Microphysiological Systems (MPS): Bridging Human and Animal Research

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Virtual-only

Session 1: Welcome Remarks

FDA's Study of Alternative Assays
Case Study: Microphysiological Systems (MPS)

Rear Admiral Denise Hinton, M.S.

Chief Scientist, U.S. Food and Drug Administration

The U.S. Food and Drug Administration (FDA) encourages the incorporation of new testing methods into regulatory submissions. FDA's newly released Report on Advancing New Alternative Methods at FDA demonstrates our commitment and highlights just some of the exciting research and activities that is taking place in FDA labs and in partnership with our stakeholders. FDA has been involved with the development of MPS from the very beginning with its partnership with the Defense Advanced Research Projects Agency (DARPA) and National Center for Advancing Translational Sciences (NCATS). The important lesson for both FDA and our stakeholders from this partnership is that it is critical to have regulators at the table from the beginning if the aim is to use a new technology for regulatory use. The Office of the Chief Scientist has established an Alternative Methods Working Group that has senior representatives agency-wide and is committed to interacting internally and externally with our federal partners and our stakeholders. We are focusing on MPS at this time and will be posting updates on our alternatives methods webpage. FDA has many ongoing MPS research projects in partnership with several different academic and commercial chip developers. Partnerships and stakeholder dialogue will add to the body of knowledge the agency can draw upon in achieving its regulatory mission.

MCM One Health and Animal Welfare

Rear Admiral Estella Z. Jones, B.S., D.V.M.

U.S. Public Health Service, Assistant Surgeon General, Deputy Director, Office of Counterterrorism and Emerging Threats, Co-chair, FDA Animal Welfare Council, Office of the Chief Scientist, Office of the Commissioner, U.S. Food and Drug Administration

One Health recognizes the interconnection between people, animals, and plants, and their shared environment at the local, regional, national and global levels. In order to achieve synergy, a collaborative, multisectoral, and transdisciplinary approach is needed.

One Health has assumed a far greater importance as certain factors have altered interactions among people, animals, and our environment. These factors have led to the emergence and re-emergence of many diseases, including the Zika virus, Yellow Fever, Influenza,

Ebola, Lyme Disease with co-morbidities --and now the coronavirus, which has unleashed the global COVID-19 pandemic.

The typical epidemic link is from wildlife to livestock to humans. For this reason, researchers are challenged to develop a global microphysiological system (MPS) bank for common zoonotic species, which can assist in testing the predictive transmissibility of an organism from species to species. This MPS bank would be subject to all federal animal welfare rules and FDA would need to consider establishing regulatory standards for these tissue banks.

Microphysiological systems in pharmaceutical safety

Ekaterina Breous-Nystrom, Ph.D.

Head Investigative Safety-Toxicology at Roche

Roughly three out of five drugs fail clinical trials based on safety issues. This is despite all tested drugs currently having undergone safety testing in multiple animal species. The limitation of predictability of human safety in animal models is often due to subtle, contextual differences which can only be understood after failure in man. This is further put on the spot by novel immunotherapy biologics. The latter together with increasing ethical concerns have driven the development of human microphysiological systems for use in safety testing. Here, I will discuss their development and provide an outline for further improvements needed to overcome current barriers.

Microphysiological Systems at NCATS: Increasing the Predictivity of Translational Assays

Christopher P. Austin, M.D.

Director of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health

The process by which observations in the laboratory or the clinic are transformed into demonstrably useful interventions that tangibly improve human health is frequently termed “translation.” This multi-stage and multifaceted process is poorly understood scientifically, and the current research ecosystem is operationally not well suited to the distinct needs of translation. As a result, biomedical science is in an era of unprecedented accomplishment without a concomitant improvement in meaningful health outcomes, and this is creating pressures that extend from the scientific to the societal and political. To meet the opportunities and needs in translational science, NCATS was created as NIH’s newest component in 2011. NCATS is scientifically and organizationally different from other NIH Institutes and Centers. It focuses on what is common to diseases and the translational process, and acts a catalyst to bring together the collaborative teams necessary to develop new technologies and paradigms to improve the efficiency and effectiveness of the translational process, from target validation through intervention development to demonstration of public health impact. A major impediment to improving the efficiency and effectiveness of translation is the limited capacity of

traditional testing systems to predict adverse or beneficial effects of chemicals and other xenobiotic agents to which humans are exposed, whether intentionally as pharmaceuticals or adventitiously via environmental exposures. As a result, NCATS has had a longstanding and multifaceted program in innovative testing platforms including Tox21, iPSC derived assays, organoid/spheroid, 3D tissue printed, and microfluidic MPS assays. This talk will briefly review these activities and their implications for human and animal research.

EPA's work plan for reducing animal testing: Role of organotypic, microphysiological, and *in silico* models

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Tens of thousands of chemicals are used in commerce and are present in the environment. Hundreds more chemicals are introduced each year. In most cases, the chemicals have limited data that can inform the diverse range of decisions that state and federal regulators may be required to make regarding potential human health risks. In 2019, EPA released a memo stating its intent to eliminate animal testing by 2035 while addressing these challenges and remaining fully protective of human health and the environment. A work plan was developed that integrates short- and long-term regulatory, scientific, and communication strategies that are necessary to achieve these goals. The development and application of organotypic, microphysiological, and *in silico* models are important component of the strategy and will be important in the longer-term success of the initiative. When integrated in a tiered testing and evaluation process, these methods enable more rapid, cost-effective, and human-relevant evaluation of potential toxicological properties. This talk will provide an overview for the role of organotypic, microphysiological, and *in silico* models in EPA's long-term strategy for chemical safety testing and evaluation. *This abstract does not necessarily reflect U.S. EPA policy.*

Session 2: MPSs for toxicology testing

FDA/CDER perspective

Amy Avila, Ph.D.

