UK Health Security Agency

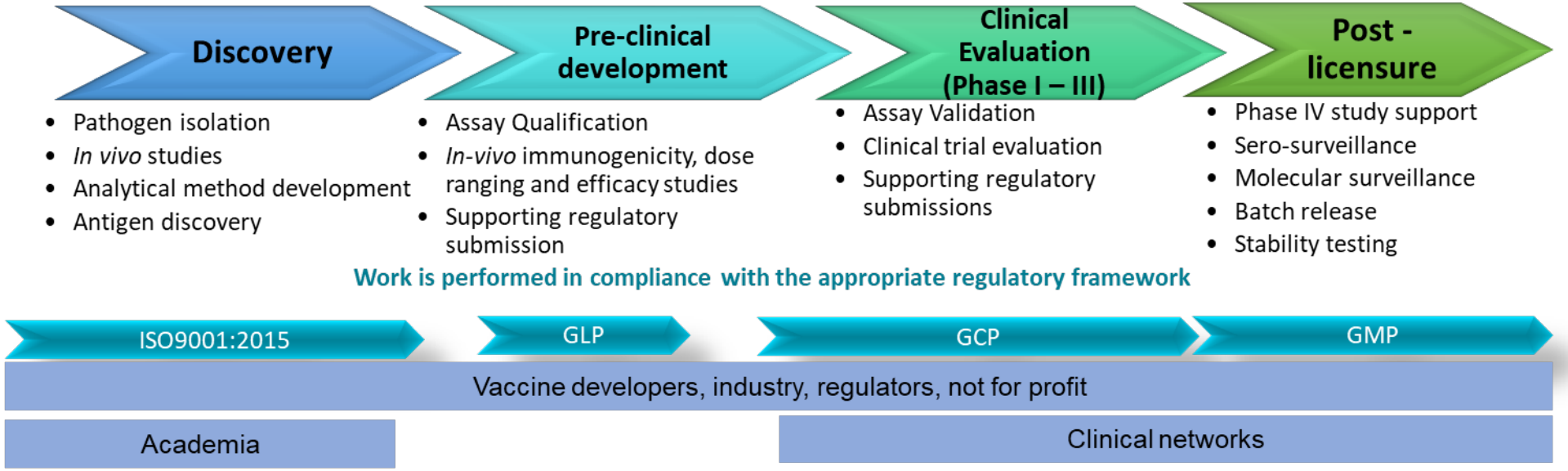
Lung on a chip to test viral infections and medicines efficacy

