INSTITUTO DE PESQUISAS TECNOLÓGICAS

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BBB-on-a-chip: a new model to mimic the human blood-brain barrier

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Palestra apresentados Pub Boston MA
23 slides.

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BBB-on-a-chip: a new model to mimic the human blood-brain barrier

Advisor: Prof. Dr. Emanuel Carrilho

Ph.D Student: Sheila Sousa Gomes Fortes

Who I am

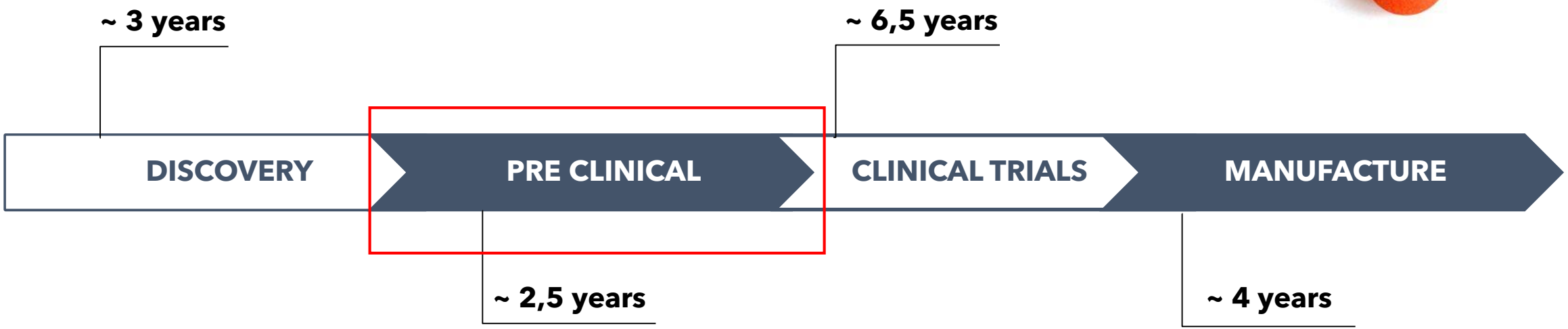
- Polymer Technologist – Fatec Mauá (2015)
- MSc in Biomedical Engineering – UFABC (2018)
- Ph.D. Student in Organic and Biological Chemistry at IQSC USP
- Researcher at IPT
- Visiting Graduate Student at Wyss Institute at Harvard University

Mauá/SP - BRAZIL

Sheila Sousa Gomes Fortes

90% new drug developments fail in clinical trials

Development of new drugs



10 - 15 years
2 - 3 billions $

Acta Pharmaceutica Sinica B, Volume 12, Issue 7, July 2022, Pages 3049-3062

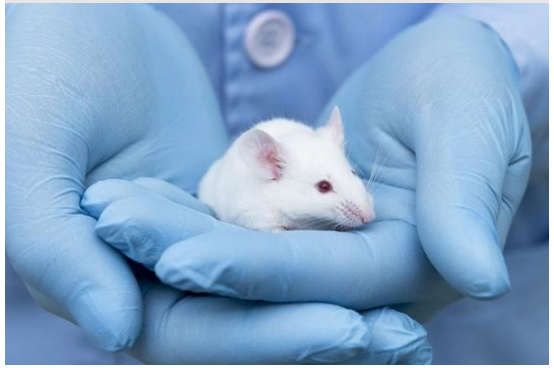
Why do this failures happens?

Current methods used during the pre-clinical trails of new drugs

2D cell culture

- Simple and reproducible
- Low cost
- High Throughput
- Real-time monitoring
- Long-term cell viability
- Patient-specific cells
- No ethical issues

Animal Models

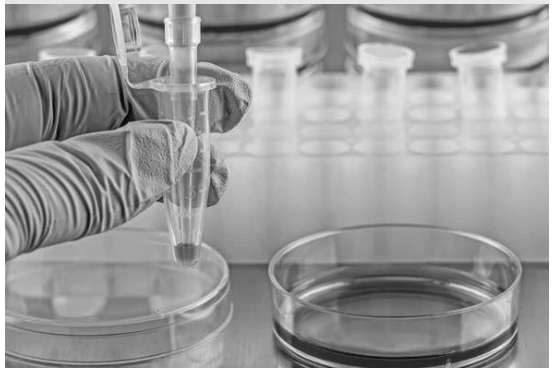


- 3D-tissue architecture
- Immune system
- Hemodynamic system
- Physiological biomechanics and biochemical cues
- Multi tissue/organ interaction

Microfluidics Innovation Center. *LUNG-ON-A-CHIP MODEL PACK* https://microfluidics-innovation-center.com/application-packs/lung-on-a-chip-model/

Current methods used during the pre-clinical trails of new drugs

2D cell culture



- Single cell types
- No physiological biomechanics and biomedical cues
- No hemodynamic system
- Does not mimic 3D tissue architecture

Animal Models

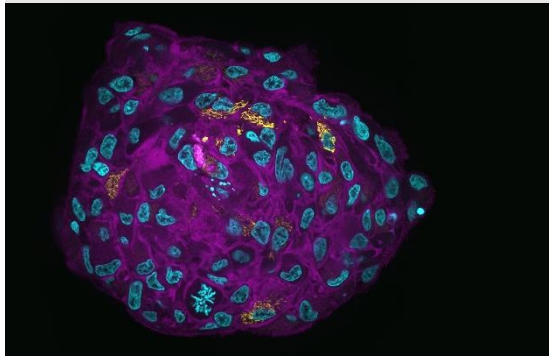
- Expensive
- Time Consuming
- Interspecies variation
- Low-troughput
- Ethical issues
- Findings can be incosistent in translation to human health

Microfluidics Innovation Center. *LUNG-ON-A-CHIP MODEL PACK* https://microfluidics-innovation-center.com/application-packs/lung-on-a-chip-model/

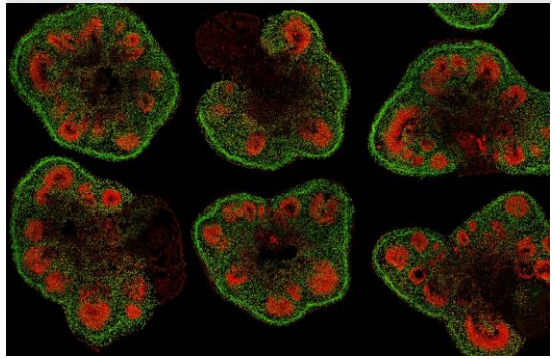
In vitro models for mimicking organ functions

Transwell

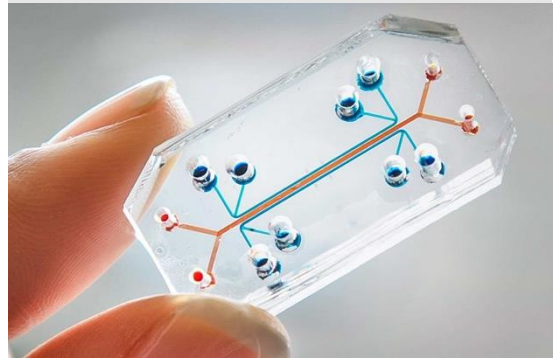
Spheroids



Organoids

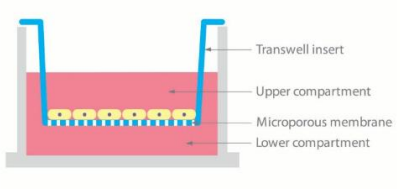
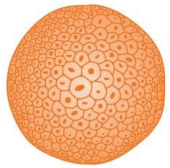