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FDA/CDER supports the use of new approach methodologies (NAMs), including MPS, in development programs with the goal of improving predictivity, while not compromising current safety evaluations, shifting studies to phylogenetically lower animals, or otherwise helping to replace, reduce, and refine animal use (i.e., the 3Rs). The use of NAMs is discussed in several ICH and FDA guidances. CDER considers that NAMs may have the potential to improve regulatory efficiency, expedite drug development, and answer unmet needs, if the technologies are fit for purpose and can answer specific questions related to assessing drug safety. However, up to now,

data generated from MPS technologies have not been included in any regulatory submissions of human pharmaceuticals (Investigational New Drug Applications (INDs), New Drug Applications (NDAs), or Biologic Licensing Applications (BLAs)). Although, MPS may have utility in assessing efficacy and safety of drugs early in pharmaceutical development outside of regulatory decision making. CDER now has a pathway for submitting information on NAMs for review and comment outside of a regulatory submission. CDER is also actively working to determine what issues need to be addressed to advance data obtained using these technologies into the regulatory decision making framework, which includes CDER's participation in various internal and external working groups, discussing/developing metrics that can be used to measure success, and determining how these technologies could be evaluated for utility in drug development.

Agrochemical perspectives on utility of micro physiological systems

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The global regulatory framework and responsible stewardship programs have entailed extensive toxicity testing for hazard and risk assessment of agrochemical active ingredients, and final products. Traditionally, these studies are conducted using *in vivo* procedures, primarily due to the lack of suitable alternative models that could recapitulate biological complexity and reliably estimate toxicity upon longer-term exposures to chemicals. Recent advancements in the development of alternative methods have advocated for the implementation of non-animal approaches to replace and/or complement *in vivo* testing. Particularly, the micro physiological system (MPS)-based models have made great progress from proof-of-concept studies to actual implementation in early discovery screens and for mechanistic profiling of molecules. This presentation will provide an overview on the potential utility of the MPS-based models to reduce animal use, refine *in vivo* study designs and improve risk assessment of agrochemicals.

Lessons Learned from the Comprehensive *In Vitro* Proarrhythmia Assay (CiPA) Initiative for Safety/Toxicology Testing with Microphysiological Systems

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The Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative provides a multi-component mechanistic-based framework for evaluating proarrhythmic risk (an electrophysiologic toxicity) linked to delayed repolarization and the rare but life-threatening arrhythmia Torsades-de-Pointes.

In vitro studies conducted with human induced pluripotent stem cell derived myocytes (hiPSC-CMs) are included in the paradigm that provide an integrated cellular concentration-dependent electrophysiologic response to verify *in silico* modeling to predict proarrhythmic risk.

This presentation will briefly summarize the utility of hiPSC-CMs in CiPA, and lessons learned that are applicable to evolving microphysiologic cardiac and cardiovascular systems.

Advancing Translational Models & Tools into the Drug Review Process: Opportunities for MPS

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Microphysiological systems (MPS) are potentially transformative models with applications being investigated in drug safety (e.g. safety pharmacology, toxicology), clinical pharmacology (e.g. drug metabolism/pharmacokinetics, drug-drug interactions) and efficacy (e.g. pharmacodynamic biomarkers, rare diseases). FDA/CDER's Division of Applied Regulatory Science (DARS) was created to move new science into the drug review process and close the gap between scientific innovation and drug review. In support of that, DARS is completing applied research on liver, heart and combined liver-heart MPS, and has plans to extend to other organ systems. Initial work has focused on 1) the performance of MPS compared to other culture systems, 2) the reproducibility of MPS systems within and between laboratories, and 3) developing quality control criteria that ensure proper assembly and preparation of functional systems. In addition to summarizing the findings from FDA's liver MPS research, this presentation will discuss experience gained from recent updates to the International Council for Harmonisation (ICH) Guidelines for QT/proarrhythmic risk (ICH S7B & E14) where standards, best practices and quality control criteria were established for nonclinical assays to reduce the need for clinical studies and to inform regulatory decision making. Overall, MPS can yield reproducible results if system preparation, drug administration and measurement schedules are strategically planned, and quality control criteria are used. Full characterization and qualification of MPS for drug development depends on the specific context of use. Initial applications may include de-risking drugs in development with potentially false-positive safety signals from animal studies and reducing the need for clinical drug-drug interaction studies.

If you build it, will they come? Testing the "value proposition" for tissue chips in drug and chemical safety assessment

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Tissue chip development is one of the rapidly growing areas in biomedical sciences. Not only are there many new exciting models developed in academic laboratories, but also a number of companies are manufacturing tissue chip platforms or provide contract research services for drug and chemical testing. The use of these devices as supplemental or replacement models for drug and chemical safety assessment is an area of interest by the industry and regulatory agencies; however, the pace of adoption of this technology has been slow. To accelerate translation of the tissue chip technology from academia to regulatory science, the National Center for Advancing Translational Sciences (NCATS) funded directed tissue chip testing activities. This presentation will describe tissue chip testing efforts of TEX-VAL Consortium that is now operating as a public-private partnership that includes Texas A&M University, several US government agencies, pharmaceutical and consumer goods companies and a trade association.

Our experience with defining fit for purpose and value proposition for tissue chips' utilization by the end-users shows that direct adoption of the technology as developed by the academic laboratories is frequently difficult as the biomedical engineers need better understanding of where and how their technology may fit in current drug and chemical safety testing paradigms and what level of evidence is needed for these models to be accepted for both internal and regulatory decision-making.