Kevin Bewley – Scientific Lead, Pre-Clinical Evaluation

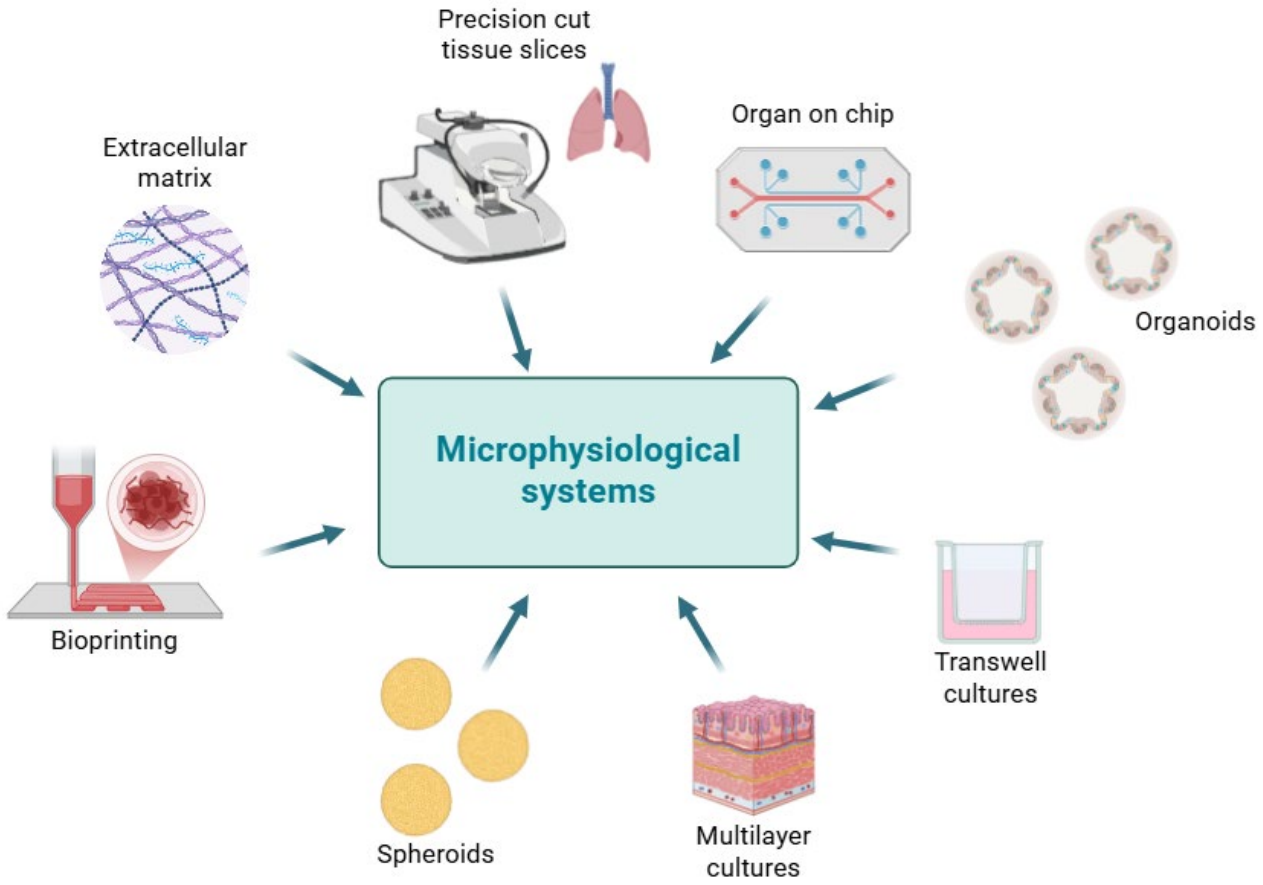
UK Health Security Agency

Vaccine Development and Evaluation Centre (VDEC)

- **VDEC integrates UKHSA's laboratory capabilities** to accelerate development and implementation of vaccines and therapeutics for pandemic threats, high-consequence, and high-risk infectious diseases.
- **Provides leadership for the UK vaccine strategy**, supporting the full vaccine life cycle through laboratory-based research and collaboration across sectors.
- **Specialized in high-containment work (ACDP 3 & 4)** with bacteria and viruses, offering unique in-vivo and in-vitro capabilities for countermeasure development.
- **Expert in preclinical and clinical research**, including animal models, assay development, regulatory-compliant data generation, and biosecurity aligned with global standards.



Microphysiological systems (MPS)



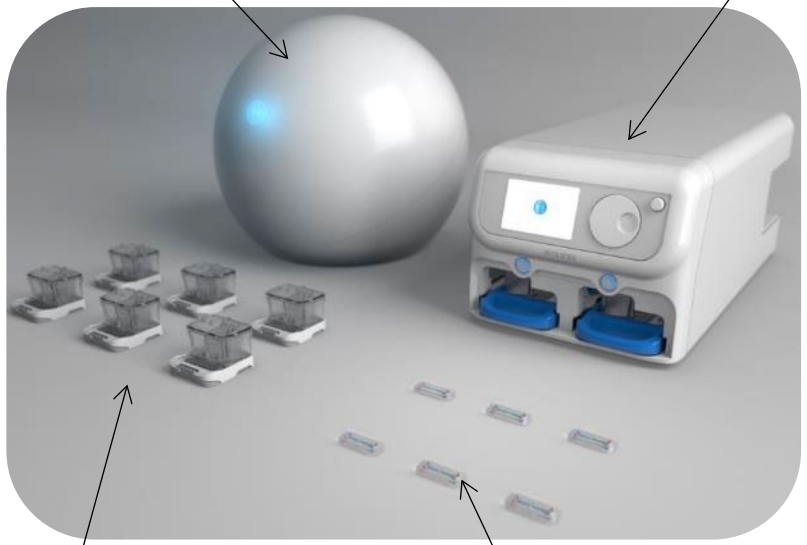
Created in Biorender
Adapted from: Pamies *et al* (2024) https://doi.org/10.1016/j.stemcr.2024.03.009.

- MPS recreate the structure and function of organs in a controlled *in vitro* setting
- Part of the global regulatory movement to reduce animal testing:
  - **EMA** – created innovation task force to support regulatory acceptance
  - **MHRA** – "data from suitably validated non-animal models to be used for evaluating new medical products and can *authorize clinical trials without animal data if justified and validated*"
  - **FDA modernisation act 3.0** – phase out animal testing for mAbs and other drugs
  - **NIH** – the Office of Research Innovation, Validation, and Application (ORIVA)
- Already being used to support clinical trials
- **We aim to use these systems to model infectious disease caused by pathogens with pandemic potential and pre-clinical evaluation of MCMs**