Organs-on-a-chip



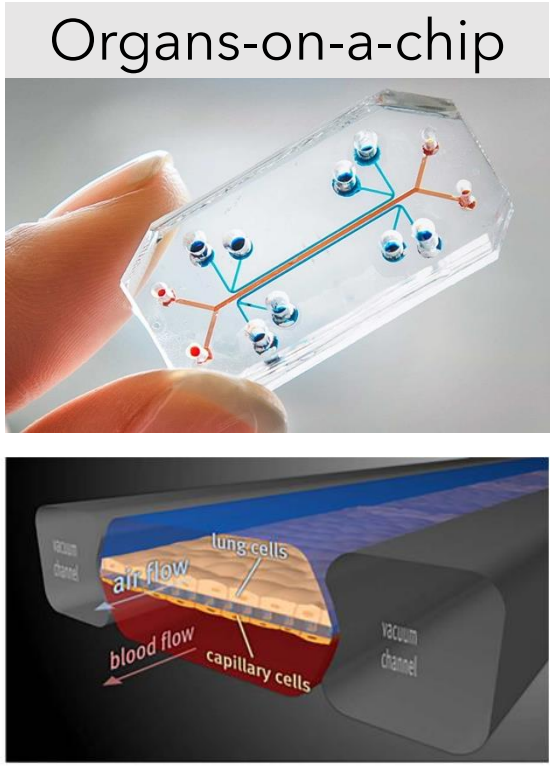
Microfluidics Innovation Center. *LUNG-ON-A-CHIP MODEL PACK* https://microfluidics-innovation-center.com/application-packs/lung-on-a-chip-model/

In vitro models for mimicking organ functions

	ADVANTAGES	LIMITATIONS
Transwell 	• Simple, reproducible and low-cost • Co-culture • High throughput (alto rendimento) • Real-time monitoring • Long-term cell viability • Patient-specific cells • No ethical issues	• No physiological biomechamics • No hemodynamic system • Does not mimic 3D tissue architecture • Inadequate nutriente and waste transport
Spheroids 	• Simple and round • Easier to manage and culture in large quantities • Mimics 3D tissue architecture • Full cell differentiation • Cell-cell and cell-ECM interaction presente • Real-time monitoring	• Limited diversity • Challenging to maintain over long time • No physiological biomechamics • No hemodynamic system • Does not mimic 3D tissue architecture • Inadequate nutriente and waste transport
Organoids 	• Phenotypical/physiological relevance • Mimic the diversity of organs • Mimics 3D tissue architecture • Full cell differentiation • Cell-cell and cell-ECM interaction presente • Real-time monitoring • No ethical issues	• Lacks imune system • Multiple tissue/organ interface absent • Lacks hemodynamic system • Inadequate nutriente and waste transport • No standard protocols

Microfluidics Innovation Center. *LUNG-ON-A-CHIP MODEL PACK* https://microfluidics-innovation-center.com/application-packs/lung-on-a-chip-model/

In vitro models for mimicking organ functions: organs-on-a-chip

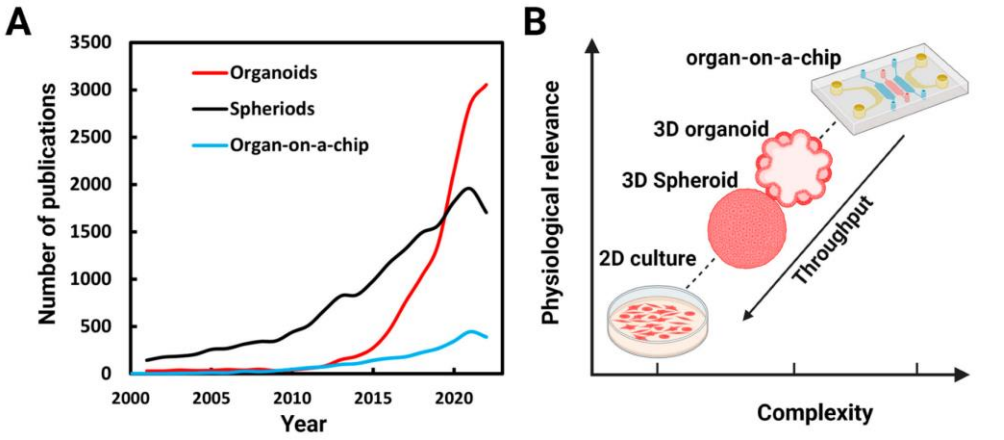


ADVANTAGES

- 3-D tissue architecture
- Controlled microenvironment
- Immune system
- Hemodynamic system
- Physiological biomechanics and biochemical cues
- Multi tissue/organ interaction
- Patient specific cells
- No ethical issues