Session 3: Going from *in vitro* to *in silico* – data and developmental tools

Synthetic Microsystems, Computational Intelligence, and Artificial Life

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Synthetic microsystems harboring biomimetic potential of the embryo, combined with dynamical computational models to simulate mesoscopic cellular behaviors, provide a path forward to animal-free testing. A synoptic view of *in vitro – in silico* microsystems can translate theories into testable hypotheses, provide sensitivity analysis, generate predictions, and design new experiments. The autopoietic capacity of pluripotent stem cells (hPSCs) has proven useful for *in vitro* profiling of chemical libraries although placing these data in the context of developmental dynamics remains a challenge. The epiblast is the tissue origin for most cell lineages of the embryo proper and is most closely resembled by hPSC cultures; however, epiblast cells retain positional information necessary for decoding the genomic blueprint of the body plan during gastrulation. Cell signaling gradients that polarize the epiblast and specify cell fate decisions during gastrulation (eg, WNT, FGF, BMP, NODAL, ATRA, …) function in complex networks. Our hypothesis is that the morphological programming logic of the epiblast provides a deep-learning platform to translate ToxCast HTS data into a mechanistic hazard prediction. This logic can be simulated in multicellular agent-based models to potentially recode positional information for the body plan. Recently developed 'synthetic epiblast' microsystems using hPSCs, microfluidics and bioprinting impose extrinsic gradients to investigate mechanisms in perturbation by chemicals. Armed with sufficient intelligence for 'quasi-gastrulation', artificial life complements *in vitro* data-driven models putting into cellular motion how chemicals might disrupt the embryo under different exposure scenarios for developmental hazard identification and dose-response modeling for human prediction. (*Disclaimer: does not necessarily reflect Agency policy).*

The Microphysiology Systems Database (MPS-Db): A platform for aggregating, analyzing, sharing and modeling of in vitro and in vivo safety and efficacy data.

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To accelerate the development and application of Microphysiology systems (MPS) experimental models in the biopharmaceutical and pharmaceutical industries, as well as in basic biomedical research, a centralized resource is required to manage the detailed design, application, and performance data that enables industry and research scientists to select, optimize, and/or develop new MPS solutions. The Microphysiology Systems Database (MPS-Db) is a unique and essential resource for the development and widespread implementation of MPS technologies. It is designed to aggregate, analyze, and computationally model experimental MPS data relative to human and animal exposure data, and serve as a centralized resource for sharing MPS data. The MPS-Db captures and aggregates data from MPS tissue/organ experimental models, ranging from static microplate models to individual organs to integrated, multi-organ microfluidic models. Links to reference data from chemical, biochemical, pre-clinical, clinical and post-marketing sources are accessible to support the design, development, validation, application and interpretation of the experimental models and study data. A dedicated Disease Portal module links to resources for the design of MPS disease models and studies. A streamlined workflow guides creating studies directly in the database and facilitates uploading experimental metadata and data. Visualization and statistical tools enable quick and convenient analysis of study data and assessment of experimental model performance. Computational tools being integrated into the database enable the utilization of MPS experimental models for understanding mechanisms of disease, compound toxicity, and predicting PK behavior. As a centralized resource, the MPS-Db is a platform for easy sharing of experimental data among collaborators. The public version currently available allows data providers to control the accessibility of their data. A commercial version of the MPS-Db is being developed to sit behind corporate firewalls enabling enhanced security according to corporate standards, and allow integration with internal databases to provide access to corporate proprietary data. The MPS-Db is an innovative advancement for the MPS community, and is the first and only publicly accessible, comprehensive resource for sharing and disseminating data and information on MPS. https://mps.csb.pitt.edu/

Harnessing Human Biomimetic Liver MPS Combined with Quantitative Systems Pharmacology to Predict Drugs/Combinations for Treating MAFLD

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Metabolic syndrome is a complex disease that involves multiple organ systems including a critical role for the liver. Non-Alcoholic Fatty Liver Disease (NAFLD) is a key component of the metabolic syndrome and fatty liver is linked to a range of metabolic dysfunctions that occur in approximately 25% of the population. A panel of experts recently agreed that the acronym, NAFLD, did not adequately characterize this heterogeneous disease given the associated metabolic abnormalities such as Type 2 diabetes mellitus (T2D), obesity, and hypertension. Therefore, Metabolic dysfunction-associated fatty liver disease (MAFLD) has been proposed as the new term to cover the heterogeneity identified in the NAFLD patient population. The challenge has been that although many investigations using animal disease models to test target-centric drug candidates have been performed over the last decade, no new therapeutic has been approved by regulatory agencies due to missed endpoints. The heterogeneity of the disease and the inability to fully recapitulate this complex disease in animal models, so far, has been identified as potential key limitations. Therefore, a complementary approach to target-centric drug discovery and animal models of disease should be explored. We have evolved a platform initially focused on human biomimetic liver microphysiology systems (HBL-MPS) that integrate fluorescent protein biosensors (FPBs) along with other key metrics, the microphysiology systems database and quantitative systems pharmacology (QSP). An experimental model of MAFLD progression has been developed in our HBL-MPS to test existing drug candidates and predicted drugs/combinations on their ability to halt or reverse disease progression. Disease progression has been induced by sequentially altering the media over a two week period to reflect the transformation of the HBL-MPS from a normal fasting state to early metabolic syndrome/MAFLD to late metabolic syndrome/T2D/MAFLD. Progressing changes in glucose levels, free fatty acids and cytokines drive the transformation. An unbiased QSP approach has been applied starting with computational analysis of patient liver biopsies to investigate the heterogeneity and mechanisms of MAFLD progression and to iteratively integrate computational and experimental methods to predict drugs/combinations for repurposing, as well as to facilitate novel drug development. A prioritized list of predicted drugs has been generated and testing within the present HBL-MPS based on human primary cells has been initiated. The future will combine QSP with patient-derived iPSCs to create a precision medicine platform to identify drugs/combinations that optimally treat patient cohorts with similar genetic and phenotypic expressions of disease. The next generation patient-derived HBL-MPS will be based on structurally organized, advanced patient-derived organoids (Organoid-MPS) and/or bioprinted iPSCs and matrix (Structured-MPS). This next generation HBL-MPS will be investigated as both a

stand-alone HBL- MPS, as well as coupled organ systems based on Organoid-MPS and/or Structured MPS of key organs involved in MAFLD/metabolic syndrome.

