ALTERNATIVES
RESEARCH & DEVELOPMENT
FOUNDATION

2018 ARDF GRANT RECIPIENTS

Established in 1993, the ARDF has been a mainstay of support for developing alternatives to animal-based methods in science. Through grant programs, achievement awards, and sponsorship of scientific conferences, ARDF advances high quality scientific research that aims to replace and reduce the use of animals.

1 MARIOLA EDELMANN, PH.D. AND CARLOS RINALDI, PH.D.

University of Florida, Gainesville, FL

Use of novel magnetic aptamer-based nanoparticles with DNAse-sensitive labels for detection and capture of exosomes followed by omics-based analysis of exosome cargo relevant to inflammatory conditions

Exosomes are nano-sized vesicles, which are a source of disease biomarkers, have therapeutic potential, and facilitate cell-to-cell communication. Unfortunately, studies of exosomes are challenging due to limited availability of methods for their purification. We designed a novel method based on CD63-specific aptamer bound to nanoparticles, which provides an excellent alternative to commercially available antibody-based enrichment methods for exosomes. Use of aptabodies for organelle purification, such as exosomes, could reduce the in the use of antibodies with animal-origin. We will optimize this aptamer-based tool and use it to changes in study protein, lipid, and metabolic cargo of exosomes released from macrophages exposed to inflammatory conditions. We will map molecules present in these exosomes and focus on the protein networks and function of molecules. We will utilize bioinformatics to identify molecules governing such processes like apoptosis, pyroptosis, alteration of phagosome maturation, or small molecule biosynthesis. We will detect exosomal metabolites, including bioactive lipid mediators and eicosanoids, which are increasingly recognized to play roles in inflammation. In summary, this in vitro study will enable examination of vesicles controlling cell-to-cell communication between inflammatory and naïve phagocytes, providing a model of extracellular signaling via exosomes in inflammatory conditions.

2 GARGI GHOSH, PH.D.

University of Michigan, Dearborn, MI

Development of 3D printed model of breast cancer metastasis to bone for preclinical drug screening

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females worldwide. The survival rate is around 24% when the cancer spreads to distant organs including bone. Since metastasis remains largely incurable, there exists the need of identifying molecular mediators that play pivotal roles in the metastatic growth and exploiting them as novel therapeutic interventions. Identifying new therapeutic interventions and subsequent screening of drug candidates is essential for successful prevention of the growth of metastatic lesion. Lack of physiologically relevant in vitro models capable of high quality triage of experimental compounds results in utilization of large number of animals for drug evaluation. Proposed here is bioprinting of a 3D breast cancer bone metastasis model, which by virtue of recapitulation of physiologically relevant aspects and 48-well plate assay format, will permit discovery and high-throughput screening of new experimental compounds. Screening for only those compounds that displayed optimal efficacy in in vitro model to proceed to in vivo studies facilitate reducing the usage of animal models significantly. Although, the project involves developing a breast cancer metastasis model, the platform can be extended to other tumor types and thus will have wide application in pharmaceutical drug discovery.

3 HYUN JUNG KIM, PH.D.

University of Texas, Austin, TX

A pathomimetic human "colitis-on-a-chip" as an alternative to chemically induced mouse models of colitis

Mouse models of colonic inflammation (colitis) have been widely used to understand the pathogenesis of inflammatory bowel disease (IBD) in humans. However, mouse colitis models are resource intensive and ethically questionable. Due to the discrepancy with human, mouse colitis models often fail to predict the efficacy and toxicity of drug candidates. Furthermore, gut microbiome in mice is considerably different from human, which seriously hampers reliable and reproducible demonstration of human inflammatory pathophysiology. Hence, development of a human-relevant colitis model that contains patient-derived cells and gut microbiome is a critical unmet need. Here, we propose to develop a human colitis-on-a-chip (Colitis Chip) by leveraging a microphysiological system to reconstitute three-dimensional (3D) lumencapillary tissue interface under mechanically dynamic bowel movement. We integrate 3D organoid culture models in the Colitis Chip to recreate a patient-specific intestinal epithelial barrier on-chip. The histo-pathophysiology of dextran sodium sulfate (DSS)-induced colitis in mice will be reproduced in the presence of gut microbiome, by which barrier dysfunction and inflammatory responses will be demonstrated. Finally, we will validate the Colitis Chip by testing beneficial probiotic therapy. We envision that our novel Colitis Chip can potentially replace mouse models for testing anti-inflammatory drugs and understanding the mechanism of IBD.

4 GRETCHEN MAHLER, PH.D.

Binghamton University, Binghamton, NY

Engineering a kidney glomerulus and proximal tubule on a chip

The kidneys are responsible for blood filtration, osmoregulation and reuptake, and receive ~25% of cardiac output. This highlights the importance of understanding interactions between the kidneys and new drug candidates. Preclinical studies using static human cell cultures lack the stimuli and tissue architecture found in vivo. The value of animal studies in predicting drug efficacy remains questionable and ethically challenging. Organ on a chip systems may provide a better prediction of human response to new drugs and reduce or eliminate in vivo animal studies. Our group has developed a microfluidic device that allows for a close approximation of the in vivo renal environment and provides an accurate, low-cost platform for testing new drug candidates, but cannot be run for long term trials. The research goal is to create a physiologically realistic in vitro model of the proximal tubule and glomerulus that features crossflow filtration and is capable of long term (seven days) operation. We will fully characterize human cell behavior within the device, including viability, function, and gene and toxicity biomarker expression. If successful, this device could reduce animal use in biomedical research and toxicology and provide a more effective method for investigating novel disease treatments.

5 LAWRENCE VERNETTI, PH.D.

University of Pittsburgh, Pittsburgh, PA

Development of an in vitro human bile duct-liver biomimetic of liver cholestasis

The bile duct is the conduit for the bile acids synthesized in the liver to empty into the intestine as an aid to the digestion and uptake of dietary fats. A third of all adult and more than 70% of pediatric liver transplantations are due to bile duct diseases including liver cholestasis. We have developed a 3D in vitro, microfluidic model of the bile duct using human cholangiocytes, the liver cell type that forms the intrahepatic bile duct. Bile duct functionality was established by tracking the uptake and elimination of a fluorescent bile acid analog through human hepatocytes into a synthetic bile media. We propose to establish a model of liver cholestasis by: a) combining the bile duct into an established liver biomimetic; b) demonstrating function by tracking bile and systemically cleared drugs and bile acids; c) establishing cholestasis by restricting the bile flow to mimic an extrahepatic obstruction with expectation this will lead to damaged hepatocytes and liver injury. Once completed, the bile duct-liver biomimetic would be used for the basic study of bile duct disease initiation and progression and as a platform technology for drug development.

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