Biomimicry of blood-brain barrier models to unravel the pathogenesis of neurotropic virus infection

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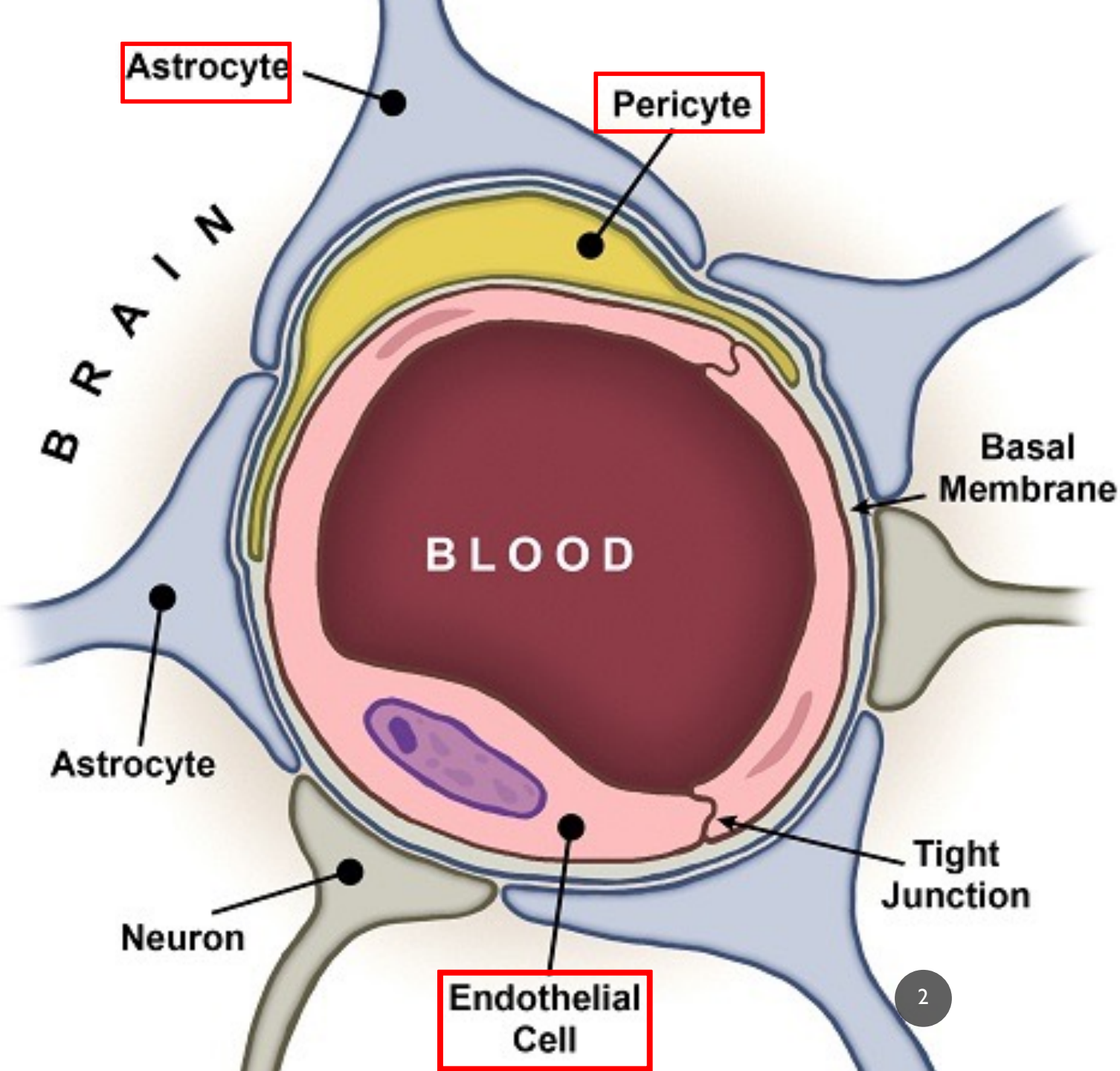
The Blood-Brain Barrier (BBB)

- Tightly regulated barrier
- Exchange of crucial ions and molecules between blood vessel and brain
- 3 major cell types framing the BBB
  1. Endothelial Cells – express tight junctions to form physical barrier
  2. Pericytes – structural support of endothelial cells
  3. Astrocytes – structural support, maintenance of neuronal functions



Physiological Role of Blood-Brain Barrier

1. Maintain homeostasis in the brain
   - Tightly regulated concentrations of ions (i.e Ca^{2+}, K^{+}, Na^{+} for neuronal firing)
   - Regulate crosstalk of multiple signals
2. Uptake of essential nutrients
   - Metabolic activities (i.e glucose, vitamins, insulin)
3. Protection from pathogens (Viruses, Bacteria, Parasites)

