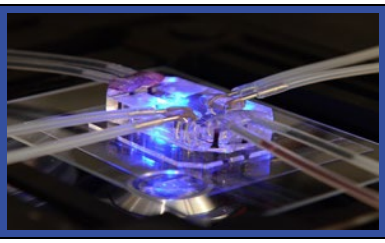
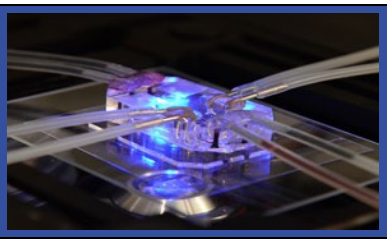


MPSCoRe Spring Workshop
April 1, 2021
Session 1: MPS Models for Testing Therapeutics

Time (EDT)	Agenda Item
10:00 AM (5 min)	**Welcome and Introductions** *Nicole Kleinstreuer, National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)* *Anthony Holmes, National Centre for the Replacement, Refinement, & Reduction of Animals in Research*
10:05 AM (20 min)	**Drug Repurposing for COVID-19 Enabled by Human Organ Chips** *Don Ingber, Harvard Wyss Institute*
10:25 AM (20 min)	**Using a Human-on-a-Chip to Evaluate Drug-Drug Interactions Associated with COVID-19 Therapeutics for at Risk Populations** *James J. Hickman, Chief Scientist, Hesperos, and University of Central Florida*
10:45 AM (20 min)	**COR-101 – Fast Track Development of an Antibody Drug with a Novel Safety Design** *Thomas Schirrmann, CEO Yumab*
11:05 AM (20 min)	**Strategies for the Development of Broadly Neutralizing SARS-CoV2 Antibodies** *Shane Miersch, Senior Research Associate, Sidhu Lab and the Toronto Recombinant Antibody Centre*
11:25 AM (20 min)	**Modeling Disease Response to Respiratory Pathogens** *Joan E. Nichols, Director: Center for Tissue Engineering, Professor: Department of Surgery, Houston Methodist Research Institute*
11:45 AM (20 min)	**Development and Validation of 3D Cellular Lung Model Platforms for Studying High Impact Respiratory Viruses and Rapid Testing of Anti-Viral Agents** *Emily M. Lee, National Center for Advancing Translational Sciences (NCATS)*



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Session 1 Abstracts

Don Ingber, Harvard Wyss Institute: Drug Repurposing for COVID-19 enabled by Human Organ Chips

We have leveraged human Lung Airway Chip microfluidic culture devices lined by highly differentiated, bronchial airway epithelium and pulmonary endothelium to model virus infection, strain-dependent virulence, host cytokine production, and recruitment of circulating immune cells in response to infection by potential pandemic respiratory viruses, such as various influenza virus strains. With the emergence of the COVID-19 pandemic, we carried out testing of multiple drugs that inhibit entry of a pseudotyped SARS-CoV-2 virus in cell lines under static conditions, including hydroxychloroquine, but found them to be inactive when flowed through Airway Chips at a clinically relevant dose. This work revealed that one of these drugs, amodiaquine, also significantly inhibits infection by the pseudotyped virus on-chip, and its efficacy as a prophylactic and therapeutic against native SARS-CoV-2 infection was validated in hamster COVID-19 models. We are now combining this approach with computational drug repurposing algorithms to identify additional potential inhibitors of viral infection as well as suppressors of the host inflammatory response in COVID-19 patients. The human Airway Chip may therefore represent a preclinical discovery platform that can rapidly identify therapeutics that are active in vitro and translate in vivo.

James J. Hickman, Chief Scientist, Hesperos: Using a Human-on-a-Chip to evaluate drug-drug interactions associated with COVID-19 therapeutics for at risk populations

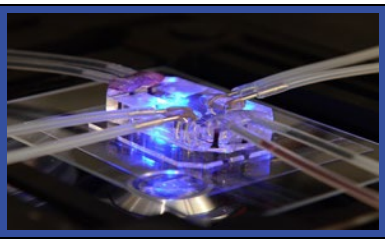
This presentation discusses how a human-on-a-chip, integrated, multi-organ system can provide rapid and accurate guidance for evaluating the side effects of drug-drug interactions, especially in at risk patients with comorbidities. The functional, interconnected platform enables unprecedented visibility into the effects of new or repurposed drugs for COVID-19 on patients that are also being treated for a separate condition, such as non-alcoholic fatty liver disease (NAFLD) and/or cardiomyopathy (CMP).