Emulate organ on chip

Orb –provides gas, power and stretch

Zoe – controls the conditions the chips are cultured in; **flow** & **stretch**

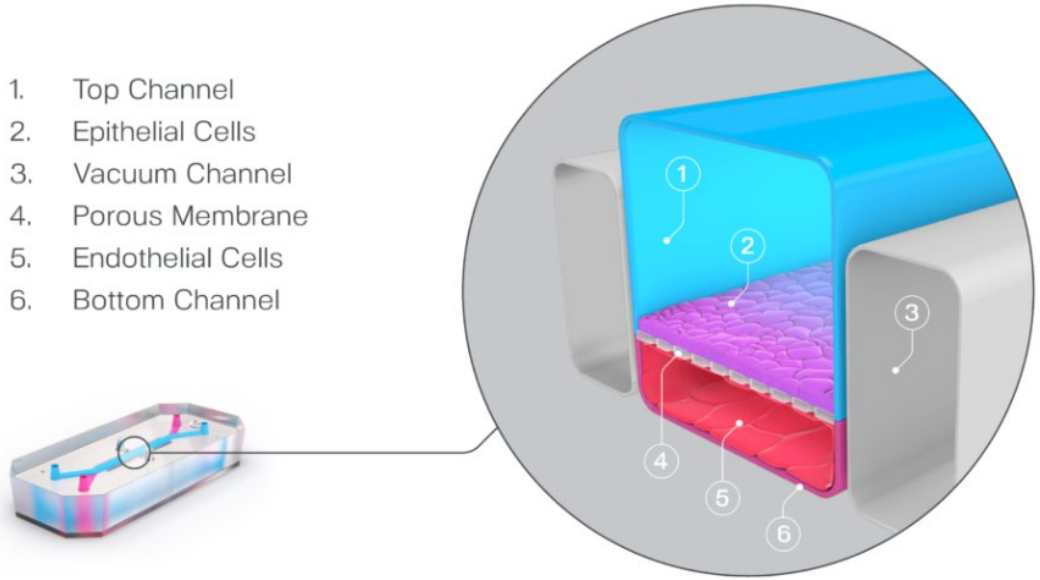


Pods – house the chips and contain media/ effluent

Chips – PDMS structure containing cellular channels separated by a porous membrane

emulate

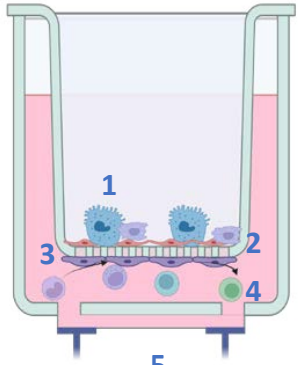
1. Top Channel
2. Epithelial Cells
3. Vacuum Channel
4. Porous Membrane
5. Endothelial Cells
6. Bottom Channel



CnBio organ on a chip

PhysioMimix Core hardware:

1. Controller
2. Docking station(s)
3. Driver(s)



1 – Epithelial cells
2 – Porous membrane
3 – Endothelial cells
4 – Immune cells
5 – Re-circulating flow

Controller –provides power and controls **flow** in the drivers

Docking station – Holds the drivers within the incubator

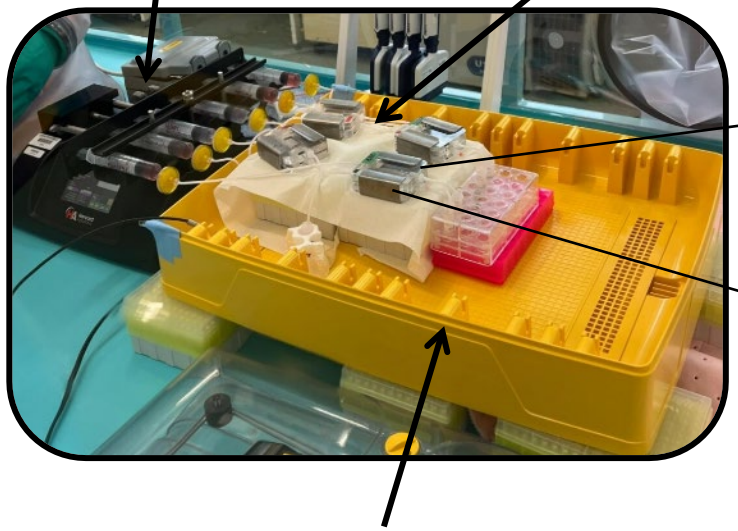
Driver – Interface between cell culture plate and docking station