Session 4: Panel Discussion on topics of public health importance (COVID)

The role of MPSs in addressing the 3Rs in research involving Zoonoses in protected species

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Seconded to the Blueprint Research and Development team at the World Health Organisation

The SARS-CoV-2 global pandemic has resulted in unprecedented global co-operation and data sharing. The WHO R&D Blueprint team has been instrumental in facilitating this collaboration and scientist have been able to share their findings at a rate not anticipated not only in the various WHO fora but also online in preprint form. Bridging the gap between preclinical development and clinical trials has been challenging for all involved. One of the many obstacles was rapid development and utilisation of biological infection models which enable drug and vaccine assessment and development. Lessons have been learned in drug repurposing and the reliance on traditional cell culture as a means for early screening. This presentation will feature a discussion on viral propagation and traditional methodology of assessment and how Microphysiological Systems (MPS) have demonstrated their value in the global response to SARS-CoV-2. As we glimpse a light at the end of this tunnel, the importance of MPS in the refinement, reduction and replacement of *in vivo* studies in protected species will be discussed not only for SARS-CoV-2 but for the future Zoonotic challenges that await us beyond SARS-CoV-2.

Bat and human gastrointestinal organoids as *in vitro* models to define pathogenic and protective responses to SARS-CoV-2 infection

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Bats are known carriers of a multitude of viruses including coronaviruses and are thought to be the original reservoir for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which shares 96% of its genetic sequence with coronavirus RatG13 found in horseshoe bats. Interestingly, coronavirus colonization of the bat gastrointestinal tract generally does not cause pathology or disease, whereas SARS-CoV-2 infection leads to strong cytopathic effects in human respiratory and gastrointestinal epithelial cells. We hypothesize that identifying cellular immune mechanisms that protect bats from exaggerated inflammatory responses to SARS-CoV-2 may point to novel treatment approaches in humans. However, no appropriate models are available to study SARS-CoV-2 infection in bats in a relevant *in vitro* system.

To address this gap, we have established and characterized organoids lines from the gut of three adult Jamaican fruit bats (*Artibeus jamaicensis),* which appear to be susceptible to

experimental gastrointestinal infection with SARS-CoV2. Organoids were successfully generated from both fresh and frozen stomach, proximal and distal small intestine and could be passaged at least 25 times and frozen and thawed with no apparent changes in growth and morphology. We confirmed that organoid lines derived from bat stomach, proximal and distal intestine had appropriate tissue-specific gene expression patterns. We used microscopic analysis to show that bat gastric and intestinal organoids were composed of a polarized simple columnar epithelium and secreted variable amounts of mucus. The presence of microvilli, tight junctions and secretory vesicles was confirmed by transmission electron microscopy. We also observed spontaneous development of gland and crypt structures, indicating appropriate differentiation. When seeded on transwell inserts, both gastric and intestinal organoid cells consistently developed a transepithelial resistance, demonstrating intact barrier function. Using confocal microscopy, we showed that both gastric and intestinal organoids from bats expressed angiotensin I converting enzyme 2 (ACE2), a key receptor for SARS-CoV-2 entry.

The novel bat organoid lines that we have developed will enable us to study multiple aspects of SARS-CoV-2 infection including viral evolution and determinants of spillover events in a relevant primary cell model system. Following optimization of SARS-CoV-2 infection protocols, we will compare the responses of gut organoids from bats and humans to SARS-CoV-2 in order to understand the cellular mechanisms that allow bats to harbor coronaviruses without developing clinical disease.

Lung-on-chip model systems to study host-pathogen interactions in respiratory infections

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The vast surface area of the distal lung, sparsely populated with resident immune cells, is the often the site of emerging (COVID-19) or established (Tuberculosis) infection diseases. Severe manifestations of COVID-19 result in microvascular thrombosis in the lung and systemic endothelialitis, but the underlying dynamics of damage to the vasculature and whether it is a direct consequence of endothelial infection or an indirect consequence of immune cell mediated cytokine storms is still unclear. This is in part because *in vitro* infection models for SARS-CoV-2 are typically monocultures of epithelial cells or fail to recapitulate vascular physiology. In contrast, the minimum infectious dose in tuberculosis can be as low as one, which makes the early stages of infection difficult to study even in animal models. Yet heterogenous outcomes in the early stages of infection significantly alter the course of infection and may explain why the proportion of exposed individuals who develop clinical tuberculosis is low. In my talk, I will describe our efforts to develop the lung-on-chip as model systems for respiratory infectious diseases and showcase the ability of these systems to enable new experiments that would not be possible *in vivo*.

In the case of COVID-19, we used a vascularised human lung-on-chip model [2] where we find that rapid infection of the underlying endothelial layer leads to the generation of clusters of endothelial cells with low or no CD31 expression, a progressive loss of endothelial barrier

integrity, and a pro-coagulatory microenvironment. These morphological changes do not occur if endothelial cells are exposed to SARS-CoV-2 apically. Viral RNA persisted in individual cells, which generated a response skewed towards NF-KB mediated inflammation and an antiviral interferon response which was transient in epithelial cells but persistent in endothelial cells. Perfusion with Tocilizumab, an inhibitor of trans IL-6 signaling slows the loss of barrier integrity but does not prevent the formation of endothelial cell clusters with reduced CD31 expression. Further work is ongoing to understand the role of cell-cell communication in the inflammation observed.

Prior to this, we developed a murine lung-on-chip model for tuberculosis which allowed us to co-culture macrophages from transgenic mice with epithelial and endothelial cells from wild-type mice and recreate a level of pulmonary surfactant deficiency that would be lethal *in vivo* [2]. Using long-term time-lapse imaging, we measured the growth rates of small bacterial microcolonies in the individual host cells at the air-liquid interface and showed that pulmonary surfactant secreted by epithelial cells dramatically reduced bacterial growth in both epithelial cells and macrophages, whereas deficient levels of surfactant led to unimpeded growth. These insights suggest a greater role for alveolar epithelial cells in early tuberculosis than previously.