Thomas Schirrmann, CEO, YumabCOR-101 – Fast track development of an antibody drug with a novel safety design

COR-101 is a novel SARS-CoV-2 neutralizing antibody developed by Corat Therapeutics from target to IMP in less than 8 months. COR-101 was derived from a convalescent patient and endowed with a unique safety design preventing ADE and inflammation. COR-101 shows potent virus neutralization in vitro and in vivo. COR-101 shall be investigated in March 2021 in a phase 1b trial of patients with moderate to severe COVID-19.

Shane Miersch, Senior Research Associate, Sidhu Lab and the Toronto Recombinant Antibody Centre: Strategies for the development of broadly neutralizing SARS-CoV2 antibodies

Emerging variants of SARS-CoV-2 threaten to undermine treatment progress as mutational escape has compromised the potency of therapeutic antibodies, convalescent plasma and vaccine sera. With the aim of enhancing the potency and breadth of neutralization of anti-SARS-CoV-2 antibodies, we engineered novel tetravalent and bi-specific antibody formats from a panel of S-protein-binding clones isolated from a synthetic phage-display library. This talk will directly compare the in vitro neutralization of both the dominant D614G and emerging B.1.351 SARS-CoV-2 variants by engineered tetravalent antibodies to those currently authorized for clinical use (Ly-CoV555 and REGN 10933). Results demonstrate that bi-specific antibodies that target either overlapping or non-overlapping neutralizing epitopes can both enhance potency and broaden the specificity of neutralization, overcoming resistance conferred by escape mutations. Importantly, the facile incorporation of a second paratope in to a tetravalent antibody opens up the possibility of targeting both virus and secondary features of SARS-CoV-2 pathology in a single molecule. The use of bi-specific antibodies in micro-physiological systems that recapitulate these pathological features may provide opportunities to explore mechanisms of disease and inform strategies for intervention.



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Joan E. Nichols, Director, Center for Tissue Engineering; Professor, Department of Surgery, Houston Methodist Research Institute: Modeling Disease Response to Respiratory Pathogens

We have used microfluidic supported 3D cultures to examine respiratory tissue response to exposure to viruses such (SARS-CoV-2, Influenza A (avian or human strains)) or bacteria (Francisella tularemia, pneumococcus) in vitro, and to dynamically monitor agent load, cytopathic effects, and host responses (cytokines, surfactant protein levels, etc.) or examine the effectiveness of therapeutics or combinations of therapeutics. I will present data using human lung MPS to examine tissue responses after exposure to influenza A H1N1 and avian influenza A H7N9. For Influenza A we also examined use of the viral neuraminidase inhibitor Oseltamivir (™Tamiflu), which is known to block the action of Influenza A virus types. Preliminary data showing exposure of human lung MPS to SARS-CoV-2 will also be presented.

Emily M. Lee, National Center for Advancing Translational Sciences (NCATS): Development and Validation of 3D Cellular Lung Model Platforms for Studying High Impact Respiratory Viruses and Rapid Testing of Anti-Viral Agents

High-impact respiratory viruses pose a significant threat to global health. The ongoing COVID-19 pandemic, caused by the recently emerged SARS-CoV2, highlights the need for well-validated, ready-to-use physiologically relevant cellular systems for respiratory viral disease modeling and drug discovery. The NCATS 3D Tissue Bioprinting Laboratory (3DTBL) exists as a core resource to collaborate with the scientific community to biofabricate functional human tissues in multi-well format to enable disease modeling, and predictive efficacy and safety drug testing. In response to the COVID-19 pandemic, we are establishing a platform of engineered 3D lung tissue equivalents of varied physiological complexity, including perfused vasculature, produced with human primary lung epithelial cells, pericytes, and vascular endothelial cells, and thoroughly validated using immunostaining and scRNAseq. These engineered in vitro lung tissue equivalents are being assessed as pathophysiologically relevant infection models for human respiratory viruses, including seasonal (e.g., influenza viruses, seasonal human coronaviruses) and newly emerging (e.g., SARS-CoV2) respiratory viral infections, in addition to exploring COVID-19 disease manifestations such as pulmonary fibrosis. We are establishing disease-relevant assay readouts for drug testing including viral infectivity, cytokine secretion, and other inflammatory markers. We are actively employing these different complex in vitro lung assay systems to assess the potential anti-SARS-CoV2 of compounds identified from high-throughput screening efforts, as a prioritization for testing compounds in animal models.