University of Hull collaborative system

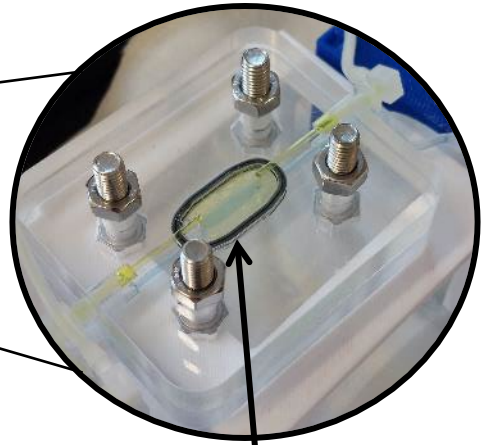
University of Hull

Syringe driver – provides media **flow** at a steady rate

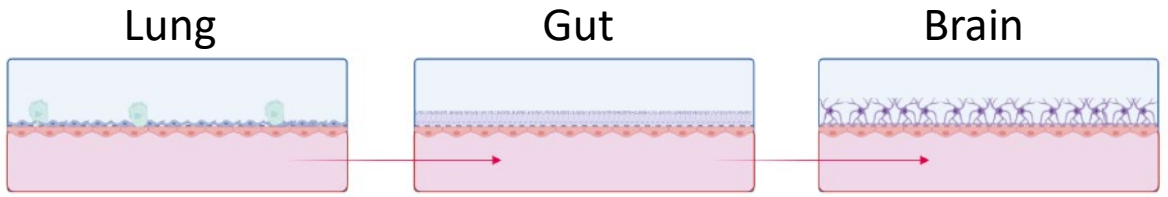
Chips connected via a common “blood” supply

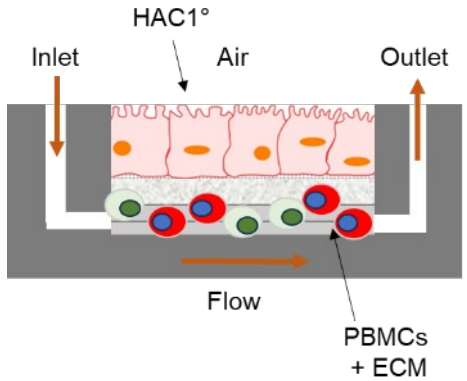


Egg box incubator – maintains temperature. This system is amenable to working in smaller spaces



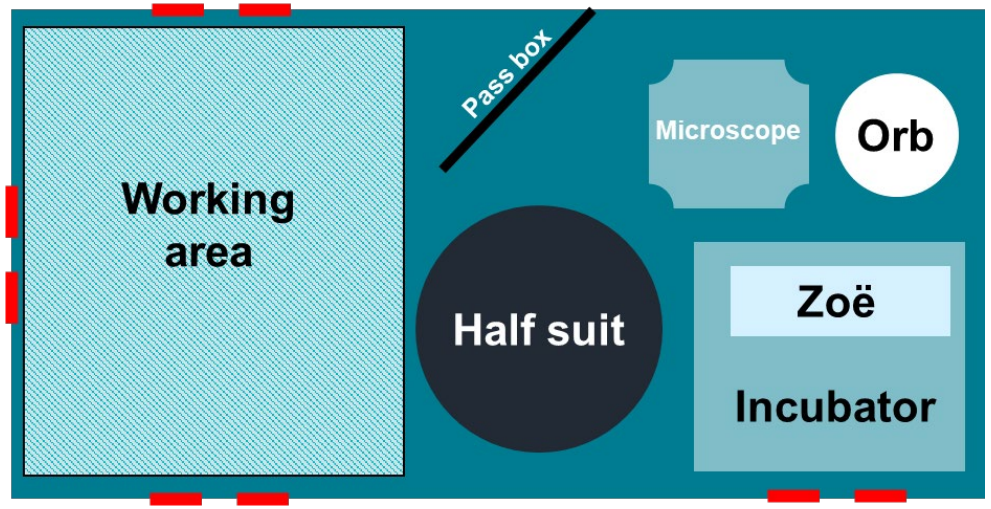
Cells seeded onto inserts assembled between two plastic supports are the only single use component





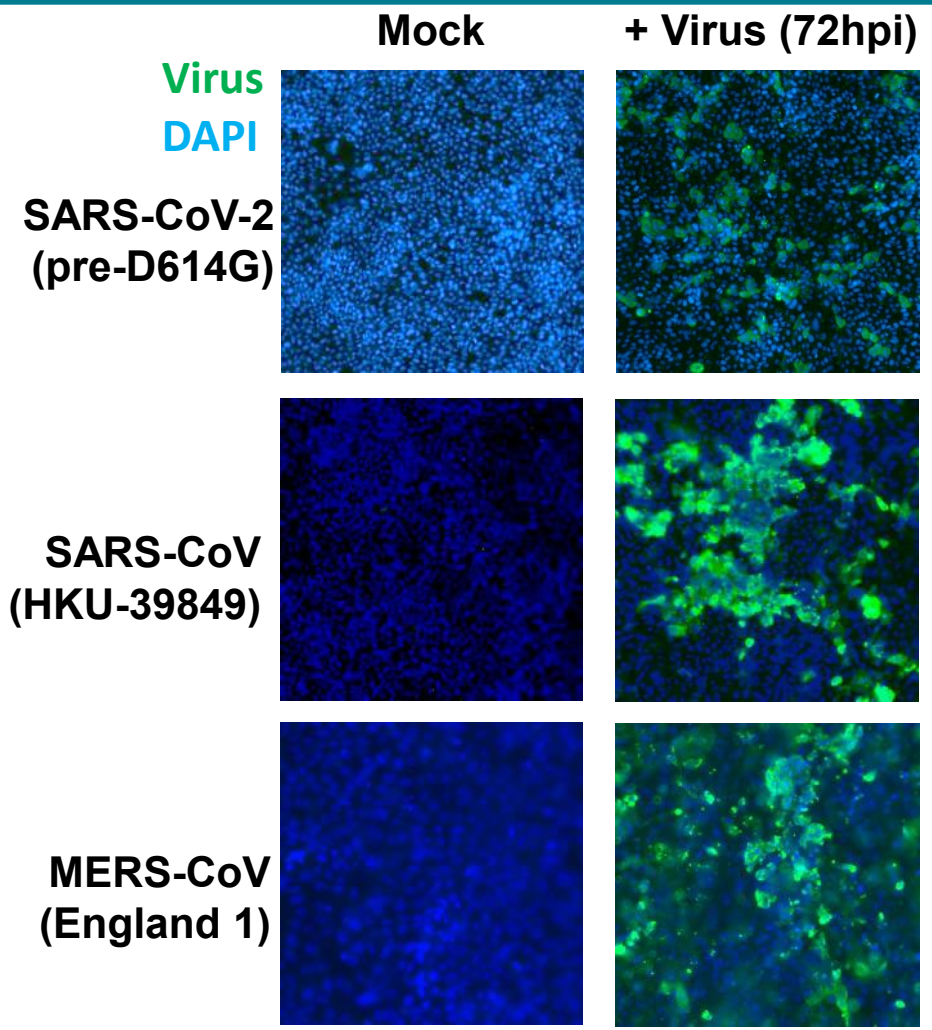
Adaptable to incorporate immune cells embedded in extracellular matrix or under flow