LIMITATIONS

- No standard protocols
- Difficult to scale up
- Complex requiring adroit users

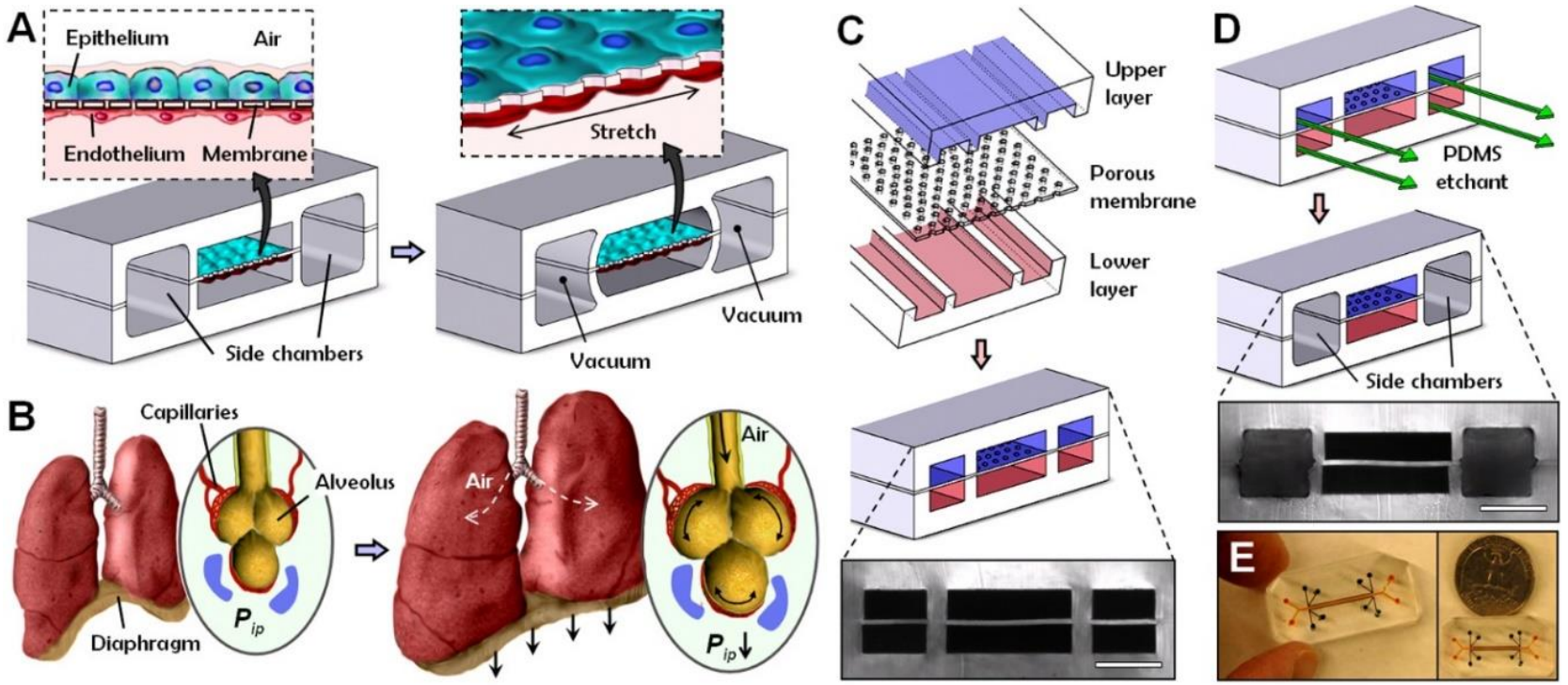


Numbers of publications on organoids, spheroids, and organs-on-a-chip by PubMed. As we get closer to in vivo conditions, the complexities of the systems increase, and throughput decreases.

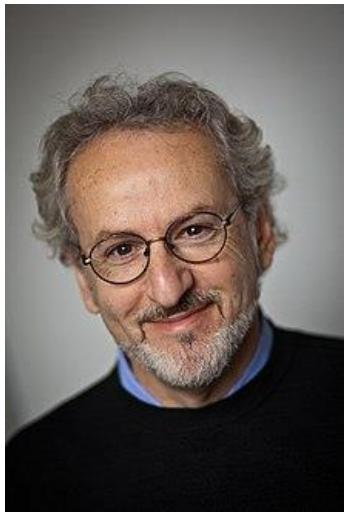
Yousafzai, M. S. & Hammer, J. A. Using Biosensors to Study Organoids, Spheroids and Organs-on-a-Chip: A Mechanobiology Perspective. *Biosensors* **13**, (2023).

Microfluidics Innovation Center. *LUNG-ON-A-CHIP MODEL PACK* https://microfluidics-innovation-center.com/application-packs/lung-on-a-chip-model/

Organ-on-a-chip: a brief history



Biologically inspired design of a human breathing lung-on-a-chip microdevice

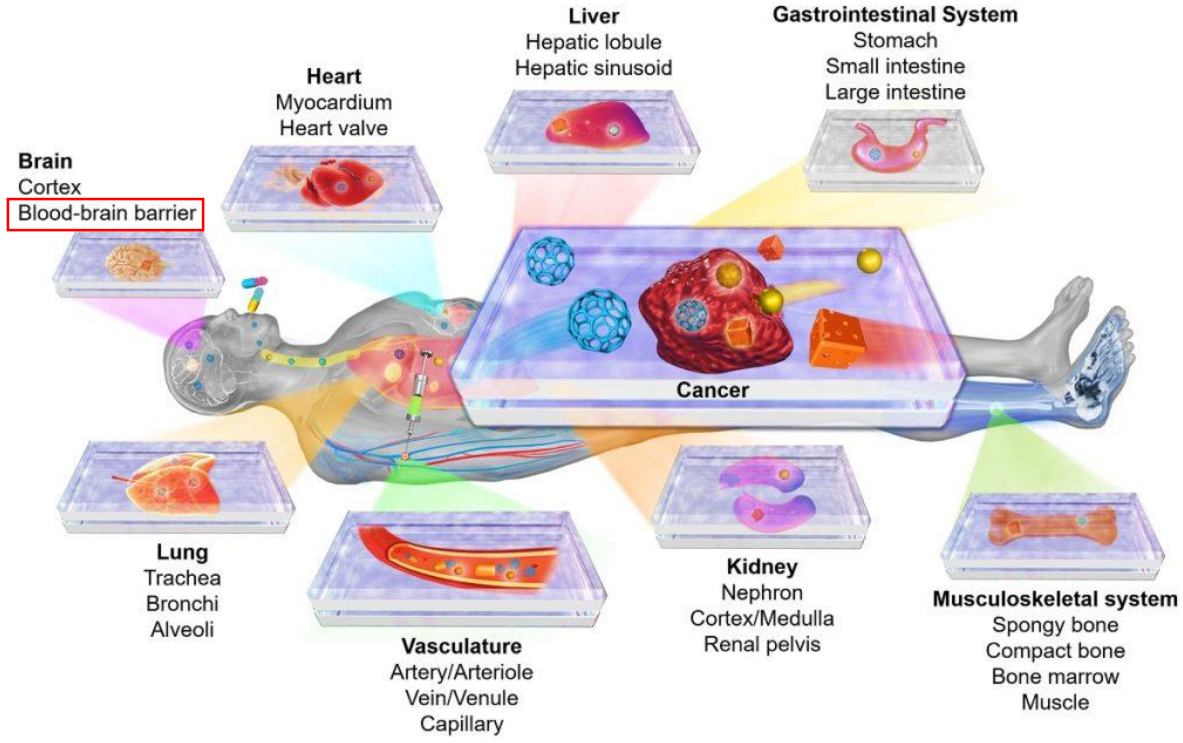


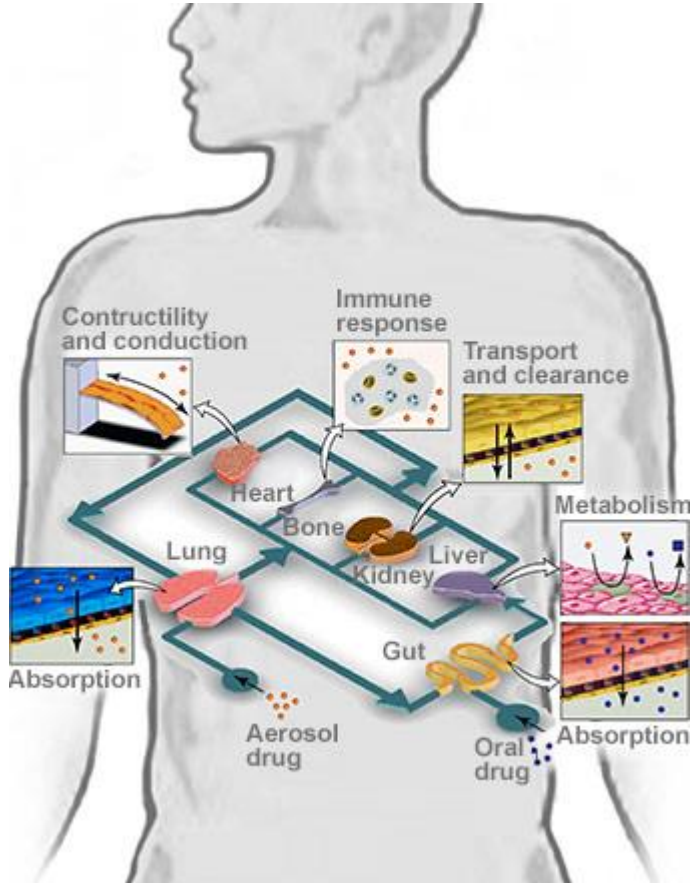
Donald E. Ingber, M.D., Ph.D.