References

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2. ***V.V. Thacker&*** *et al.,* A lung-on-chip infection model of early *M. tuberculosis infection* reveals an essential role for alveolar epithelial cells in controlling bacterial growth. *eLife.* 2020; 9: e59961

Human Organ Chip-enabled discovery of therapeutics and prophylactics for viral pandemics

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The rising threat of pandemic viruses, such as SARS-CoV-2 or novel strains of influenza, requires development of new preclinical discovery platforms that can more rapidly identify therapeutics that are active *in vitro* and also translate *in vivo*. We have used human organ-on-a-chip (Organ Chip) microfluidic culture devices lined by highly differentiated, primary, human, lung airway epithelium and endothelium to model virus entry, replication, strain-dependent virulence, host cytokine production, and recruitment of circulating immune cells in response to infection by respiratory viruses with great pandemic potential. We provide a first demonstration of therapeutic drug repurposing by showing that co-administration of the approved anticoagulant drug, nafamostat, with oseltamivir in influenza A virus-infected Lung Airway Chips doubles oseltamivir's therapeutic time window. With the emergence of the COVID-19 pandemic, the Airway Chips were used to assess the potential prophylactic activities of approved drugs that showed inhibition of infection by a pseudotyped SARS-CoV-2 virus in traditional cell culture assays only to find that most failed when administered under flow at a clinically relevant dose in

human Airway Chips. Proof of concept was shown by demonstrating that the drug that most potently inhibited virus entry on-chip – amodiaquine - prevented infection of Vero E6 and human lung 549 cells by native SARS-CoV-2 in vitro, and significantly reduced viral load in both direct infection and animal-to-animal transmission COVID-19 models when administered in either prophylaxis or treatment modes in hamsters. Using similar Organ Chip models, we also discovered a novel class of immunostimulatory duplex RNAs that exhibit broad spectrum inhibition of SARS-CoV-2, SARS-CoV, MERS-CoV, NL-63, and multiple influenza A strains, by inducing type I interferon expression. These data highlight the value of Organ Chip technology as a more physiologically relevant preclinical platform for drug repurposing and discovery, and suggest that amodiaquine should be considered for clinical testing as a potential therapy in the current COVID-19 pandemic.

Session 5: Commercialization/engineering/collaborations

Learning from Tissue Chips in Space: Development and Commercialization of Next Generation MPS Platforms

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Tissue Chips in Space is a collaborative initiative between the National Center for Advancing Translational Sciences (NCATS) and the Center for the Advancement of Science in Space (CASIS) in partnership with NASA. The program uses MPS technologies aboard the International Space Station (ISS) to decipher the impact of microgravity on human biology with the ultimate goal to improve human health on Earth. In 2019, tissue chips commercialized by MPS developer Nortis were successfully used on the ISS to study critical conditions of the human kidney that are accelerated by space travel, such as proteinuria, osteoporosis, and kidney stones. Follow-up missions are in preparation. Besides its scientific value, the lessons learned by MPS developers, implementation partners, and MPS users at the ISS and on the ground underline the importance of robust performance, user-friendliness, standardization, and stable quality. These insights provide valuable guidance for the design of compact, automated, and high-performing next-generation MPS platforms for use in pharmaceutical drug screening and other areas.

The Use and Applications of 3D Tissue Models for Respiratory Toxicology and Efficacy Testing within the CRO Industry

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3D human tissue models have been used in regulatory toxicology for many years with test guidelines for many of the acute tests (e.g. skin irritation and corrosion and ocular irritation and severe damage). The availability of models has increased to include oral, gingival, vaginal and the lung. The airway is a particularly important route of administration of drugs as well as

environmental pollutants, cosmetic (e.g. deodorant) ingredients, agrochemical sprays and pathogens. One of the fundamental questions is how relevant these models are in predicting toxicity or efficacy when our benchmark tests are using animals, rather than the patient. Are the differences observed between the animal in vivo data and the human in vitro data to do with the species or the cellular model and if it is the former, is the latter a better model? How also can we protect animals, which are still very much required for regulatory testing? Therefore, a rat upper airway model has been created using the Charles River rat by MatTek. This presentation evaluates the different human upper and lower airway models and the rat upper airway model for predicting toxicity and also in evaluating efficacy in human disease derived tissue – the most important translation that we can assess is the human patient derived model. This presentation will also examine where the tests may be able to be further developed.

Addressing the Opioid Crisis: A Microphysiological Model of Synaptic Transmission of Pain

Michael J. Moore, Ph.D.

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Chronic pain is a debilitating and increasingly pervasive condition that may result from injury, heredity, or acquired neuropathy. Peripheral sensory nerves, derived from dorsal root ganglia, generate pain signals and transmit them to the central nervous system through synaptic transmission within the dorsal horn of the spinal cord. Opioid analgesics, often used to treat pain, target opioid receptors within the dorsal horn synaptic circuitry and elsewhere. Over-prescription of increasingly powerful and addictive opioids has led to the current epidemic of prescription drug abuse.

Our laboratory has been developing a 3D *in vitro* microphysiological model of synaptic transmission between sensory peripheral nerve and dorsal spinal cord tissues. As a proof of principle, dorsal root ganglion and dorsal spinal cord tissues were each harvested from embryonic rats, dissociated into single-cell suspensions, re-aggregated into homogenous spheroids, placed 3mm apart in a bioengineered 3D hydrogel culture system, and matured for up to three weeks. We used virally-expressed fluorescent proteins and calcium indicators to visualize the functional histoarchitecture of the circuit. The 3D tissue architecture facilitated extracellular field potential recording in spinal cord spheroids following electrical stimulation of peripheral nerve tissue to assess the effects of analgesic drugs applied to the co-culture.

Immunofluorescent staining confirmed that expression of glutamatergic markers, GABAergic markers, μ-OR, and synaptic proteins were appropriately localized within mature *in vitro* circuits. Electrophysiological analysis confirmed the presence of functional and appropriately directional synaptic connections. A multiplexed waveform was reproducibly identifiable, whose components could be teased apart with pharmacological probes. Importantly, each analgesic applied perturbed this waveform in unique dose-dependent fashion, providing an interpretable and quantifiable signature for each type of drug applied.

