Tufts | CTSI

Tufts Clinical and Translational Science Institute

2023 Team Science Summit

Advances, Applications, and Future Directions in Disease Models

Friday, October 27
9:00 am – 2:15 pm

9:00 am WELCOME

Opening Remarks: Harry P. Selker, MD, MSPH, Dean, Tufts Clinical and Translational Science Institute

9:10 am Session 1: *IN VITRO ADVANCES*

Chair/Moderator: David Kaplan, PhD, Tufts University School of Engineering

Tania Konry, PhD, Northeastern University Bové College of Health Sciences
Development of Integrated Platform of Lymphocyte Phenotyping, and Immunotherapy Validation in Single Cell and 3D Droplet Microfluidic Systems

Nisa Iyer, PhD, Tufts University School of Engineering
Biomanufacturing Spinal Diversity with Human Pluripotent Stem Cells

Nervous system diversity comes from coordinated patterning events during development that define thousands of subtypes, which in turn self-organize into precise neural circuits that shape nuanced behaviors. We are working to recapitulate this diversity with human pluripotent stem cells (hPSCs) to better understand human spinal development, create more accurate in vitro models, and develop therapies for regenerative medicine. Here I will discuss the development of protocols can be used modularly to differentiate spinal phenotypes from different anatomical levels spanning the hindbrain through lumbar spinal cord, and how this cellular toolbox fills needs in both basic and translational research as we move towards a region-specific approach to tissue engineering and personalized cell therapies.

Lauren Black, PhD, Tufts University School of Engineering
Increasing complexity and biological relevance with in vitro models of myocardial infarction

In this talk I will be discussing the importance of biologically relevant models of heart diseases to both aid in the development of new therapeutics and also gain a more mechanistic understanding of disease progression and the many factors involved in it. I will start by introducing a relatively simplistic 2-D model system that my lab has previously developed and demonstrate that while increasing the model complexity increases the biological relevance of the model and its potential impact, it also leads to more significant challenges in implementation that need to be overcome.

Ying Chen, PhD, Tufts University School of Engineering
3D Bioengineered In Vitro Model of Functional Human Intestine

There is a need for 3D in vitro human intestine models to transition from regular cell culture to human trials. In this talk, I will highlight our team's work using silk as a scaffold, combining it with human intestinal cells, to create lab-engineered intestines for various applications.

Vicky Yang, PhD, Tufts University Cummings School of Veterinary Medicine *and*
Howard Chen, PhD, Tufts Medical Center

Novel cardiac slice culture system using canine and rodent hearts

Chemotherapy-induced impairment of autophagy is implicated in cardiac toxicity. We optimized an adult heart tissue culture technique using canine and mouse cardiac slices to explore the impact of cancer therapy on intact cardiac tissue. This novel cardiac slice culture overcomes the difficulties in culturing adult cardiomyocytes and creates a translatable model that maintains autophagy in culture and is amenable to autophagy modulation

Juan Gnecco, PhD, Tufts University School of Engineering

Tissue engineering endometrial organoid models to dissect reproductive health and disease

The endometrium is a paradigm for regenerative and dynamic biology, yet our understanding of the mechanisms regulating tissue function remain elusive. The Gnecco Lab uses 3D tissue imaging and organoid systems, miniature tissue-like constructs, coupled with synthetic biomaterials to study the role of the tissue microenvironment in reproductive function. We show how these platforms can help to understand the biomechanic and inflammatory origins of endometriotic disease.

Marly Coe, Tufts University School of Engineering

Studying Traumatic Brain Injury Using a Bioengineered 3D Human Brain-like Tissue Model

The inaccessibility of living human brain tissue has led to a reliance on animal models that do not always accurately recapitulate human neuropathologies, limiting their clinical translatability. Our lab has developed a 3D human “triculture” brain model comprised of human neurons, astrocytes, and microglia in a silk-collagen composite scaffold, which can withstand physiologically relevant impact injury. Here we will describe recent applications of our 3D in vitro brain-like tissues as a platform for the study of molecular mechanisms following traumatic brain injury in humans, including metabolic dysregulation, viral re-activation, neurodegeneration and regeneration.