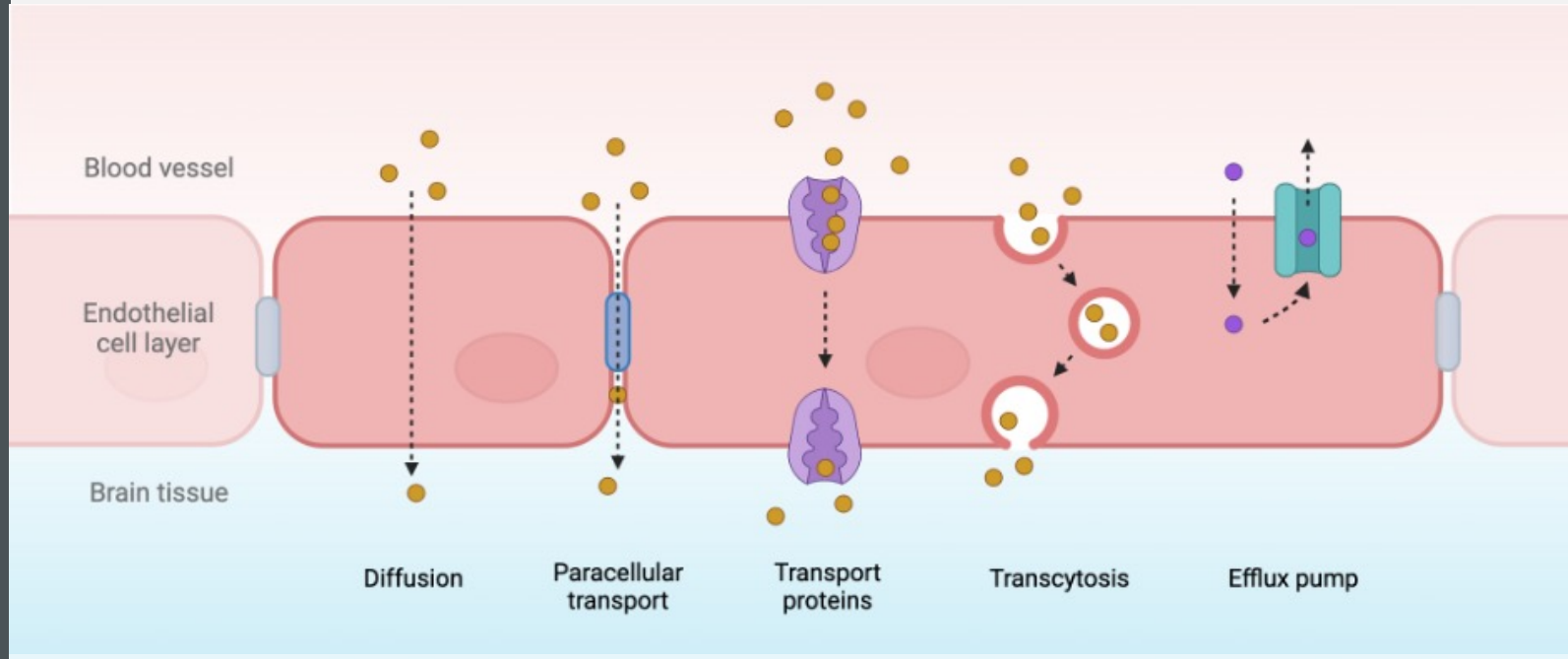
Regulation of Blood-Brain Barrier

Transport of micromolecules – lipid soluble, small molecules

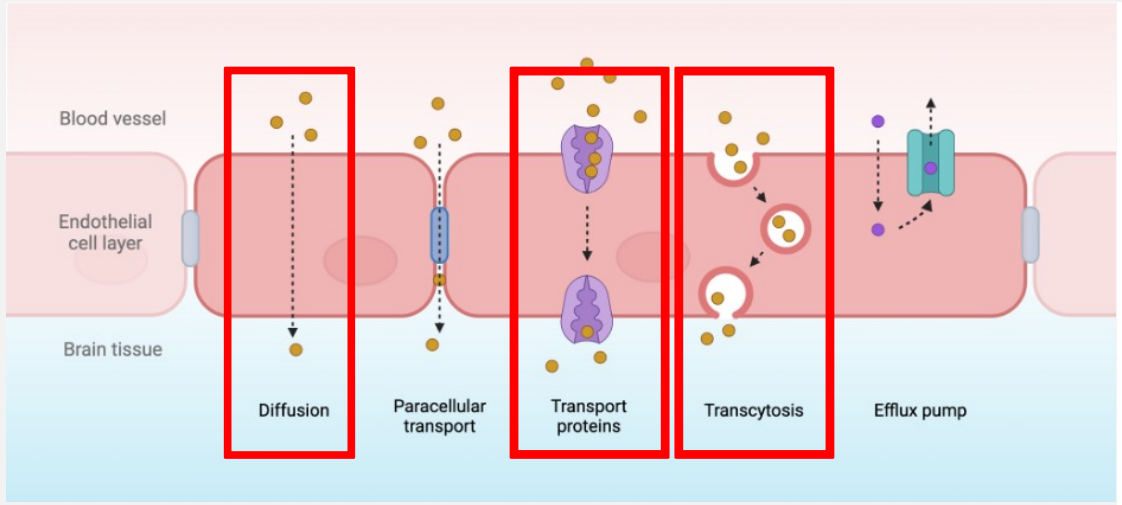
1. Transcellular transport (Diffusion)
2. Paracellular transport

Transport of macromolecules- glucose, amino acids, metabolites, insulin, etc.

