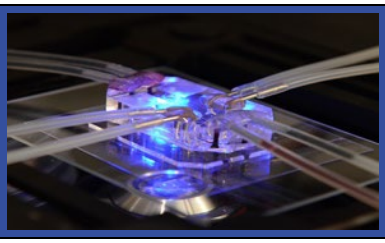
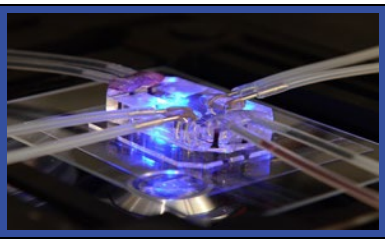


MPSCoRe Spring Workshop
April 1, 2021
Session 2: MPS Models for Understanding Disease Mechanisms

Time (EDT)	Agenda Item
1:05 PM (20 min)	**'Omics Analysis and Characterization of the Effects of SARS-CoV-2 in Lung Chips** *Tyler Goralski, Department of Defense*
1:25 PM (20 min)	**SARS-COV-2 and brain organoids** *Lena Smirnova, Johns Hopkins University*
1:45 PM (20 min)	**The Use of Human Precision Cut Lung Slices for Studying SARS-CoV-2 Infection and Anti-Viral Drug Development** *Armin Braun, Division Director of the Preclinical Pharmacology and Toxicology of the Fraunhofer Institute for Toxicology and Experimental Medicine.*
2:05 PM (20 min)	**Applying Intestinal Organoids to Understand SARS-CoV-2 Biology and Infectivity in the Gut** *Joep Beumer, Hubrecht Institute*
2:25 PM (20 min)	**The Landscape of Host Responses and Disease Pathology in SARS-CoV-2 Infection** *Shuibing Chen and Robert Schwartz, Weill Cornell Medicine*
2:45 PM (20 min)	**MicroRNA-155: Role in Pulmonary Inflammation** *Roopa Biswas, Associate Professor, Department of Anatomy, Physiology and Genetics* *Uniformed Services University of the Health Sciences, School of Medicine*
3:05 PM (10 min)	**Break**
3:15 PM (20 min)	**N3C National COVID Cohort Collaborative** *Ken Gersing, NCATS*



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Session 2 Abstracts

Tyler Goralski, Department of Defense: 'Omics Analysis and Characterization of the Effects of SARS-CoV-2 in Lung Chips

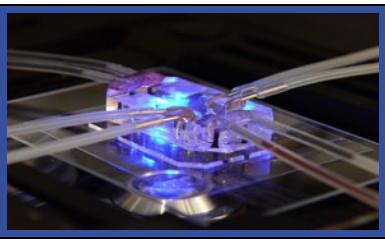
The ongoing COVID-19 pandemic has wreaked havoc on the world, putting enormous strain on emergency medical infrastructure, causing significant economic fallout from idled supply chains and markets, and killing over 1.5 million people to date. The need to understand this disease has sparked globally synchronized research efforts to find potential treatments and provide critical information to front line health care workers. While the successful development and distribution of multiple vaccines has given the world hope and promise, the effects of SARS-CoV-2 on human cells at a molecular level are not fully known. Organs-on-Chips could play an important role in elucidating outcomes of infections in cells. Emulate' s Organs-on-Chips systems use microscale engineering technologies combined with cultured living human cells to recreate the physiological and mechanical microenvironment of whole living organs. Each Organ-on-a-Chip is composed of a clear elastomeric polymer that contains hollow microfluidic channels lined by living human cells. Cells experience the sheer stresses and mechanical forces known to influence cell function *in vivo*, such as the continuous flow of blood and the expansion and contraction of breathing lungs. We are utilizing Emulate' s lung alveolus and small airway chips to assess the effects of SARS-CoV-2 on human cells. With these chips, we hope to reproduce viral entry, replication and release, determine outcomes of infectious dose, obtain insight on viral mechanisms of action and affected host cell pathways via proteomic, transcriptomic, and metabolomics analysis, and hopefully provide additional targets for prophylaxis and anti-viral drug design.

Lena Smirnova, Johns Hopkins University: SARS-COV-2 and Brain Organoids

Reports from Wuhan suggest that 36% of COVID-19 patients show neurological symptoms, and cases of viral encephalitis have been reported, suggesting that the virus is neurotropic under unknown circumstances. This is well established for other coronaviruses. In order to understand why some patients develop such symptoms and others do not, we and others have addressed the infectability of the central nervous system (CNS). Reports that the ACE2 receptor – critical for virus entry into lung cells – is found in different neurons support this expectation. We employed a human induced pluripotent stem cell (iPSC)- derived BrainSphere model, which we used earlier for Zika, Dengue, HIV and John Cunningham virus infection studies. A short-term infection of the BrainSpheres with SARS-CoV-2 led to infection of a fraction of neural cells with replication of the virus evident at 72 hpi. Virus particles were found in the neuronal cell body extending into apparent neurite structures. PCR measurements corroborated the replication of the virus, suggesting at least a tenfold increase in virus copies per total RNA. These findings were supported by others in similar brain organoid models. The recent findings by us and others will be summarized and discussed to understand the advantages and limitations of the brain MPS, optimization steps and usefulness of MPS in infectious disease field.