Dongeun (Dan) Huh, Ph.D.

Huh, D. *et al.* Reconstituting organ-level lung functions on a chip. *Science (80-.).* **328**, 1662–1668 (2010).

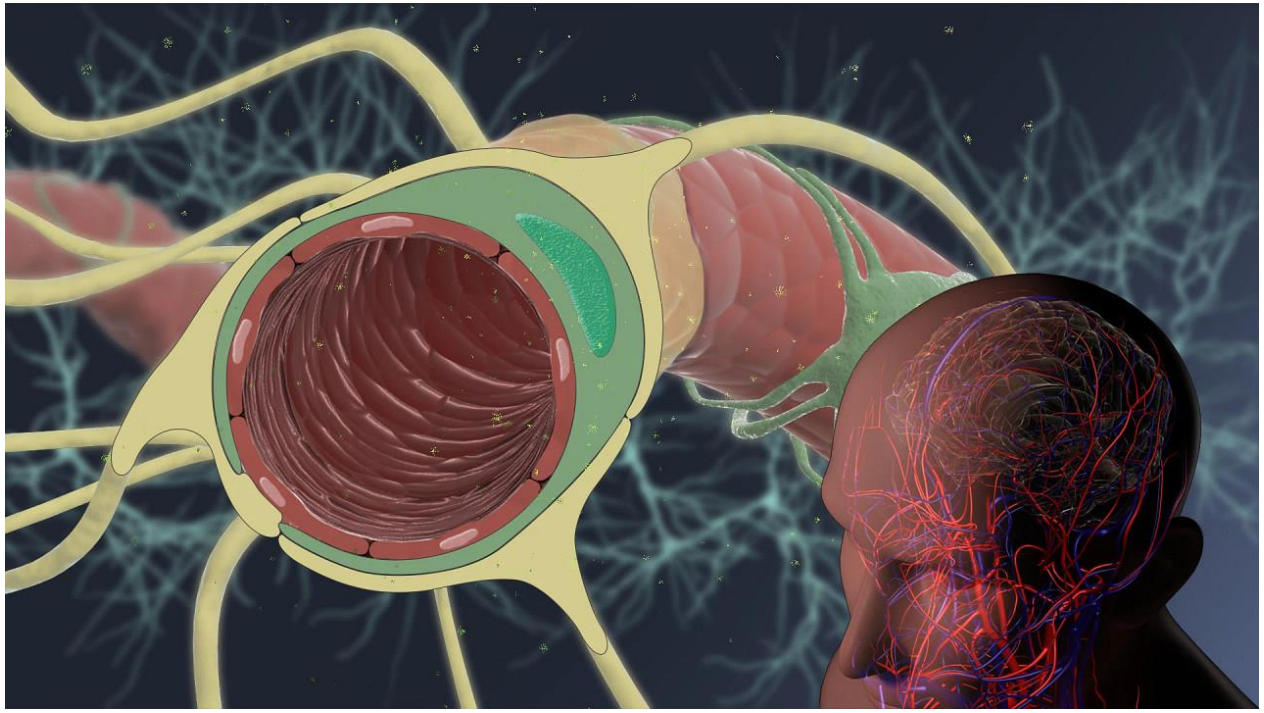
Organs-on-a-chip for different porposes



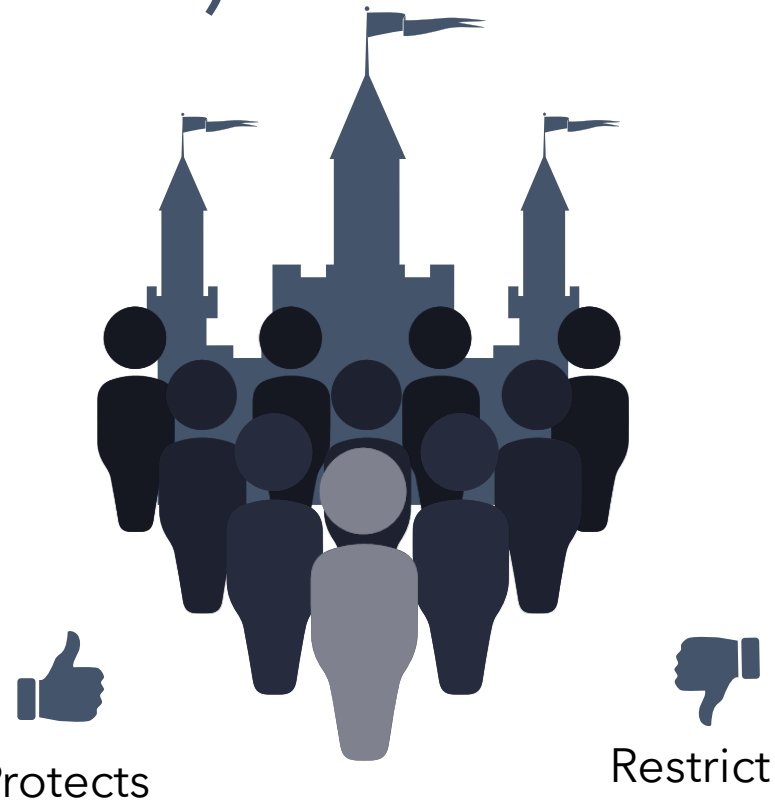


Conceptual schematic of a human-on-a-chip, a whole-body biomimetic device. Image: MIT

The Blood-Brain Barrier (BBB)



The human brain contains about 100 billion capillaries stretching about 650 kilometres (400 miles).