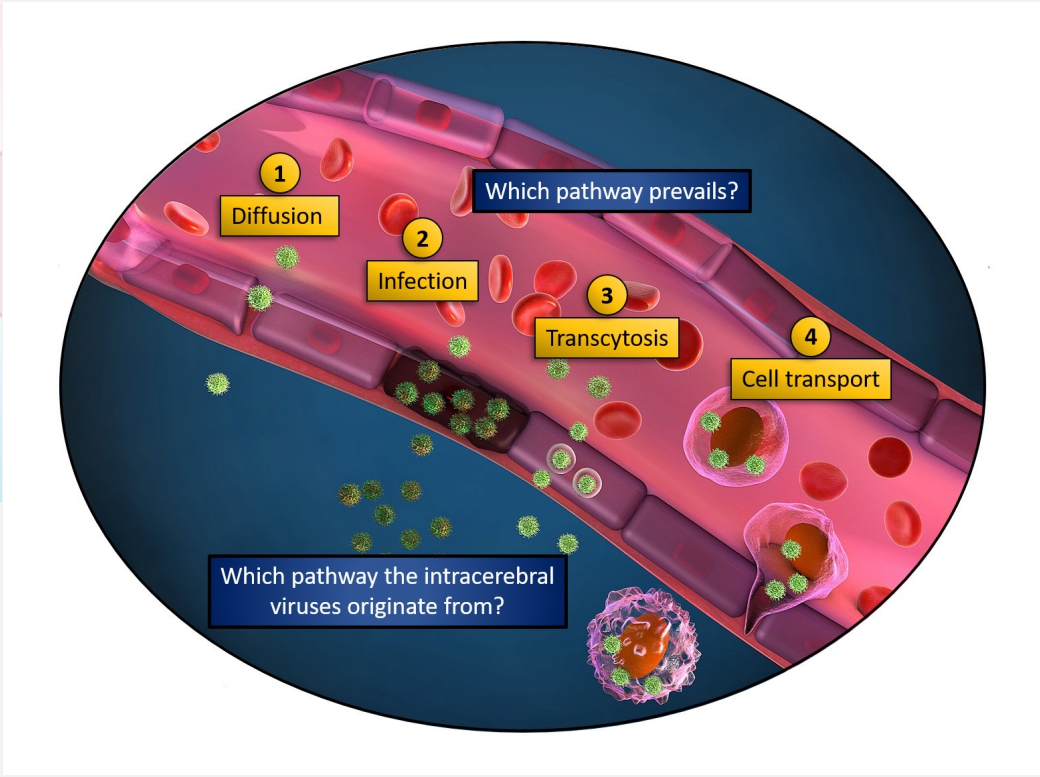
1. Transport proteins
2. Transcytosis
3. Efflux pumps