This microphysiological synaptic circuit recapitulates critical aspects of *in vivo* physiology and cytoarchitecture. This model may provide a viable alternative to behavioral testing in animals

for early-stage investigation of pain-modulating compounds at lower cost and with higher throughput. We are currently in the process of generating a corresponding human model with pluripotent stem cell-derived neural tissue and integrating tissue constructs with a custom 3D microelectrode array system to facilitate real-time stimulation and recording.

Session 6: Multi-organ chips and emerging applications for biologics studies

Emulating human organ interactions on a universal multi-organ-chip platform

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Microfluidic microphysiological systems (MPS) have proven to be a powerful tool for recreating human tissue- and organ-like functions at research level. Single- and multi-organ-chip models are increasingly in use for academic discoveries. This provides the basis for the establishment of qualified preclinical assays with improved predictive power. However industrial adoption of microphysiological systems and respective assays is progressing slowly due to their complexity. Here we introduce the use of the HUMIMIC® platform to model the interaction of various human organ models with each other in two-organ or four –organ arrangements. The underlying universal microfluidic chip designs of a size of a microscopic slide integrating an on-chip micro-pump and capable to interconnect different organ equivalents will be described. Sixteen different single organ equivalents have been established on that platform so far and twelve organ combinations have been tested for stable long-term crosstalk yet. Two case studies with two-organ-models will be highlighted. Finally, challenges to translate a HUMIMIC®-based combination of four human organ equivalents into a commercially useful tool for ADME profiling and toxicity testing of drug candidates will be addressed. This chip combines intestine, liver and kidney equivalents for adsorption, metabolism and excretion respectively. Furthermore, it provides a culture compartment for an additional organ model. Issues to ensure long-term performance and industrial acceptance of such complex microphysiological systems, such as design criteria, tissue supply and qualification standards will be discussed.

Integrated human multi-organ platforms

Gordana Vunjak-Novakovic, Ph.D.

Columbia University in the City of New York

Bioengineered “organs on a chip” platforms are evolving into a new paradigm for modeling human pathophysiology, with utility in both biological and clinical studies. Establishing physiological communication between different tissues while preserving their individual phenotypes remains a challenge that must be overcome to model whole-body physiology and systemic diseases. An approach to meet these conflicting requirements is to establish a modular, configurable multi-organ platform in which each human tissue is cultured in its own optimized environment and separated from the recirculating flow by a selectively permeable endothelial barrier. Under these conditions, the tissues linked by vascular perfusion can maintain their

molecular, structural and functional phenotypes over at least four weeks of culture. These platforms allow individualized studies, as all tissues as well as endothelium and circulating cells can be derived from iPS cells. This presentation covers the design requirements, key components and operation of these platforms, and the biological and engineering opportunities and challenges for their application in studies of development, regeneration, physiology and disease.

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Humanizing Models of Systemic Inflammatory Diseases with Multi-Organ Platforms and Systems Biology

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Chronic inflammatory diseases, many of which preferentially afflict women, affect multiple organ systems and remain among the most difficult drug development targets in part because these diseases are among the most challenging to model in animals. To illustrate the potential his talk will describe our recent work using a multi-organ platform with on-board microfluidic pumps suitable to model the human gut-liver axis in inflammatory bowel disease and the gut-liver-central nervous system axis in Parkinson's, including challenges on the technical side (pumping immune cells; pharmacokinetic analysis especially of sticky compounds) and the conceptual side (choosing system subcomponents to model, cell sources, interpretation of multi-omics data and heterogeneous data sets), and provide perspective on how these systems can (for now) complement animal studies and ultimately move beyond them for additional diseases, such as endometriosis and adenomyosis.

Multi-organ, integrated female reproductive system for disease modeling and environmental exposure toxicity testing.

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Polycystic ovary syndrome (PCOS) is the most common form of anovulatory infertility of reproductive age women. PCOS is a complex endocrine disorder that affects 1 in 5 women of reproductive age and presents with a wide spectrum of phenotypes primarily characterized by hyperandrogenism, oligomenorrhea/ amenorrhea, and polycystic ovaries. In this work, we are developing a multi-tissue microfluidic model of PCOS that includes a number of reproductive and non-reproductive tissue models including the ovary, uterine endometrium, fallopian tube, and pancreas. We used a microphysiological system (MPS) to co-culture pancreatic islets with ovary explants and found that the tissues are supported by the islets in insulin-free media for up to 21

days in culture. When co-cultured with ovary explants, islet spheroids supported ovarian function including production of estradiol and ovulation. We have developed a method to generate scaffold-free endometrial organoids containing both primary epithelial and stromal cells. These organoids express androgen, estrogen and progesterone receptors, and undergo baseline proliferation during a 14-day culture with a hormonal profile of a normal follicular phase of the menstrual cycle. Human fallopian tube epithelium (hFTE) cultures of both PCOS and normal profiles were tested. Gene response profiles were altered with PCOS-like hormones including markers of estrogen responsiveness, such as OVGP1, were repressed by androgen addition. Key pathways that were altered included the regulation of cilia function, tumorigenesis and metabolism. This was consistent with previous functional data where we measured a reduction in ciliary beating in response to androgens, a potential unexplained aspect of infertility in these patients. These unique organ cultures and MPS are being deployed to study the impact of endocrine disrupting compounds on reproductive function, including their impact on PCOS. www.burdettelab.com

Microphysiological Systems to assess the functional capacity of regenerative medicine cellular products