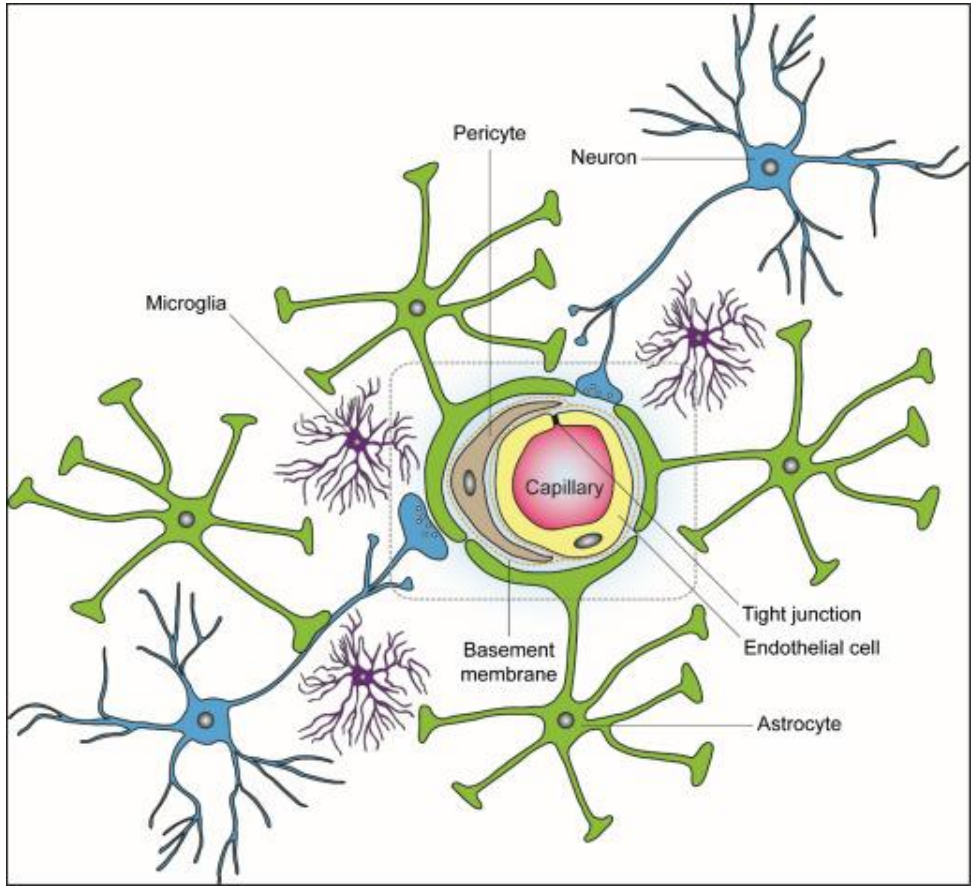
Protects

Allows only what is important for the CNS to pass through, protects from toxic or harmful agents .

Restrict

Limits the access of drugs that need to pass through the BBB to treat the CNS.

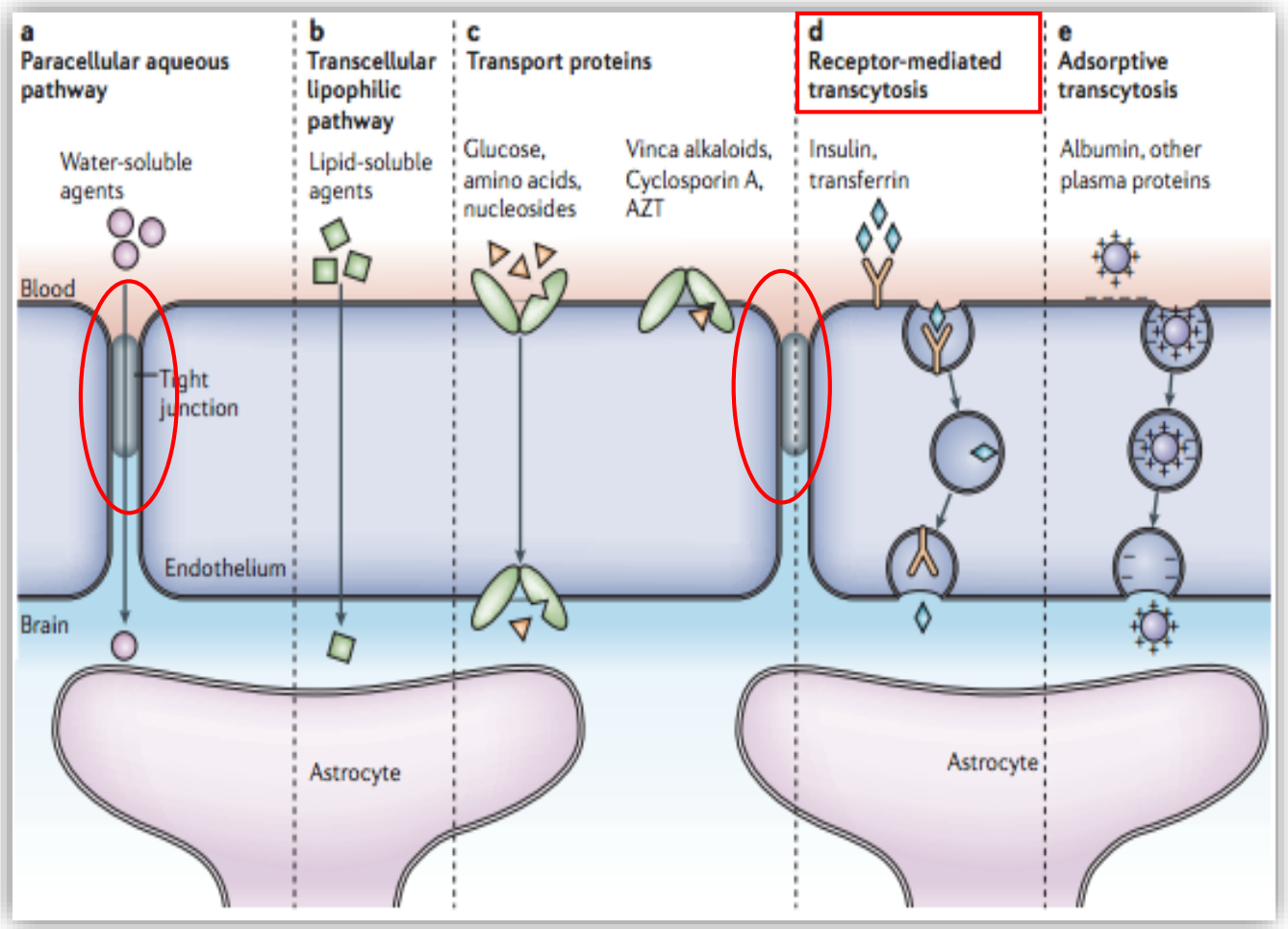
BBB composition



- Capilary lumen
- Endothelial cell
- Tigh junction
- Pericyte
- Basement membrane
- Astrocyte
- Neuron
- Microglia

Chin, E. & Goh, E. *Blood–brain barrier on a chip*. *Methods in Cell Biology* vol. 146 (Elsevier Inc., 2018).