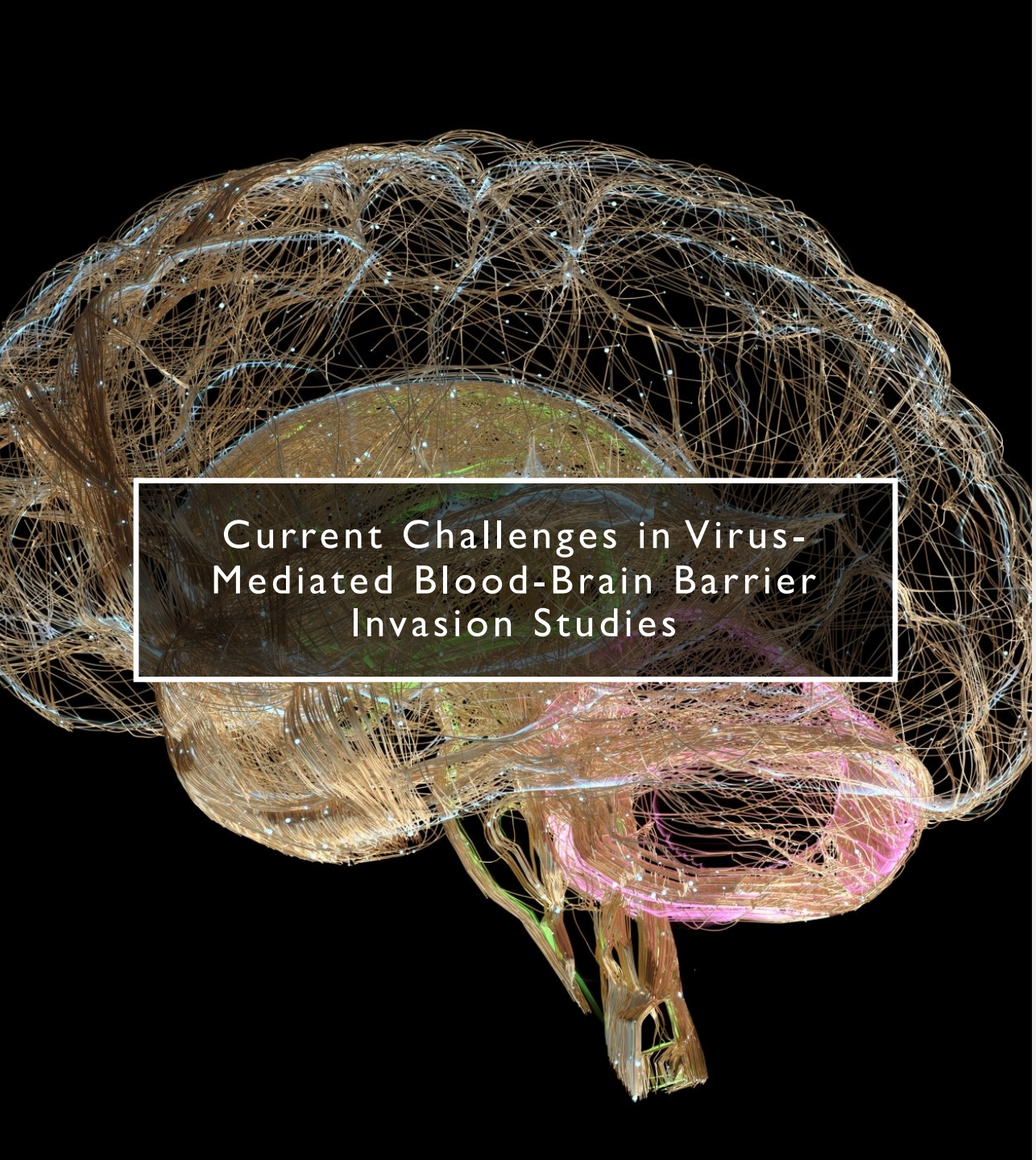
Virus-Mediated Blood Brain Barrier Disruption



1. Passive diffusion
2. Endothelial cell infection
3. Virus transcytosis
4. Cell-associated virus transport (Trojan-Horse mechanism)



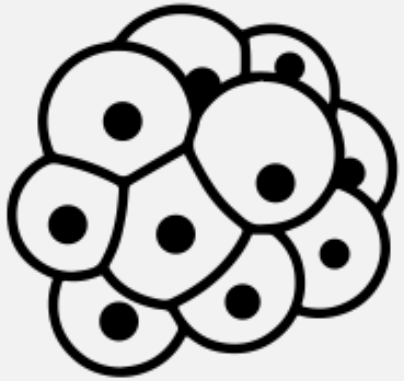
Interplay of mechanisms?
Sequential events?



Current Challenges in Virus-Mediated Blood-Brain Barrier Invasion Studies

1. Studying multiple pathways simultaneously
2. Model human neuropathology
3. Mimicking immunological mechanism and vascular structure of BBB
4. Lack of screening platforms for potential therapeutic candidates