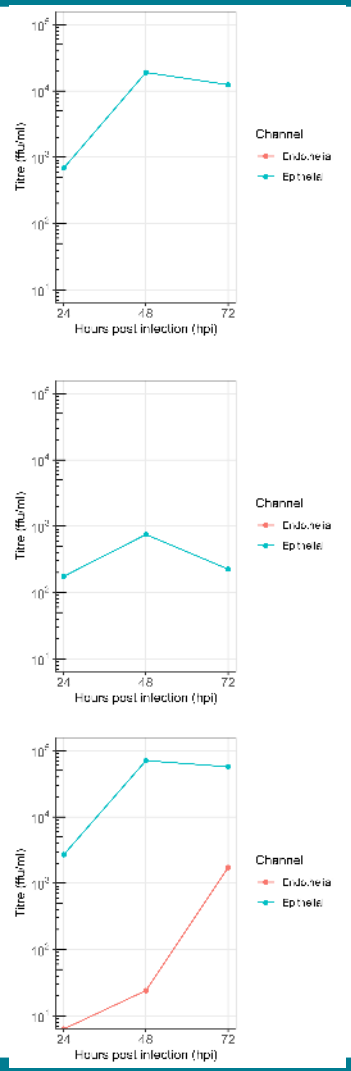
Working with organ chips at high containment



The custom-made flexible film isolator (FFI) at UKHSA Porton and aerial layout plan used for containing the Emulate MPS equipment at BSL3 (with capabilities to move to BSL4).

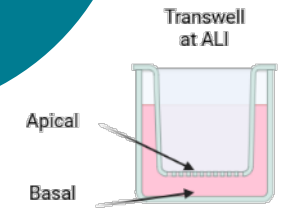
Coronavirus infection of human alveolar Emulate model



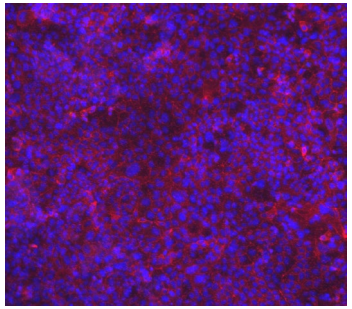


- Alveolar Emulate chips infected with SARS-CoV-2, SARS-CoV and MERS-CoV at 1 MOI then monitored for 72 hours.
- All produced a robust infection with highest levels of shedding following MERS infection
- Virus shedding into endothelial channel observed following MERS-CoV infection only
- **The Emulate human alveolar chip can model human coronavirus infection**

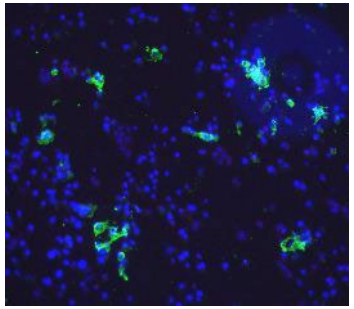
Screening MCMs in alveolar transwell model