Armin Braun, Division Director of the Preclinical Pharmacology and Toxicology of the Fraunhofer Institute for Toxicology and Experimental Medicine: The use of human precision cut lung slices for studying SARS-CoV-2 infection and anti-viral drug development

Human precision cut lung slices are viable lung sections with full viability and immune competence. The slices can be infected with respiratory viruses including influenza, parainfluenza, rhinovirus or RSV. In the current pandemic situation PCLS infected with SARS-CoV-2 represent a suitable model to test new antiviral drugs. Profiled by high throughput screening of repurposing drug libraries, Nafamostat was identified as promising drug for COVID treatment. In PCLS we could define the therapeutic window for Nafamostat in lung tissue and show its efficacy as well as its safety.



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Joep Beumer, Hubrecht Institute: Applying Intestinal Organoids to Understand SARS-CoV-2 Biology and Infectivity in the Gut

Organoids derived from adult stem cells (ASCs) retain most features of the source tissue, including cellular heterogeneity and genetic stability. Human intestinal organoids (IOs) are increasingly used to model human disease and are amenable to most genetic engineering techniques. We have employed IOs to evidence the ability of SARS-CoV-2 to replicate in the human gut, explaining extensive gastrointestinal symptoms observed in COVID-19 patients. We used IOs combined with transcriptomics to model the epithelial response to the virus and assess its cellular tropism. We applied CRISPR-Cas9 genetically engineered IOs to study the role of putative host factors in viral replication, as well as the regulation of these genes using fluorescent reporters. These findings could evaluate host factors as drug targets and identify novel regulators of their expression.

Shuibing Chen and Robert Schwartz, Weill Cornell Medicine: The landscape of host responses and disease pathology in SARS-CoV-2 infection

Coronavirus disease 2019 (COVID-19) is driven by an inflammatory syndrome caused by hyper-activation of the immune system resulting in lung tissue injury. Aberrant cellular and innate immune responses to SARS-CoV-2 infection is believed to be a driver of tissue injury, clinical morbidity, and patient mortality. Current model systems leveraging human cancer cell lines while permissive to viral infection do not phenocopy host antiviral responses. hPSC-derived cells/organoids provide a human platform to systematically evaluate the tropism and cellular response upon viral infection. Here, we set up a large consortium effort to set a platform containing twelve different types of hPSC-derived cells and organoids and apply this hPSC based platform to understand the tropism of SARS-CoV-2, explore cellular response, and perform anti-viral drug screening.

Roopa Biswas, Uniformed Services University of the Health Sciences, School of Medicine: MicroRNA-155: role in pulmonary inflammation

Dysregulated expression of the pro-inflammatory cytokine and chemokine genes are known to contribute to pulmonary inflammation. The expressions of such genes are known to be regulated by post-transcriptional mechanisms. Recently, microRNAs (miRNAs) have been proven to be key post-transcriptional regulators of gene expression by directing their target mRNAs towards degradation and/or translational repression. The mis-regulation of specific miRNAs has been demonstrated in a variety of diseases in humans including cancer, heart disease and diabetes. Since each miRNA governs the expression of multiple genes, the most effective way to overcome the effects of a mis-regulated miRNA is to modulate its expression in diseased cells. Thus, miRNAs have emerged as important therapeutic targets in the frontier of biomedical research. Recent studies indicate that even a single miRNA can induce a therapeutic response in an animal model of disease. Our goal is to investigate the role of miR-155 in the regulation of lung injury in diseases associated with pulmonary inflammation including COVID-19. We find that miR-155 production is significantly elevated in SARS-CoV-2 positive patients, whereas higher viral load and upregulation of miR-155 is found in male relative to female. The treatment of anti-miR-155 leads to a significant reduction of miR-155 expression and increased mice survival and body weight. Further, anti-miR-155 treated mice showed reduced pro-inflammatory cytokines responses and increased anti-viral and anti-inflammatory cytokines responses in the lungs of tg-mice hACE2r infected with SARS-CoV-2. We will further analyse the in vivo therapeutic efficacy of anti-miR-155 for pulmonary inflammation and injury in SARS-CoV-2 infections using alveolus lung chip systems. Our study will lead to novel non-coding RNA-based therapeutic strategies for SARS-CoV-2 infection as well as for similar viral and lung-inflammatory diseases.

Ken Gersing, NCATS: N3C National COVID Cohort Collaborative

Description of an open data portal of > 1 million COVID EHR records for research.