Emerging Blood Brain Barrier Models to Study Neuro-Invasion of Viruses



2D iPSC-derived blood-brain barrier model

Microfluidic model

Brain Microvascular Endothelial Cells (iBMECs) from human PSC cells

IMR & DF19: induced pluripotent stem cells

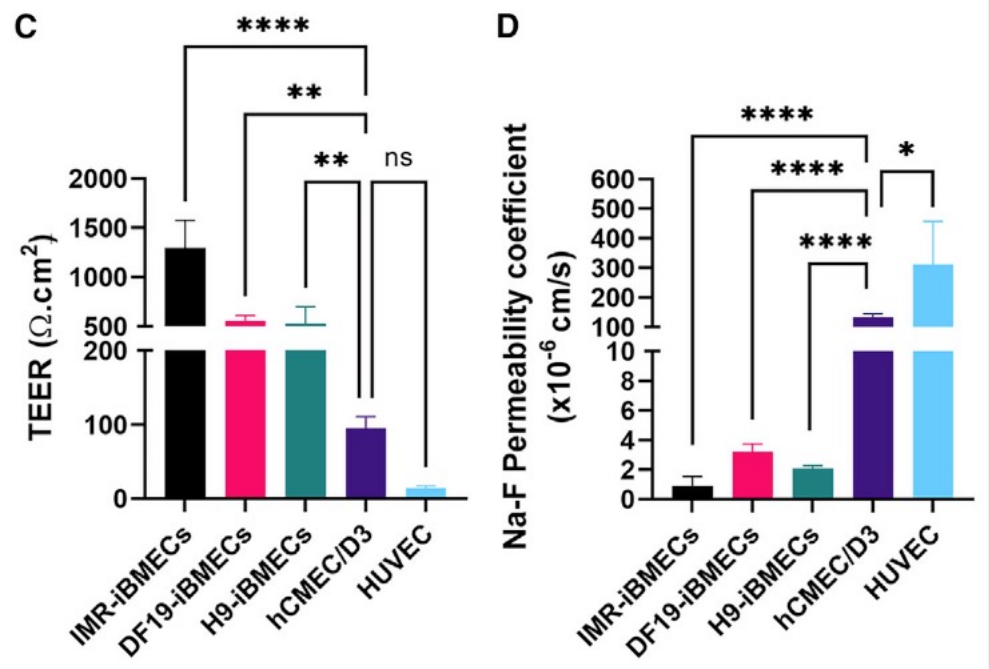
H9: embryonic stem cell

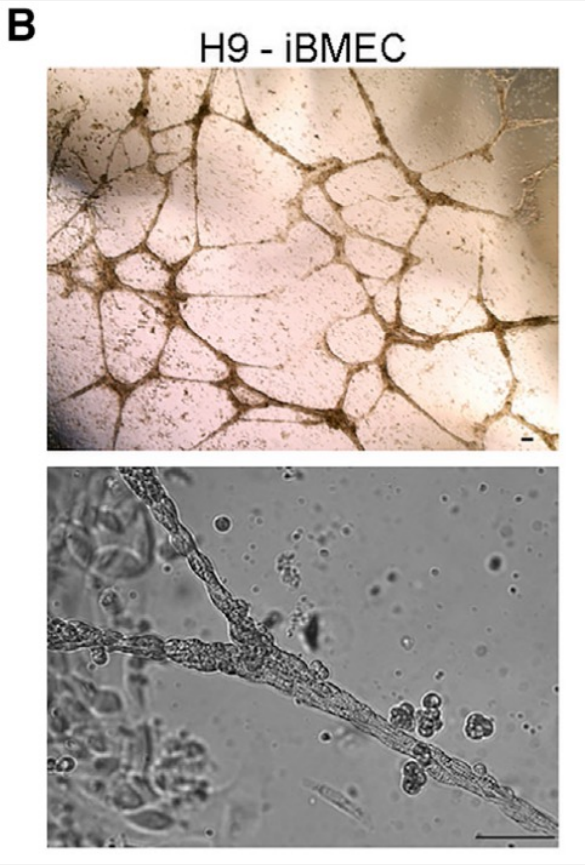
hCMEC: human cardiac microvascular endothelial cells