BBB transport pathways



Abbott et al., Nature Reviews Neuroscience, 2006

Challenges in BBB studies

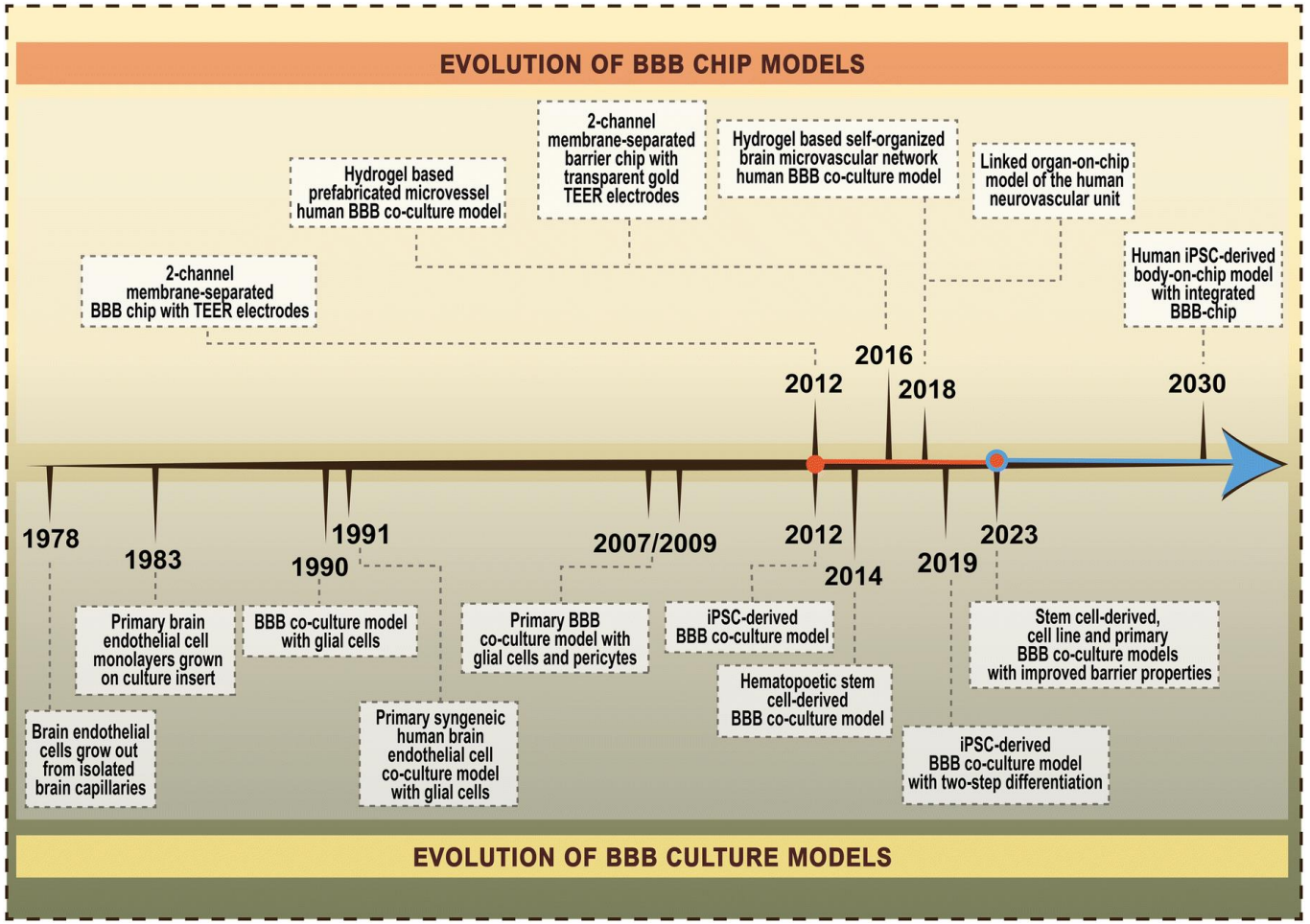
< 1% of small molecule across BBB

< 0,1% of big molecule across BBB

TEER: Transendothelial Electrical Resistance

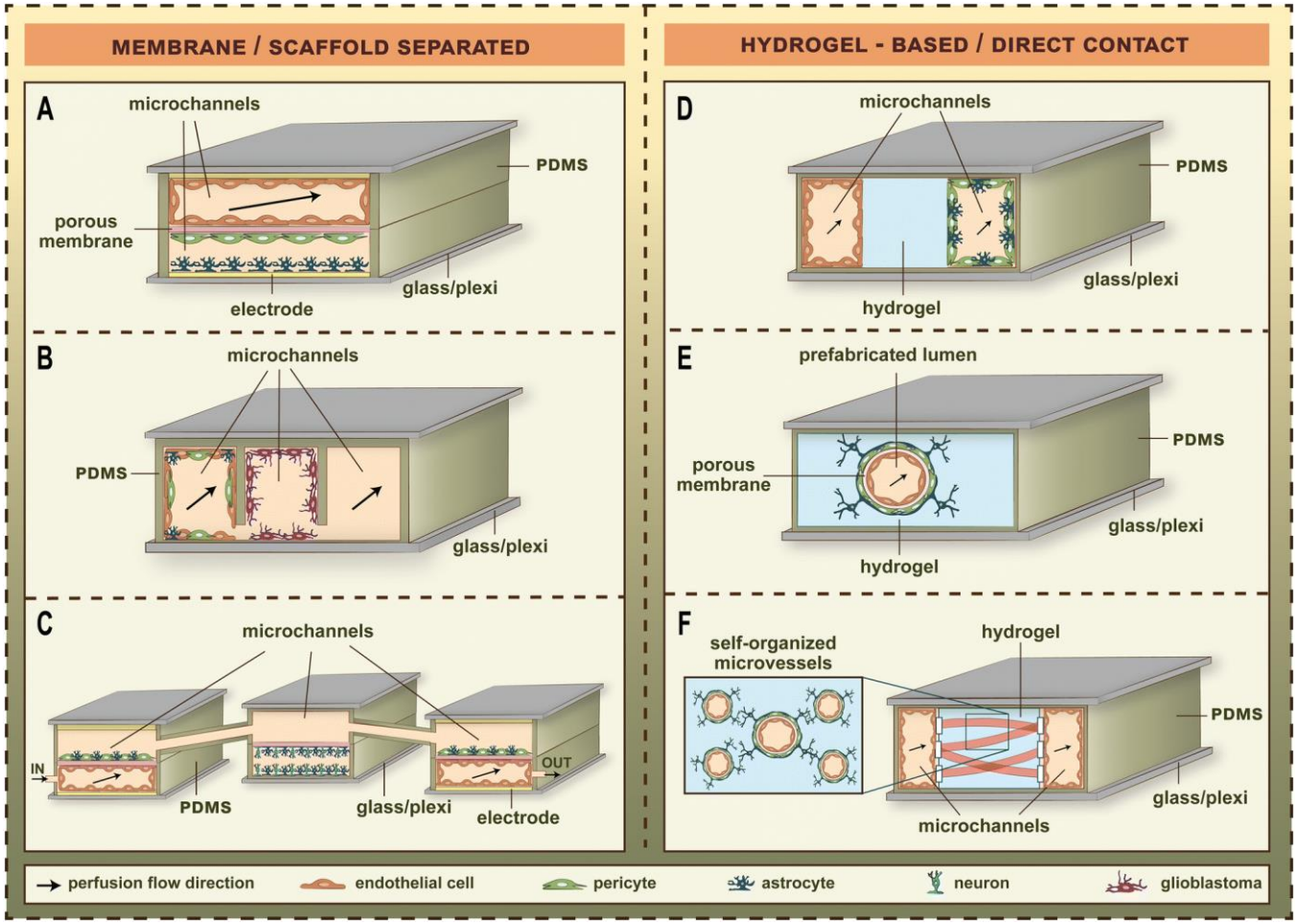
Abbott et al., Nature Reviews Neuroscience, 2006

Time-line of BBB models



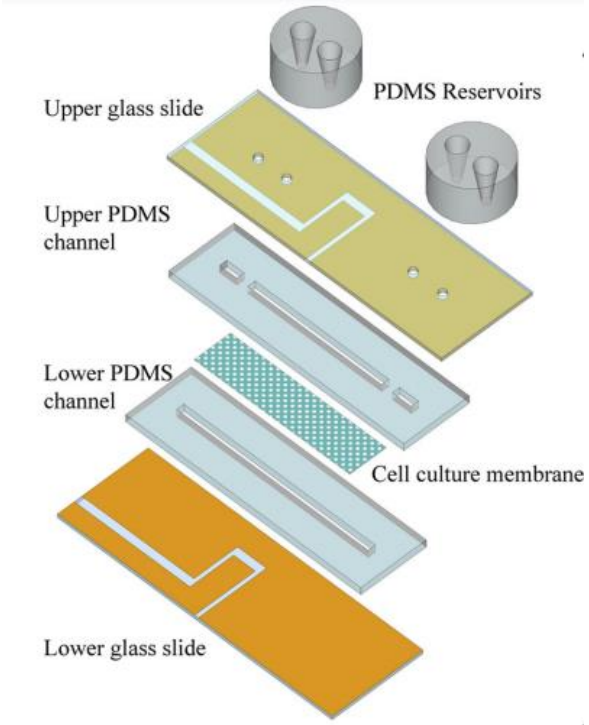
Deli, M. A. *et al.* Lab-on-a-chip models of the blood-brain barrier: evolution, problems, perspectives. *Lab Chip* **24**, 1030–1063 (2024).