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As described in the 21st Century Cures Act, products eligible for Regenerative Medicine Advanced Therapy (RMAT) designation include cellular therapies, therapeutic tissue engineered products, human cell and tissue products, or any combination products that use such therapies or products. Multipotent stromal cells (MSCs) and induced Pluripotent Stem Cells (iPSCs) have been popular sources for manufacturing RMAT products due to their ability to undergo lineage-specific differentiation. For successful clinical translation of such cell-based products, there is a paucity of reliable markers that can predict the products' *in vivo* performance. For instance, MSCs are heterogeneous and responsive to their surrounding environment, resulting in distinct subpopulations of cells with potentially different qualities needed for product potency. Since there are numerous biochemical and biomechanical factors regulating the functions of MSCs, it is critical to develop reliable high-throughput assays that enable the efficient exploration of large and complex parameters for evaluating cellular function. Microphysiological systems offer the practicality to fulfill this unmet need. Several simple microfluidic channel arrays have been successfully implemented in screening the influence of paracrine mediators and various tissue microenvironment components in the regulation of cellular functions. In addition, microphysiological three-dimensional organoids and tissue-like structures such as chondrogenic cell aggregates and blood vessels have been incorporated into high-throughput, cell-based screening platforms in efforts to provide functionally relevant conditions. This presentation will give an overview of practical microscale technologies that are simple to operate while enhancing throughput, relevance, and reliability. How such technologies could be employed in the assessment of cell-based products will be discussed.

Exosomal Cardiotherapies on a Chip

Kevin Kit Parker, Ph.D.
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Extracellular vesicles derived from various stem cell sources have been found to induce cardioprotective effects during ischemia reperfusion injury. These have been found to be mediated mainly via the anti-apoptotic, pro-angiogenic, miRNA cargo within the stem cell-derived EVs. However, vesicle-mediated endothelial signaling to cardiomyocytes, as well as their therapeutic potential toward ischemic myocardial injury are not clear. Our goal was to characterize the protein cargo of human vascular endothelial extracellular vesicles (EEVs), to identify lead cardioactive proteins, and assess the effect of EEVs on engineered, human laminar cardiac tissues in an ischemia-reperfusion injury (IRI) model on a chip. We mapped the protein content of human vascular EEVs, and identified proteins that may affect myocyte metabolism, redox state, and calcium handling, among other processes. Analysis of human cardiomyocytes protein landscape revealed corresponding modifications induced by the EEVs treatment. Using our instrumented heart on a chip based on muscular thin film technology, we found that EEVs alleviate cardiac cell death as well as the loss in contractile capacity during and following simulated IRI, in an uptake- and dose-dependent manner. Moreover, we found that EEVs increase respiratory capacity in normoxic cardiomyocytes. These results suggest that vascular EEVs may rescue hear muscle enduring IRI possibly by supplementing injured myocytes with cargo that supports multiple metabolic and salvage pathways, and therefore, may serve as a multi-targeted therapy for IRI.

The challenge of disease modeling, quality assurance and validation of organ-on-chip models

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The enormous advance of bioengineering organ architecture and functionality comes at the price of an enormous increase in complexity. Disease modeling and substance testing requires dramatically increased efforts for standardization and validation. The cell models are moving targets, which change over time due to internal programs of (de-)differentiation especially in case of stem-cell-derived systems in response to cocultured cells, media, growth factors, the physical environment of the chip platform and perfusion etc.. In addition, disease inducing and promoting agents such as infectious agents, cancers, immune responses, environmental and genetic factors among others are dramatically increasing this complexity. The number of factors to control and document can be mind-blowing. Standardization of Microphysiological Systems and their components by commercial providers is of critical importance for the broad availability and comparability of test systems. Running something like this under Good Laboratory Practice is an enormous challenge while it is obvious how

important this is for regulatory purposes. A major step forward is the current finalization of Good Cell Culture Practices (GCCP 2.0). In extension, Good In Vitro Reporting Standards (GIVReSt) are on the way. Traditional validations with multi-laboratory ring trials are difficult to imagine and we might need to rethink our paradigms.

Session 7: Perspectives and strategies on the need for animal cell and chip-banks

Animal Drugs, Animal Studies, and MicroPhysiological Systems.

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The FDA Center for Veterinary Medicine regulates animal drugs, animal foods, and (post market) animal devices. This is true for dogs and cats in the home, cattle producing meat and milk on the farm, and even fish in the stream. For brevity today's talk will focus on animal studies used for animal drugs.

Target animal studies are conducted in the animal receiving the drug and are conducted to a standard of substantial evidence of effectiveness. Studies range from clinical trials conducted in in client owned dogs or cats, to agricultural field trials in animal such as cattle, swine, or poultry. As in human clinical trials, these studies endeavor to assure that the drug does what it is claimed to do and adverse effects are carefully evaluated to inform the safety of the drug. Margin of safety studies in the target animal typically precede the clinical trial and specific safety studies can range from reproductive toxicity to neurotoxicity, depending on the nature of the animal drug. Generic animal drugs are evaluated with pharmacokinetic blood level bioequivalence studies in the target animal; when those are not possible or practical clinical bioequivalence studies may be needed.

The safety of residues in foods derived from treated animals is established by traditional repeat dose oral toxicity studies, typically in animals, to establish a human health protective value (usually an acceptable daily intake (ADI) or acute reference dose (ARfD). Studies in the target animal determine the nature, disposition, and depletion of drug in the edible tissues. The goal is to assure that the concentration of residues in the food resulting from that treated animal will not result in human consumer exposure that exceeds the ADI. Other studies can include comparative metabolism studies to assure that the residues in the edible tissue were evaluated in the toxicological studies, or studies to inform the risk of antimicrobial resistance, or to inform the potential exposure of the human gastrointestinal microbiome to antimicrobial residues. The latter may result in development of a microbiological ADI (mADI).

Animal studies may contribute information on the safety to the human user administering the animal drug or handling the treated animal and inform qualitative risk assessment for labeling.

Animal drugs pose some unique considerations for the development of microphysiological systems (MPS). Veterinary drugs are developed for multiple species (there are 7 major animal species) and multiple breeds (some 195 breeds of dogs; 44 breeds of cats), for homeotherms to poikilotherms, and for animals ranging in size from a 2 lb pheasant to a multi-ton elephant. Considering safety to the human consumer of food derived from treated animals, human toxicity data are limited, requiring extensive extrapolation from in-vitro, in-vivo, and in-silico models.