HUVEC: human umbilical vein endothelial cells

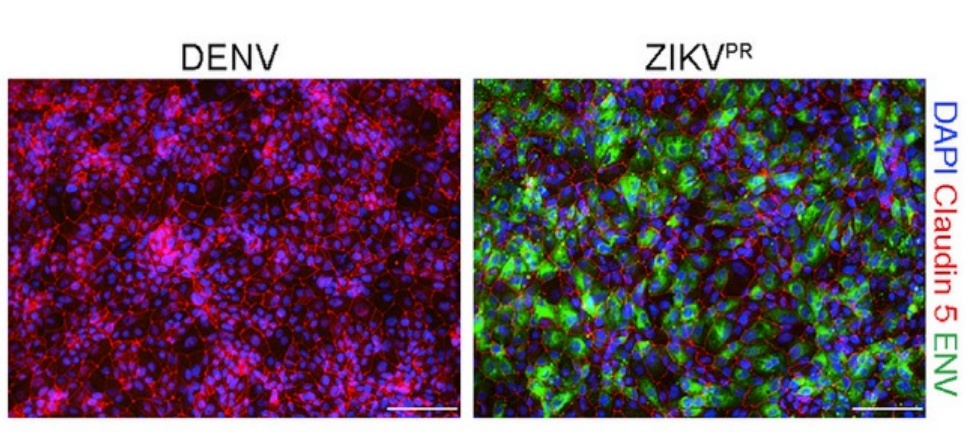
Endothelium Integrity

Endothelium Permeability



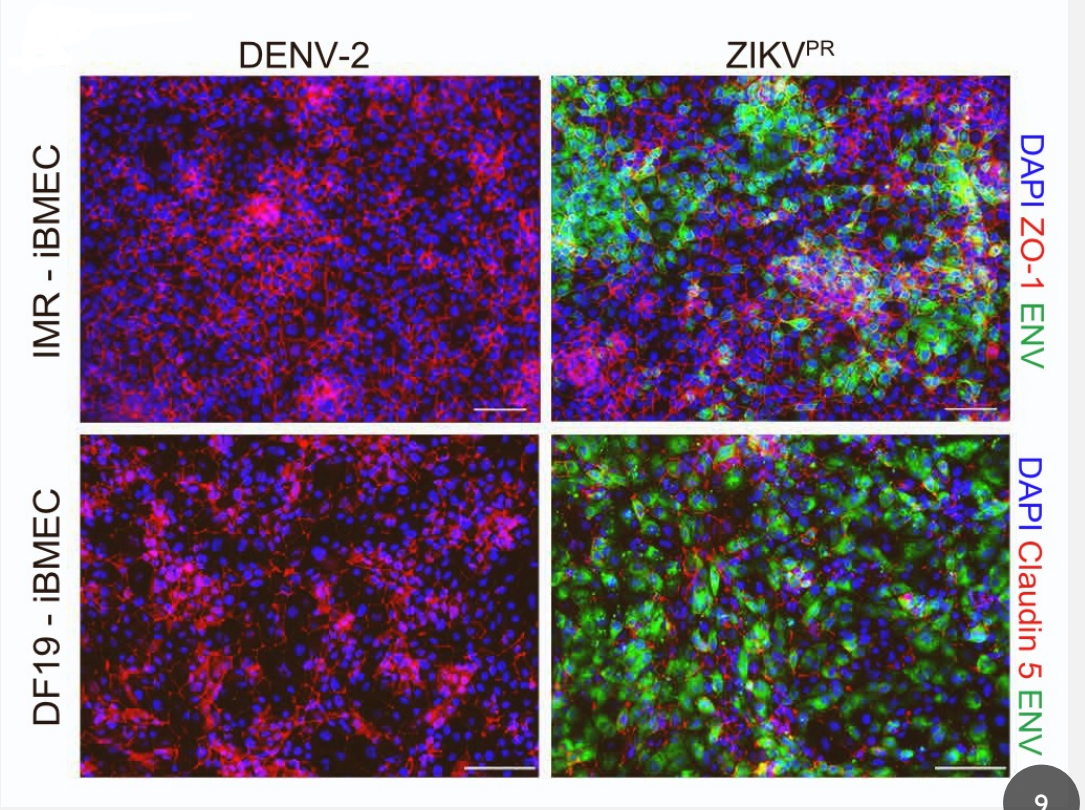


2D Infection Model of iBMEC supports infection of neurotropic virus



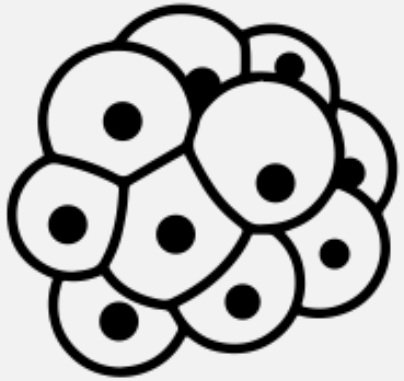
Claudin 5: marker of tight junction

ENV: marker of virus envelope protein



Cheng et al., Cell Reports, 2022, doi.org/10.1016/j.celrep.2022.110885

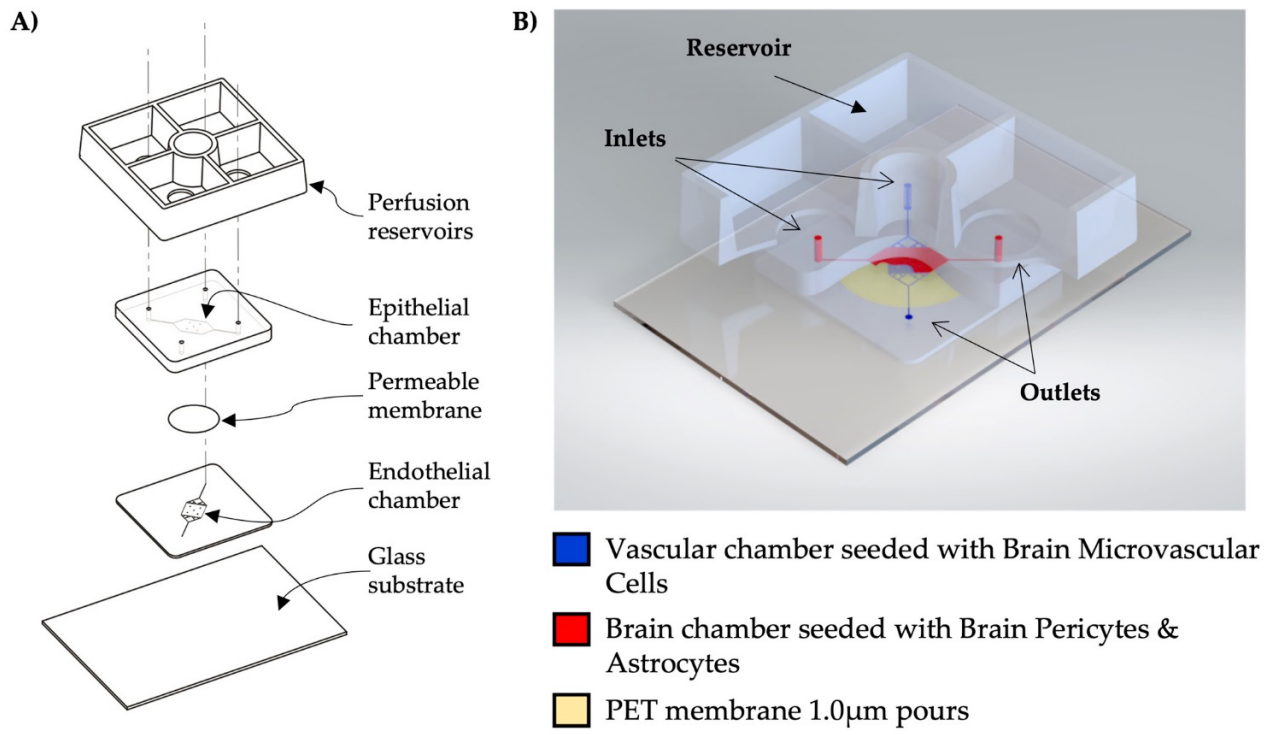
Emerging Blood Brain Barrier Models to Study Neuro-Invasion of Viruses