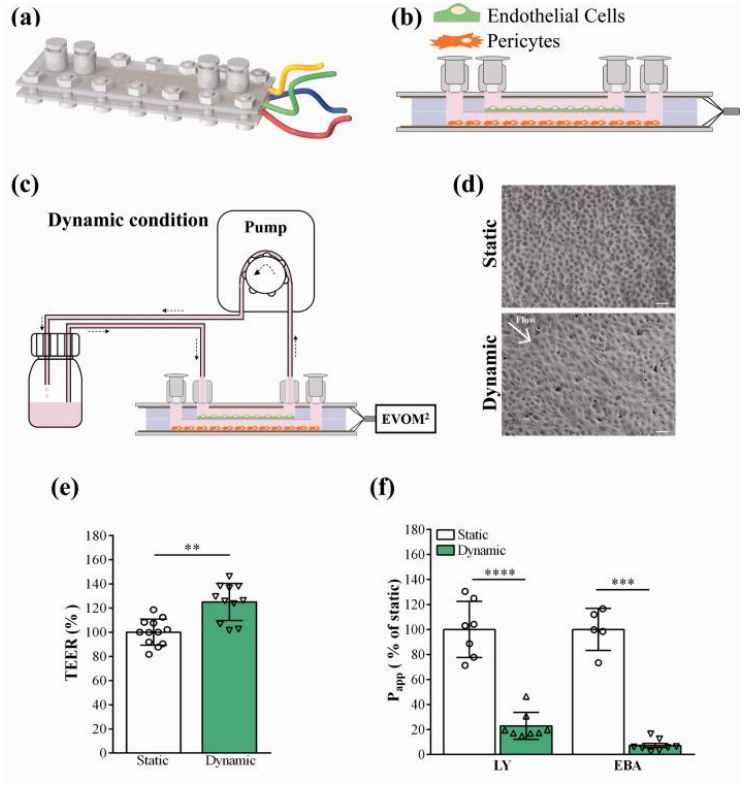
Types of BBB chip models



Deli, M. A. *et al.* Lab-on-a-chip models of the blood-brain barrier: evolution, problems, perspectives. *Lab Chip* **24**, 1030–1063 (2024).

Membrane separated

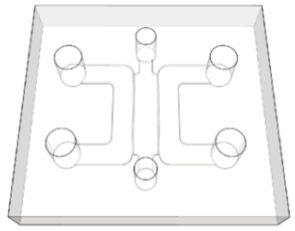




Schematic drawing of the flow circuit and biochip setups with two types of cells.

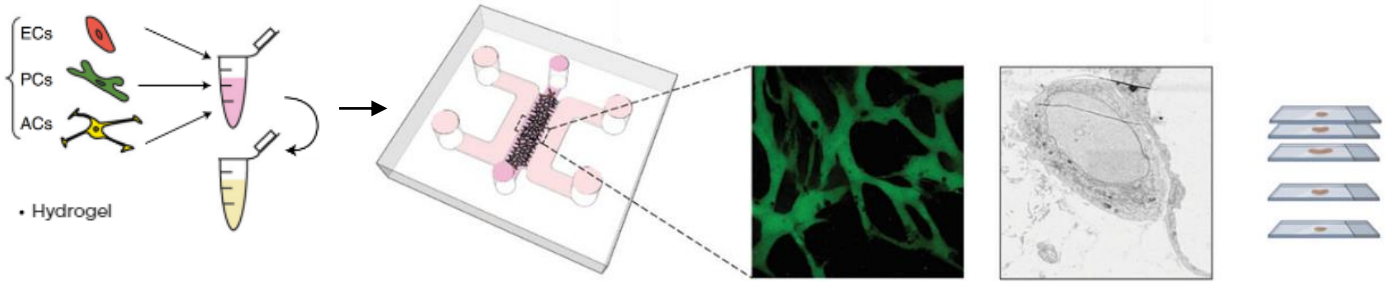
Kincses A, Santa-Maria AR, Walter FR, Dér L, Horányi N, Lipka DV, Valkai S, Deli MA, Dér A. A chip device to determine surface charge properties of confluent cell monolayers by measuring streaming potential. Lab Chip. 2020

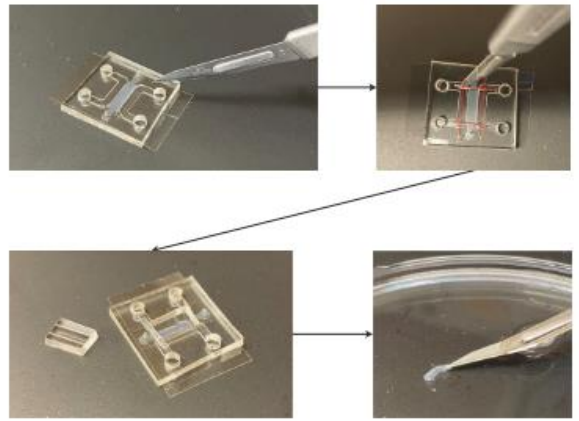
Hydrogel-based/ direct contact

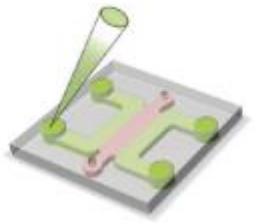


Macrodevice with
3D printed wafer

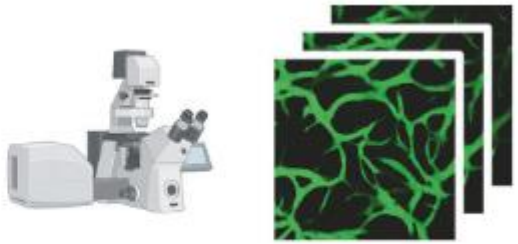
Device fabrication and
PDMS bonding (Steps 1–2)



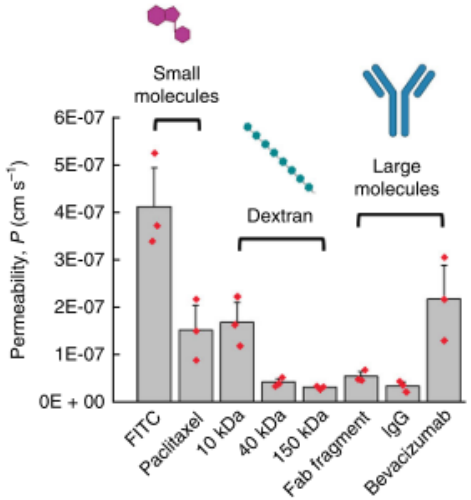




Device perfusion (Steps 21–24)



Confocal image acquisition (Steps 25–29)



Hajal, C. *et al. Engineered human blood–brain barrier microfluidic model for vascular permeability analyses*. *Nature Protocols* vol. 17 (Springer US, 2022).