Given these considerations, it is important for the developer of MPS models to start with the goal in mind. What are the regulatory questions being asked? Is the target population the treated animal? The human consumer of animal derived food products? The veterinarian administering the drug? The human handling the treated animal? Will the model provide definitive data for a regulatory decision, or offer additional data to inform testing design?

Some areas of promise are models that inform adverse outcome pathways as well as those that develop information to address breed differences within a species. MPS models offer particular promise for insight on the impact of inflammation and disease on animal drug uptake, metabolism, and distribution. One area of unique potential is presented as an example.

There is a regulatory requirement to evaluate a human health protective value for residues of an antimicrobial veterinary drug in food based on the potential impact on the human gastrointestinal microbiome. An internationally harmonized approach developed under the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH GL36) currently recommends use of 10 bacterial species from 10 human subjects, using MIC data from traditional plate microbiology, or MIC and population data either from an in-vitro flask culture or from mice with ah humanized gut microbiome. FDA is currently collaborating with an industry partner to develop a model using a human intestine on a chip, incorporating a multispecies bacterial population. The goal is to provide a model more representative of the human gastrointestinal microbiome for the estimation of a mADI.

Looking at Microphysiological Systems through the One Health Lens.

Bernadette Dunham, D.V.M., Ph.D.

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The One Health concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals, and the environment. One Health defined, is a collaborative, multisectoral, and transdisciplinary approach - working at the local, regional, national, and global levels - with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment[1]. Microphysiological systems (MPS) technology, courtesy of tissue chips and organs-on-a-chip, is transforming the way diseases are studied in humans and animals; as well as enabling the safety/efficacy of human/animal pharmaceutical drugs to be evaluated,

thereby potentially reducing the use of animals in traditional disease models and toxicology studies. Moreover, MPS is opening up the window on how we study environmental toxins and their impact on human/animal/environmental health. However, validation of these alternative methods will be required for regulatory purposes, as well as for society to embrace the benefits of these scientific advancements. Innovative thinking, action, and productive collaborations across multiple disciplines exemplify the benefits of embracing a One Health approach to issues of mutual concern such as the exciting venues presented by the adoption of various MPS technologies. ([1]https://www.cdc.gov/onehealth/basics/index.html)

Pharma Perspective on Animal Microphysiological Systems

PJ Devine, Ph.D.

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The pharmaceutical industry discovers and develops safe and effective drugs that improve the health and wellbeing of patients. Following regulatory guidelines, compounds are typically evaluated in animals for safety, pharmacokinetics, and efficacy in improving disease conditions. High throughput *in vitro* models provide tools for early selection of potent compounds with few safety signals, although there are limitations to the information these models can provide. Increasingly, pharmaceutical companies are utilizing complex *in vitro* models to complement current *in vitro* and animal models. Microphysiological systems (MPS) may offer unique insights into drug efficacy and safety and could be more predictive of *in vivo* biology than simpler models. To that end, the MPS affiliate of the Innovation and Quality consortium of pharmaceutical companies is actively working towards influencing MPS development for drug discovery and development. This talk will provide an overview of current IQ MPS activities, including organotypic manuscripts, interactions with external partners, and cross-pharma collaborations. The IQ MPS affiliate supports the development and utilization of animal cell-based MPS in addition to human cell-based MPS, leveraging the greater amount of animal data available to advance MPS characterization and development. The IQ MPS hopes to use the growing field of MPS to improve the success rate of the pharmaceutical industry in developing useful drugs.

Microphysiological Systems: A cellular dilemma

E. Sidney Hunter, III, Ph.D.

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Recent advancements have increased the availability and diversity of differentiated cell types. This diversity continues to expand the breadth of organotypic and microphysiological system (MPS) models being developed and used to evaluate the biological effects of chemical exposure. The cellular dilemmas of determining the cell type requirements of each model must be resolved in order to understand the applicability of that model for hazard identification and safety assessments. Our laboratory has focused on establishing organotypic and MPS models of

the developing embryo in order to protect children's health by evaluating the effects of chemicals on potential chemical targets. We have established both static and dynamic three-dimensional models of the embryo-fetal neurovascular unit. This model uses neuroprogenitor cell proliferation and differentiation as critical endpoints for assessment. The blood-brain barrier function was established in both models, and selected test chemicals established that a functional chemical barrier was formed. Application of the model to understanding chemical effects on early neural developmental have raised question regarding species comparisons and extrapolations. Applying lesson learned from other MPS models, such as multi-species Liver-Chips, will advance further development of the neurovascular unit MPS. Solving the cellular dilemmas for each MPS is critical to establishing its applicability in assessing the effects of chemicals and xenobiotics. This is an abstract of a proposed presentation and does not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Development of Human, Rat and Dog Liver-Chips to facilitate safety assessment of candidate drugs

Lorna Ewart, Ph.D.

Executive Vice President, Scientific Liaison, Emulate Inc.

Development of new candidate drugs across all therapy areas are mandated to demonstrate their safety prior to first time in human administration. Typically, this involves testing in two animal species, a small animal such as a rat and a larger animal such as a dog. Integration of data from these studies, in addition to *in vitro* and *in silico* data leads to an assessment of risk to humans that may receive the candidate as part of a Phase I clinical trial. However, it has been widely documented that combined animal studies may not correctly identify up to 30% of new drug candidates that carry a safety liability thereby contributing to clinical stage attrition due to safety concerns. Organ-Chip technology offers a potential bridge between the preclinical and clinical phases of drug discovery and development. By faithfully recreating the microenvironment of a particular functional unit of an organ, the platforms create a "home away from home" for cells and enable them to behave as if they were *in vivo*. The data therefore offer increased translational confidence for clinical stage testing and should improve decision-making for progression of candidate drugs. In this presentation, I will share the development of human, rat and dog Liver-Chips and demonstrate how they can be used to detect species-differences for drug-induced liver injury which remains a major cause of attrition.