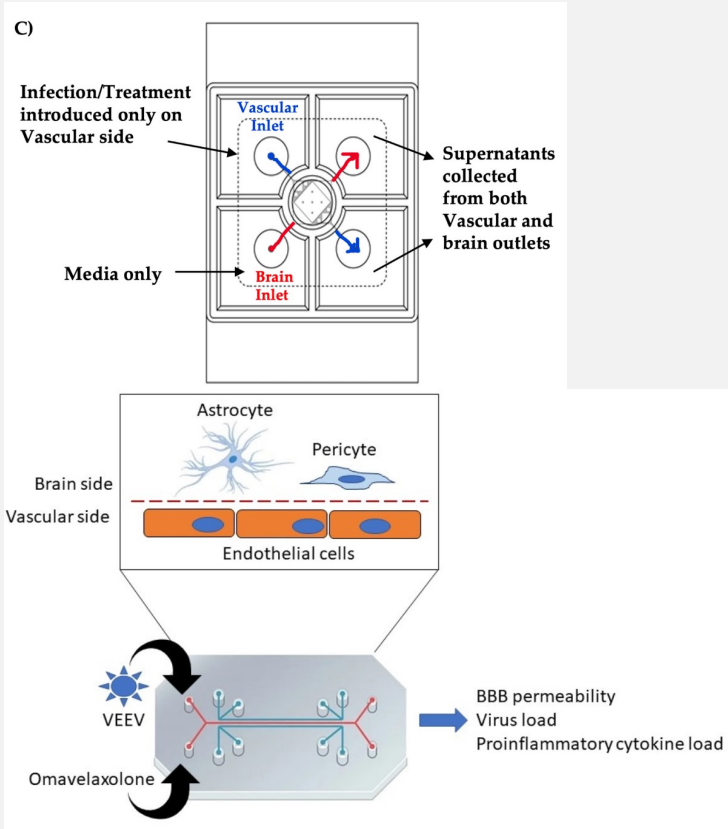


2D iPSC-derived blood-brain barrier model

Microfluidic model

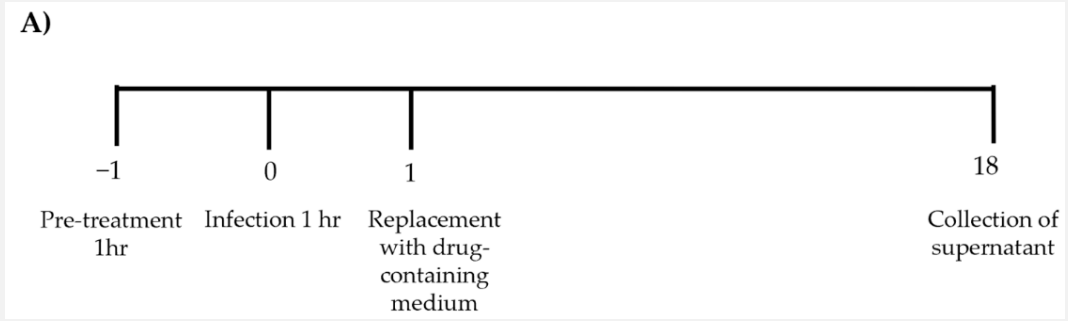
Major components of the neurovascular unit (NVU)

