INFRAFRONTIER via PRIM-TEC3R

INFRAFRONTIER Complex *In Vitro* Models:

Lung Bud Microarray Platform for Precision Infection Diseases Modelling and Drug Discovery

Brief description:

The Lung Bud Microarray CIVM is an advanced organotypic in vitro model that enables the generation of genetically identical “micro-lungs” derived from human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), or murine ESCs. These cells are cultured on micropatterned microarray chips under tightly controlled exposure to defined signalling molecules, including KGF and BMP4, which drive rapid self-organization into lung bud structures. Within approximately two weeks, the system produces highly reproducible lung-like organoids that recapitulate early fetal lung development, including airway and alveolar-like compartments.

This CIVM addresses a major limitation of patient-derived tissues and conventional organoids: biological variability and lack of immune context. By using genetically identical cell populations, the model reduces experimental noise and enables high-throughput, quantitative assessment of infection dynamics, tissue responses, and drug efficacy.

The platform supports large-scale parallel infection studies with respiratory pathogens such as SARS-CoV-2, influenza viruses, RSV, and HMPV. It allows precise mapping of infection kinetics across cell types, identification of virus-sensitive compartments (notably alveolar-like regions), and evaluation of host-pathogen interactions under controlled conditions.

A key advancement of this CIVM is its modular extension to include immune and stromal co-culture systems, overcoming a major limitation of standard organoids. Integration with primary immune cells enables investigation of inflammatory responses and tissue-immune crosstalk in physiologically relevant settings.

This scalable microarray-based system provides a robust preclinical platform for infection biology, drug screening, and translational respiratory disease research.

How is the model generated?

Stem cells are expanded under standard pluripotency conditions and subsequently transferred onto microarray chips designed to restrict spatial growth and promote controlled differentiation. A defined cocktail of signalling molecules is applied to guide lineage commitment toward lung progenitor fates. Over a two-week period, cells self-organize into structured lung bud organoids that mimic early developmental stages of the human lung. These organoids can then be exposed to infectious agents, therapeutic compounds, or immune cells depending on the experimental design. The platform is compatible with automated high-content imaging systems, enabling large-scale quantitative analysis across thousands of organoids in parallel.

- Differentiation of hESCs/iPSCs or mESCs into lung progenitor populations
- Seeding of cells onto micropatterned microarray chip substrates
- Exposure to defined morphogen cocktail (e.g., KGF, BMP4 and additional pathway modulators)
- Self-organization into structured lung bud organoids over ~14 days
- Optional integration of immune or mesenchymal co-cultures
- Quality control via imaging, molecular profiling, and functional validation
- Infection or drug exposure experiments under controlled conditions
- High-throughput imaging and downstream single-cell / multi-omics analysis

Potential applications:

This CIVM enables advanced biomedical investigations including:

- Mechanistic dissection of early-stage respiratory infections
- Identification of cell-type-specific viral susceptibility
- Evaluation of therapeutic compounds in physiologically relevant human lung tissue
- Study of immune–epithelial interactions during infection and inflammation
- Development of predictive preclinical screening platforms for antiviral and anti-inflammatory drugs
- Reduction of variability compared to patient-derived samples through genetically controlled organoid systems

This platform enables the following applications:

- Investigation of respiratory infections (COVID-19, influenza, RSV, HMPV)
- Host-pathogen interaction mapping at single-cell resolution
- High-throughput antiviral and monoclonal antibody screening
- Drug repurposing and preclinical efficacy testing
- Study of inflammation and immune cell recruitment in lung tissue
- Modelling of pulmonary diseases (fibrosis, infection-induced damage, cancer)
- Integration with immune co-culture systems for mechanistic immunology
- Comparative validation against in vivo mouse models (reduction/replace strategies)

Who provides this model?

CIPHE has a recognised expertise in mouse genetics, genome editing and immunology. CIPHE integrates a suite of cutting-edge technological platforms dedicated to the development and comprehensive characterisation of preclinical in vitro and in vivo models. It designs and generates mouse and rat models that closely mimic human diseases across diverse therapeutic areas, including immunology, infection, cancer, autoimmunity, inflammation, neurology, and rare diseases.

The center performs detailed phenotypic and functional analyses of these models under both physiological and pathological conditions (e.g., inflammation, infection, cancer, autoimmunity), leveraging expertise that spans from molecular biology to whole-organism systems.

CIPHE's core facilities support research projects through its scientific expertise, advanced infrastructure and equipment, aiming to model human diseases, uncover pathological mechanisms, and elucidate therapeutic modes of action. In parallel, CIPHE actively engages in R&D programs to implement emerging technologies and continuously enhance the relevance and precision of its preclinical models. CIPHE is actively involved in numerous national and international research programs and strategic alliances, including ERC, ANR, LabEx, RHU, PIA, and European collaborative projects. These initiatives focus on key areas such as mouse genetics, immunology, infectious diseases, cancer, and rare genetic disorders.

CIPHE is a founding member of the French national infrastructure PHENOMIN and CELPHEDIA, both of which support the development and characterisation of preclinical models. It is also actively involved in several major international consortia, including EMMA, INFRAFRONTIER, and the International Mouse Phenotyping Consortium (IMPC), contributing to global efforts in functional genomics and disease modelling. In the field of infectious disease and therapeutic development, CIPHE is a key partner in the ISIDORe project and a member of the ViroCrib platform, dedicated to antiviral compound screening. Additionally, CIPHE is part of the GDR Organoids network, fostering collaboration around organoid-based research and advanced in vitro modelling.

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INFRAFRONTIER, the European Research Infrastructure for Modelling Human Diseases, is a non-profit organisation dedicated to advancing disease understanding and treatment through cutting-edge models. Operated by a network of over 20 leading biomedical research institutes, it empowers research on human health and disease. Committed to excellence, INFRAFRONTIER adheres to rigorous scientific benchmarks and prioritises animal welfare. Through collaboration with other infrastructures, it fosters global data sharing and contributes to tackling significant health challenges. INFRAFRONTIER serves as a platform for innovative technologies and knowledge exchange, leveraging the power of disease modelling to improve human health.