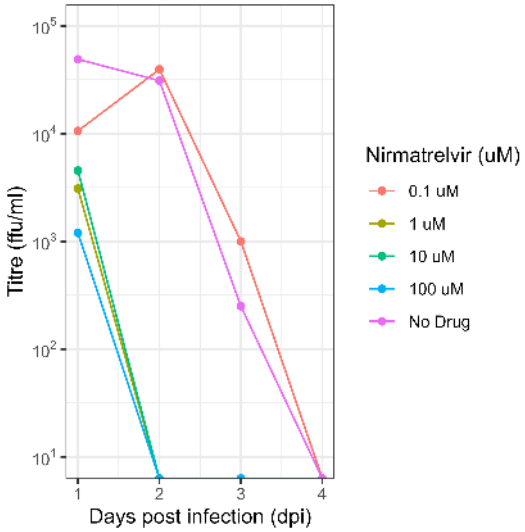
Mock
-Nirm



+MERS-CoV
-Nirm

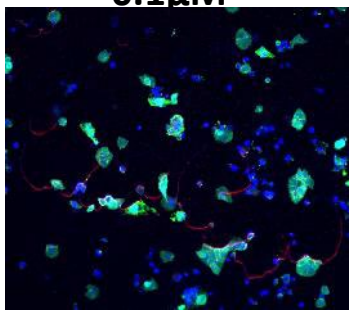


ZO-1 (tight junctions)
DAPI
Virus

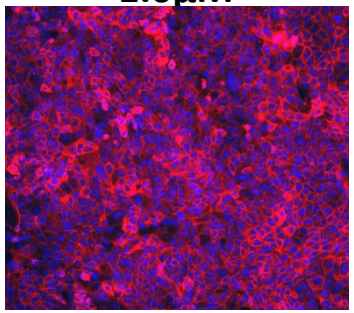


+MERS-CoV
+Nirmatrelvir

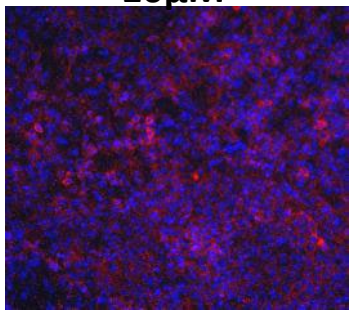
0.1µM



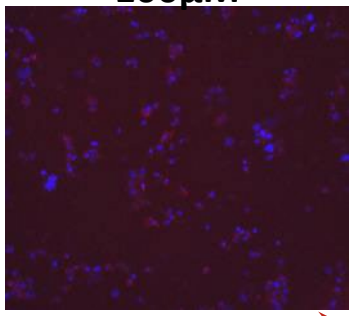
1.0µM



10µM



100µM

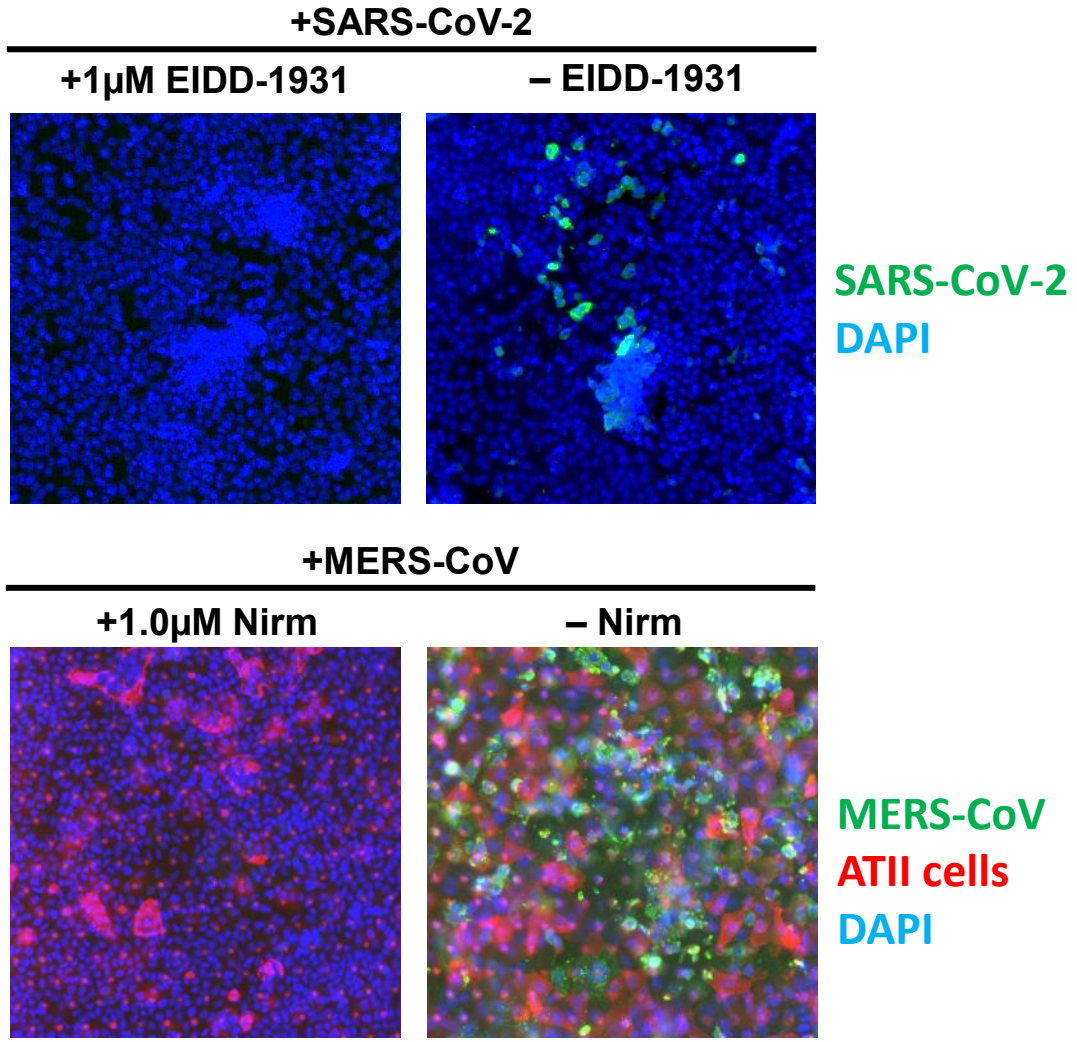


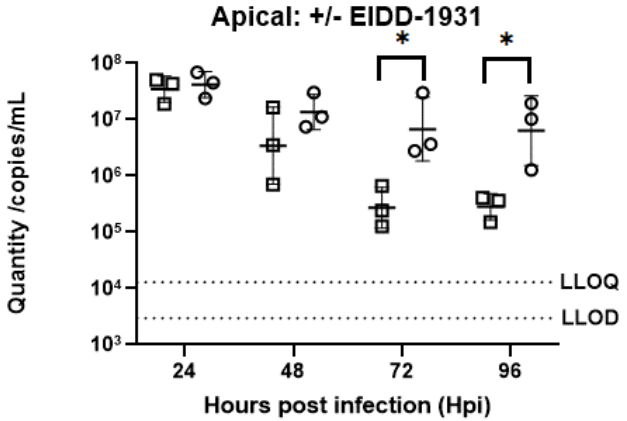
Tight junction breakdown

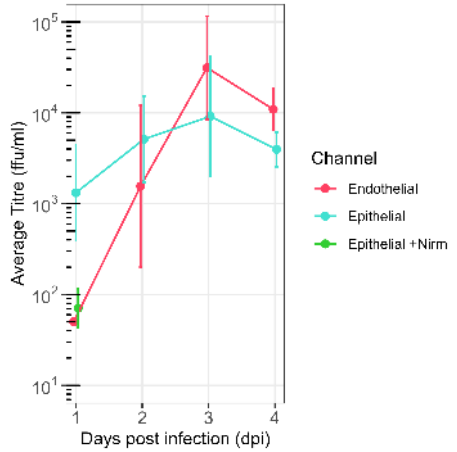
- Medical countermeasures (MCMs) screened in alveolar transwell experiments (static) to assess toxicity and effective dose

- MCMs screened to date:
  - **EIDD-1931** (active metabolite of Molnupiravir) – nucleoside analogue