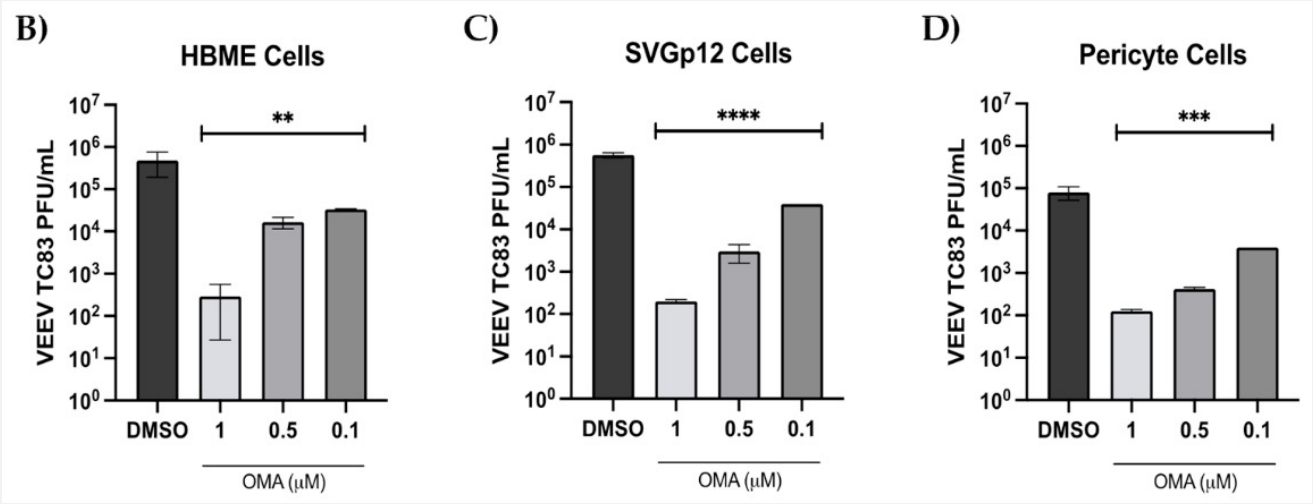




Boghdeh et al,Viruses, 2022

Treatment with Omaveloxolone (OMA) decrease viral load in BBB cells





HBME: Human brain microvascular endothelial cells
SVGp12: human fetal astrocytes cells

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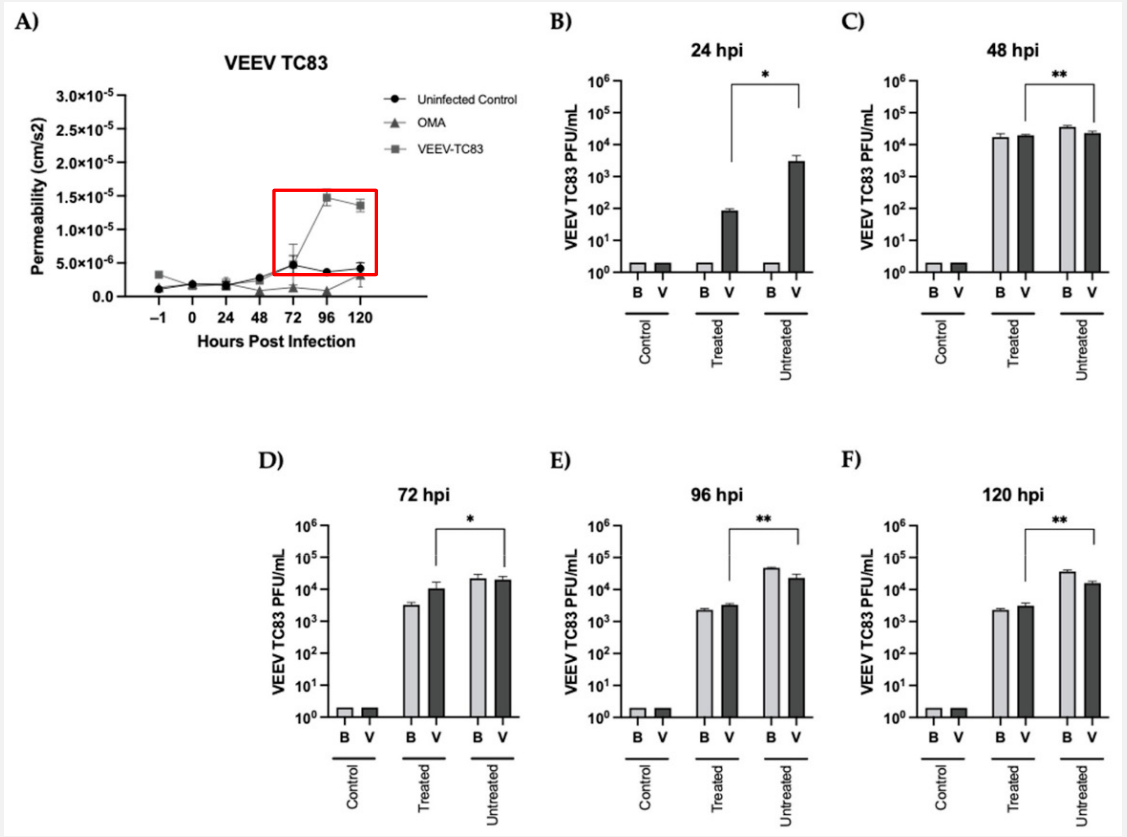
BBB integrity preserved and viral load decreased after treatment of OMA



B: Brain
V: Vascular

Boghdeh et al, Viruses, 2022

How Well Do Emerging Models Recapitulate the Blood Brain Barrier?

	Advantage	Disadvantage
2D model	• Simple culturing in transwell • Mimic tight junctions • Successful infection of viruses to model entry	• Lack vasculature and multicellular environment
Microfluidic model	• Simultaneous observation • Integration of vascular fluid flow • Aid in drug-screening	• Complex establishment • Further validation and optimization needed

Conclusion: Future direction and takeaways

1. Emerging viruses are expected to increase due to environmental factors
    - i.e. SARS-CoV-2
2. Most problematic infectious agents are the RNA viruses that have caused multiple outbreaks and public health concerns.
3. Drug candidate screening to address the limited treatment of neurotropic viruses

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