BBB cells in chips - challenges

Immortalized brain endotelial cell lines

nonphysiological characteristics, weak barrier properties

Primary brain endotelial cells

species diferences, hard to source

Stem cell derived brain

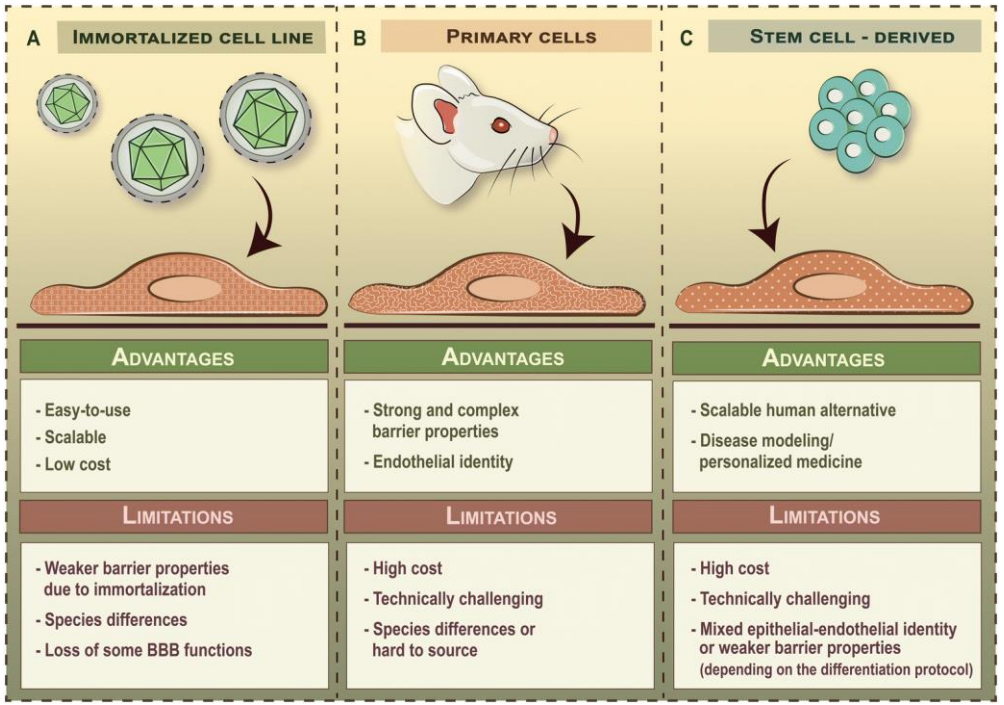
tight barriers and mixed neuroepithelial and endotelial identity

Enfothelial idenditty and low tighsness

Lack of guidelines

For barrier properties in BBB-on-a-chip models

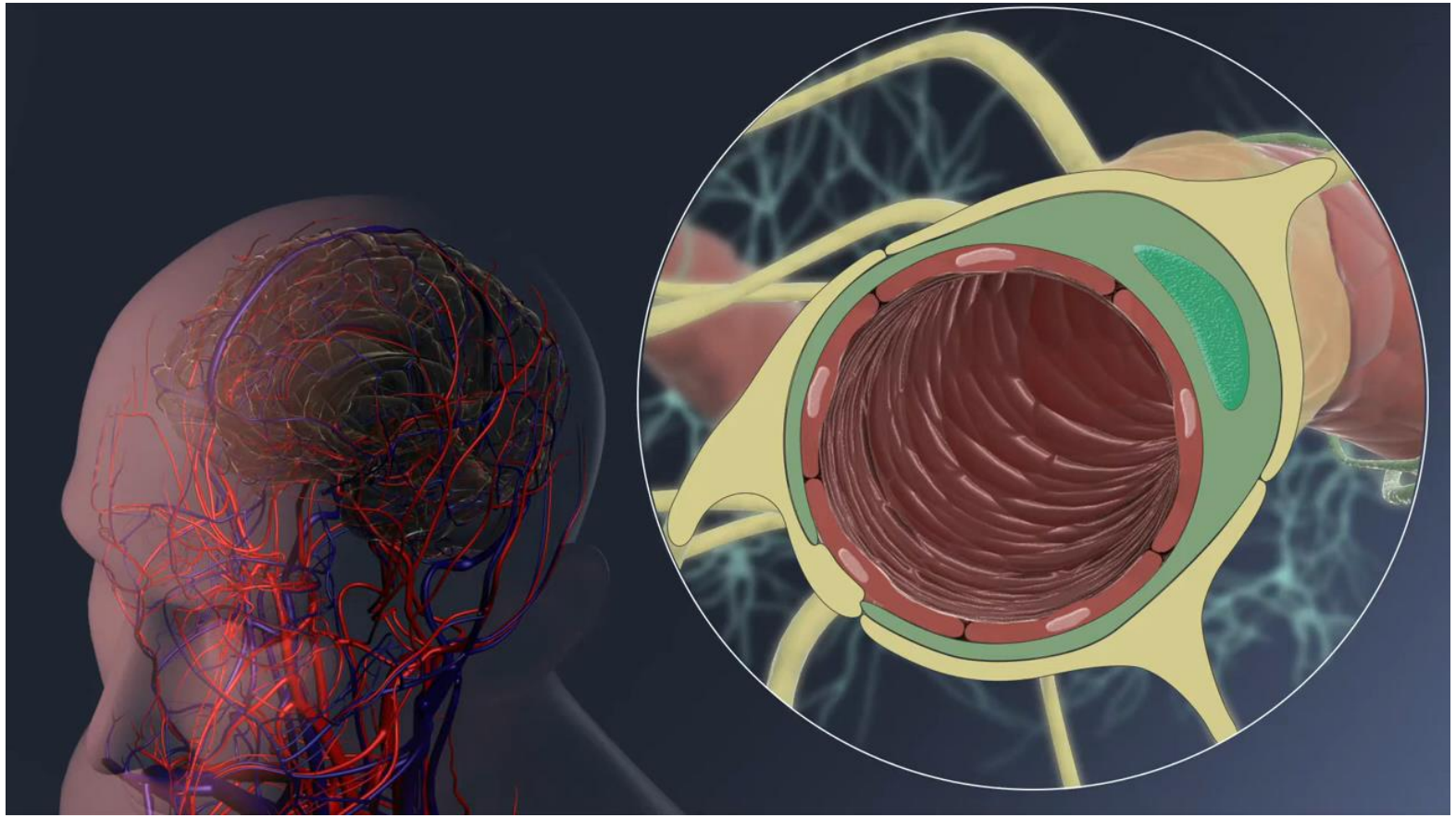
Hard to comparate and benchmark results from diferente laboratories



Deli, M. A. *et al.* Lab-on-a-chip models of the blood-brain barrier: evolution, problems, perspectives. *Lab Chip* **24**, 1030–1063 (2024).

“Brain Targeting Program”

- Strategies to get drugs to the brain more effectively.



Wyss Institute for Biologically Inspired Engineering. *Brain Targeting Program* https://wyss.harvard.edu/collaboration/brain-targeting-program/.

“Brain Targeting Program”

Wyss Institute for Biologically Inspired Engineering. *Brain Targeting Program* https://wyss.harvard.edu/collaboration/brain-targeting-program/.

Thank you!

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