  - **Nirmatrelvir** (antiviral component of Paxlovid) – protease inhibitor
  - **Tilorone** – interferon inducer
    - Toxic – not taken forward
  - **GS-441524** (active metabolite of Remdesivir) – nucleoside analogue
  - **Oseltamivir Carboxylate** (active metabolite of Oseltamivir) – inhibits release of new virus

Use of MCMs in alveolar Emulate chip infection model



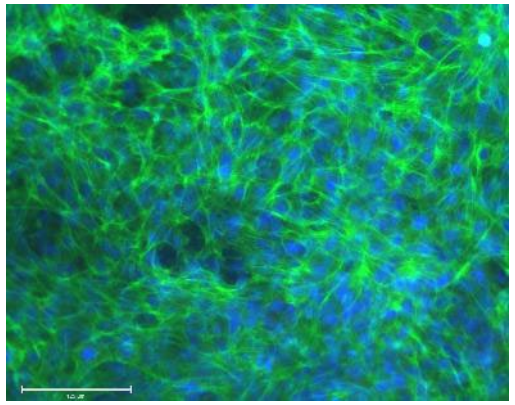




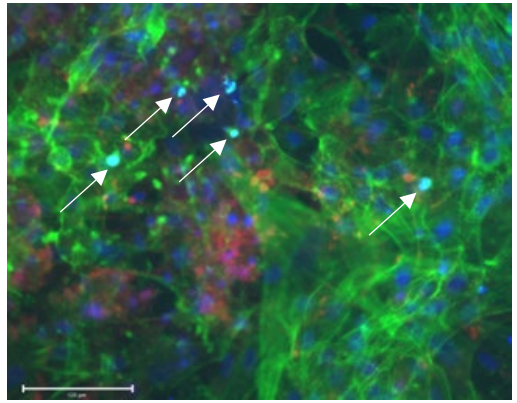
- Human alveolar Emulate chips infected with virus at 1 MOI and MCM introduced into vascular compartment.
- EIDD-1931 and Nirmatrelvir effectively inhibited SARS-CoV-2 or MERS-CoV, respectively
- **The Emulate human alveolar chip can model MCM inhibition of human coronavirus infection**

