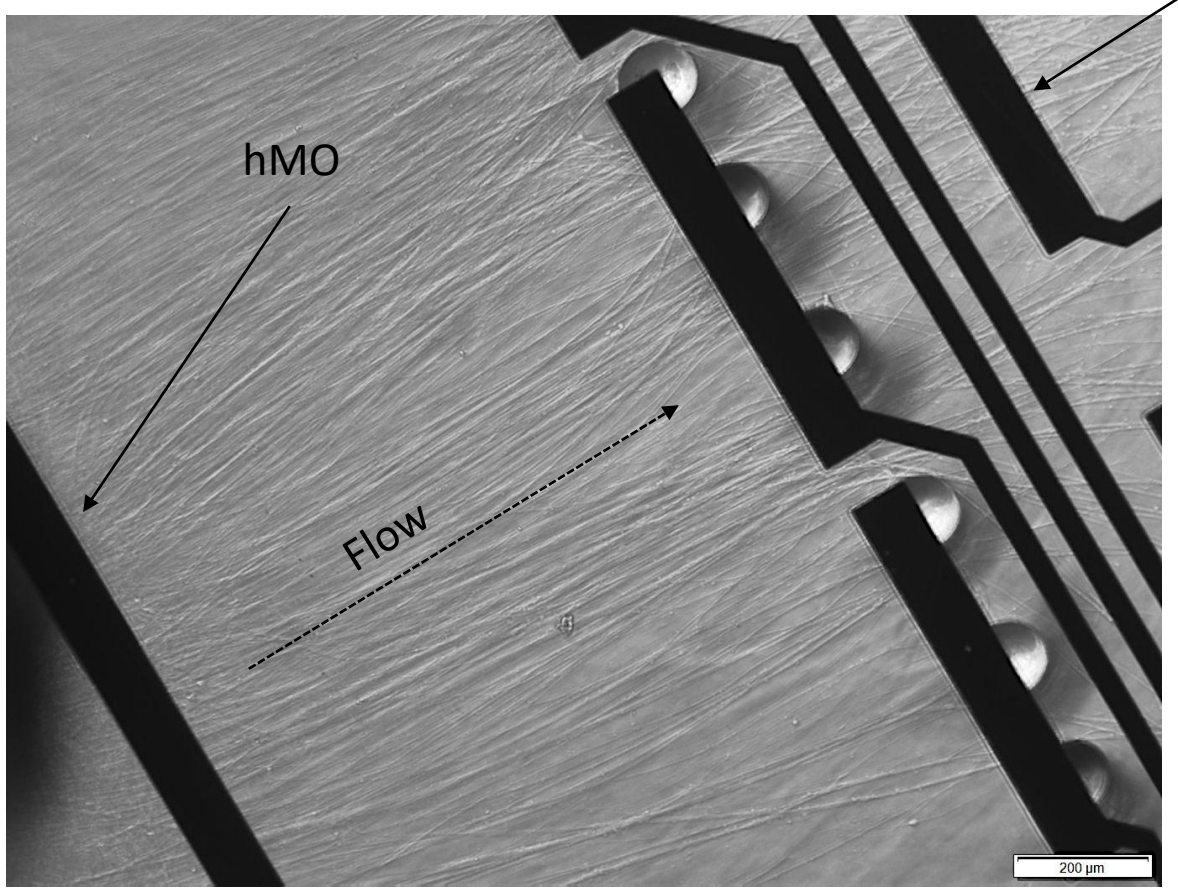


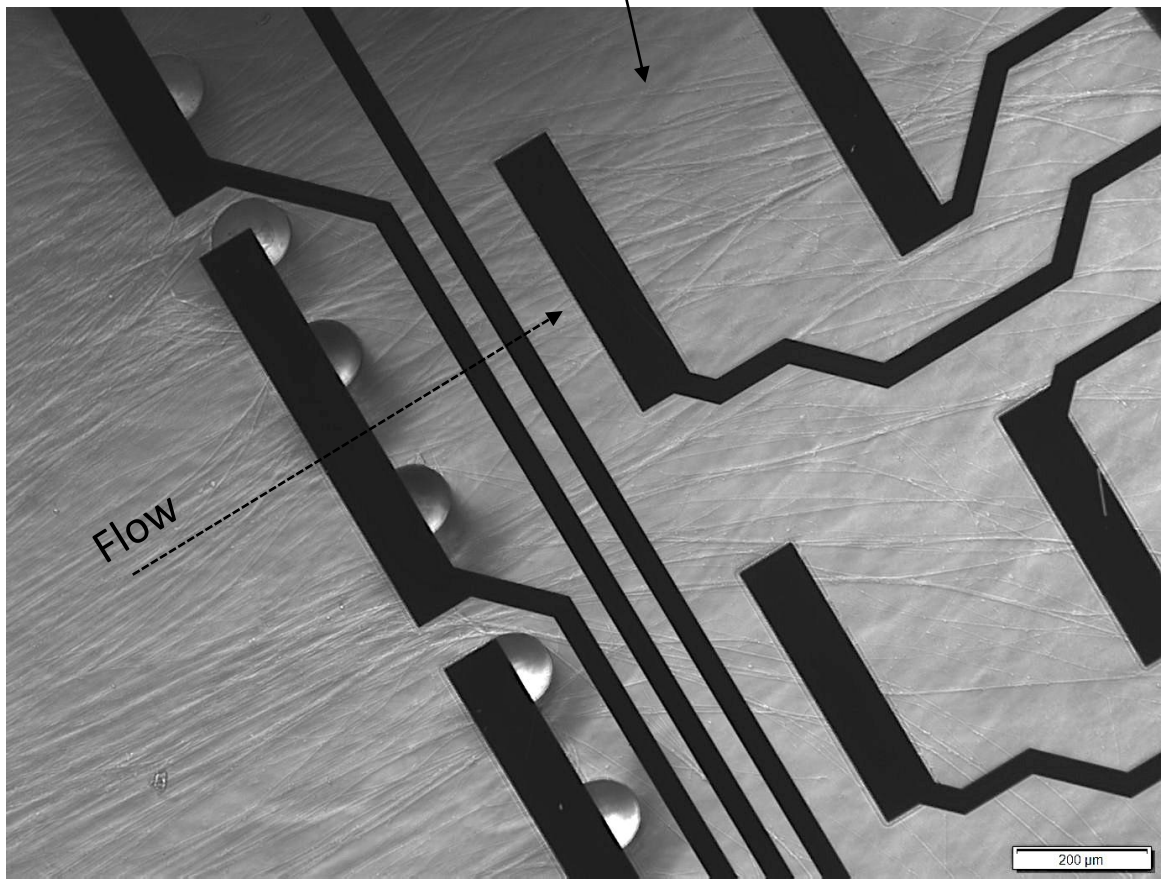
Flow Directed Neurite Outgrowth onto MEA Electrodes

Hydrogel Chamber (3D)

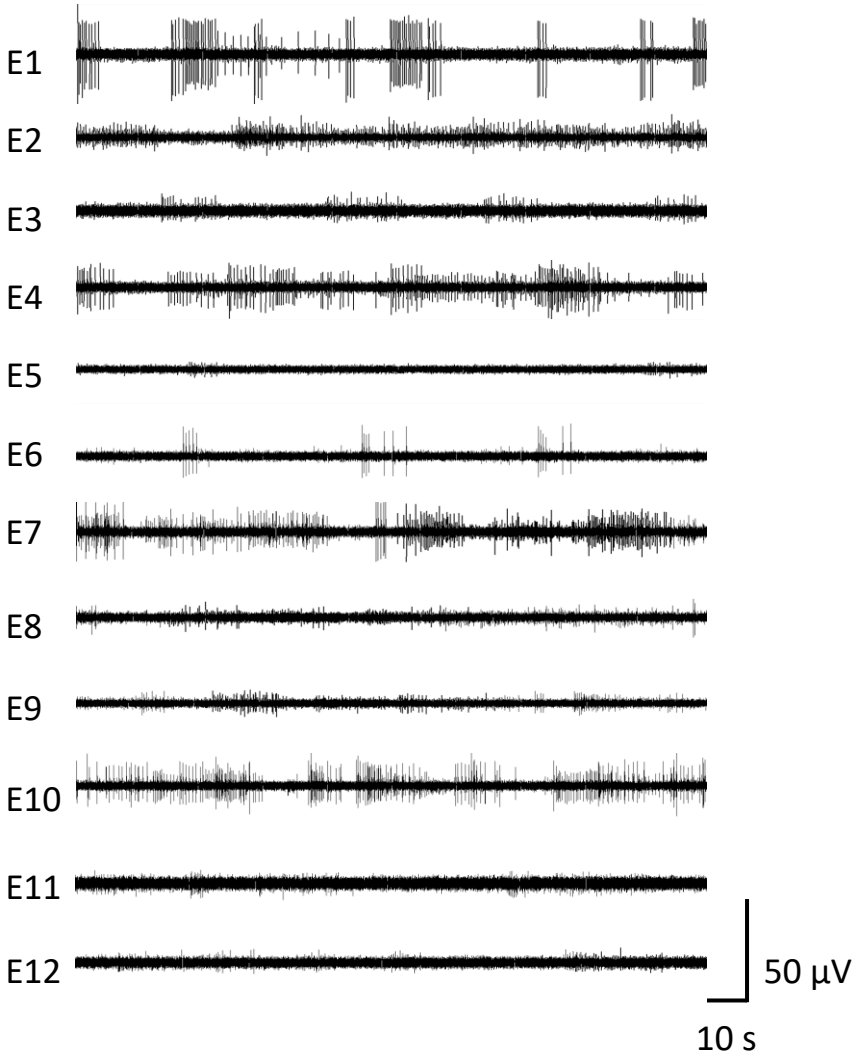
Electrode

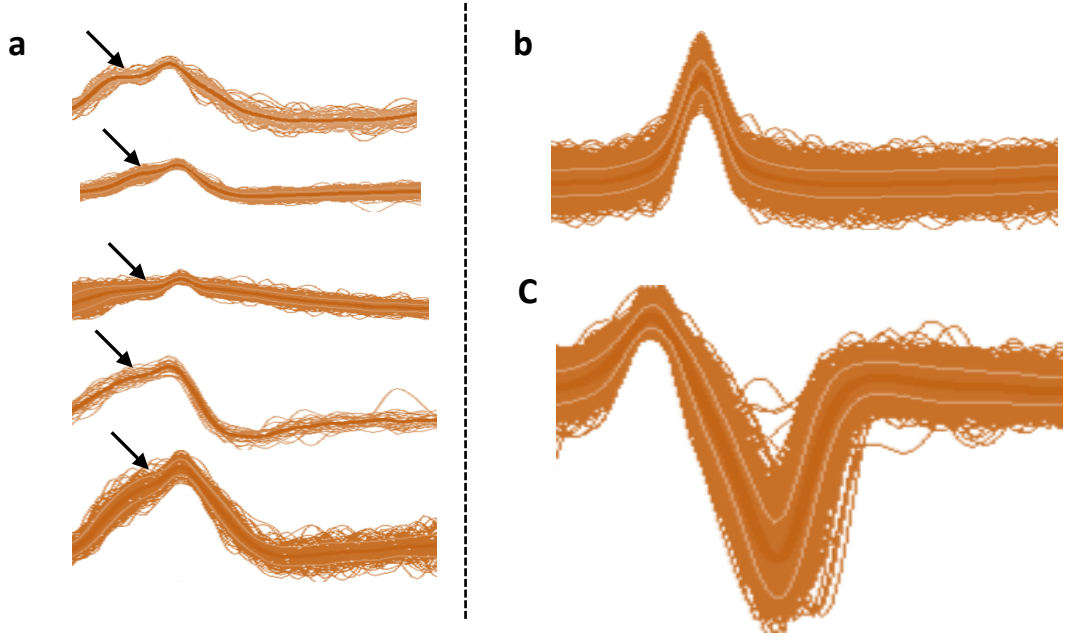
Medium Channel (2D)





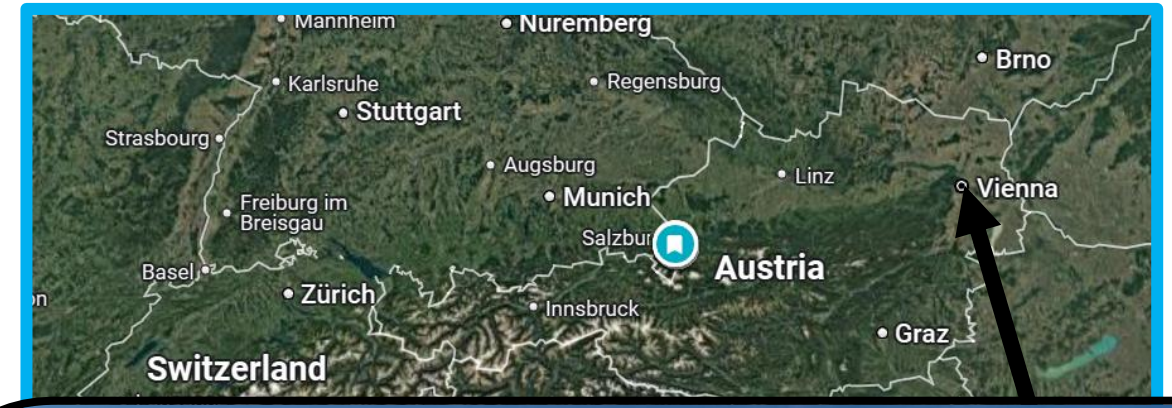
Flow Directed Neurite Outgrowth Favours Electrophysiological Recordings





- Integrated electrodes enable electrophysioloigical recordings of cultivated hMOs
- 66,67 % ± 14.43 of active electrodes display a bursting firing behavior
- Analysis of recordings reveals dopaminergic characteristics → IS breaks

Cell Chip group



CELLCHIP GROUP

linkedin.com/company/cell-chip-group

www.ias.tuwien.ac.at/cellchipgroup