Infection of an **immune competent** alveolar model (CnBio) with influenza A virus

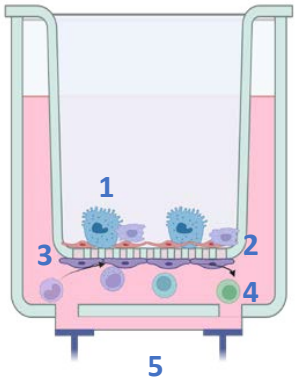
Mock infected



Infected with IAV



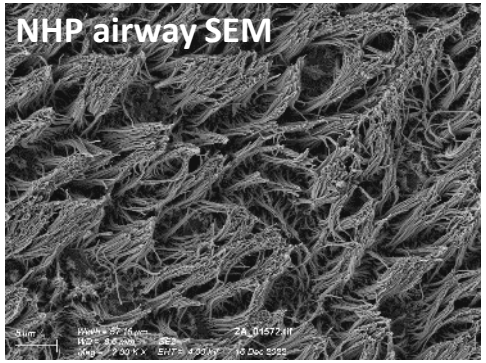
Cytoskeleton (F-actin)
Cell nuclei (DAPI)
PBMC
IAV nucleoprotein (NP)

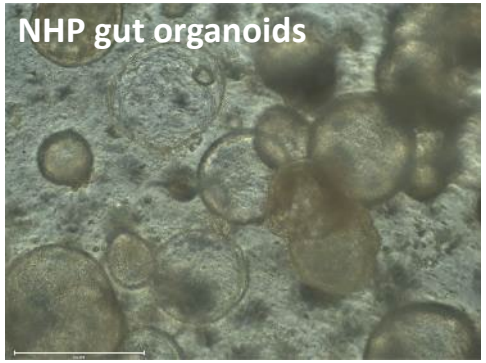


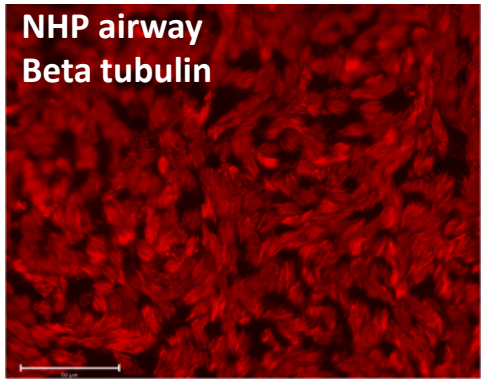
1 – Epithelial cells
2 – Porous membrane
3 – Endothelial cells
4 – Immune cells
5 – Re-circulating flow

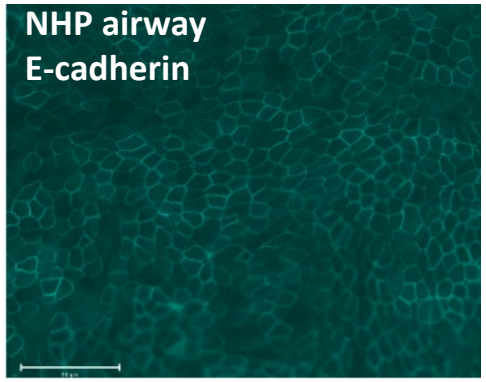
- Immune competent Alveolar CnBio chips infected with influenza A virus at 1 MOI then monitored for 72 hours.
- Immune cell **recruitment** to site of infection observed following IAV infection (white arrows)

Non-human primate “on chip” Bronchial airway and Colon









- NHP organ chips can help regulators and researchers bridge the gap between legacy animal models and human systems.
- Generating organoids from tissues for seeding organ chips supports longer term viability/expansion and retains tissue architecture.
- We have attempted to isolate alveolar, airway and gut cells from NHPs.
  - Airway and gut successful
- **NHP organ chips may be an important stepping stone on the way to reducing animal use in research**

Summary

- MPS are an important tool in the drive to **reduce** and **replace** animal use in scientific research
- Established models on various platforms with bespoke solutions for use at high containment
- Demonstrate **robust infections** with three severe human coronaviruses and **effective inhibition with MCMs**
- We are **increasing model complexity** by incorporating **immune elements** and **interconnect** chips to study systemic disease & virus tropism
- **Pathogen-agnostic models** enable us to be better prepared for future pandemics and the next Disease X
- We are working towards **NHP chips to bridge the regulatory gap** between existing animal data and human organ chip data
- Model validation challenge is to compel & convince regulators:
  - Predictive for human outcomes (breaking the in vitro/in vivo disconnect with cell culture assays)
  - Effective across different model systems & donor demographics

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