10:35 am **BREAK**

10:40 am **Session 2: *CUTTING EDGE APPROACHES USING ESTABLISHED AND ALTERNATIVE IN VIVO MODELS***

Chairs/Moderators: **Gregory Cox, PhD, The Jackson Laboratory**
Cheryl London, DVM, PhD, Tufts Cummings School

Jennifer SanMiguel, PhD, The Jackson Laboratory

Rare Disease Modeling and Preclinical Testing at The Jackson Laboratory Rare Disease Translational Center

I will be presenting an overview of the goals and capabilities of the Jackson Laboratory Rare Disease Translational Center, including genetically engineered mouse modeling and preclinical testing. I will also share two high level examples of current studies to highlight our process and discuss how to work with our center.

Anuj Srivastava, PhD, The Jackson Laboratory

Patient-Derived Xenograft (PDX): A Valuable Tool for Preclinical Cancer Research

I will be providing a short description of efforts to establish robustness and standards in Patient-Derived Xenograft experiments and analysis, followed by a brief update on two consortia focused on PDX research and resource development. Finally, I will describe examples of PDX studies identifying potential drug candidates.

Andrea Varela-Stokes, DVM, PhD, Tufts University Cummings School of Veterinary Medicine

Re-envisioning the guinea pig model to clarify spotted fever rickettsiosis

Compared to mice, guinea pigs have an immune system more like humans, their size is large enough for collecting multiple and various antemortem samples in longitudinal studies, and there is added value from their easy handling. Our lab uses the guinea pig- tick-spotted fever group Rickettsia system to address the limitations of mice as a translational model for human spotted fever rickettsiosis. As a foundation for future mechanistic studies, we are developing immunological and other assays for the guinea pig model to evaluate local and system immune responses after natural tick transmission.

Pam Yelick, PhD, Tufts University School of Dental Medicine

Zebrafish and teeth as tools for disease discovery and therapeutics

Zebrafish are an excellent vertebrate animal model to study human development and disease based on their highly conserved nucleotide and amino acid sequence, and gene function. I will introduce a number of zebrafish mutants identified in a forward genetic mutagenesis screen that have identified novel genes regulating human craniomaxillofacial and skeletal development and disease. I will also describe how dental stem cells, isolated from healthy and diseased individuals, can be used to guide the design of improved diagnostic and treatment therapies.

Daniel Promislow, PhD, University of Washington School of Medicine

Dogs, Disease, Data

The Dog Aging Project is a nationwide longitudinal study of aging in tens of thousands of companion dogs. This brief presentation will illustrate the potential of this study to use AI/ML and systems biological approaches to help us better understand the causes, progression and consequences of age-related disease.

Heather Gardner, DVM, PhD, Tufts University Cummings School of Veterinary Medicine

Leveraging dynamic changes in the multiome to improve accuracy of liquid biopsy in cancer

Katherine Megquier, PhD, The Broad Institute

Optimizing blood biopsy in the canine cancer model

Blood biopsy enables noninvasive quantification and sequencing of cell-free tumor DNA (ctDNA) present in the bloodstream. This technique has the potential to improve clinical cancer diagnostics and patient monitoring. I will present data on the use of this technique in dogs with spontaneous cancers for longitudinal assessment of patient response to therapy, as a diagnostic tool, and to assess the effect of preanalytical variables such as time of day and blood draw site on ctDNA yield.

Kelly Metcalf Pate, DVM, PhD, Massachusetts Institute of Technology

A Trained Monkey Could Do This: Refining How We Work With Animals Towards Improving Translational Value"

No animal model can perfectly model human disease. Dr. Metcalf Pate's work seeks to refine the way we work with animals in infectious disease research to increase their translational value, while simultaneously improving animal welfare.

12:15 am **LUNCH BREAK**

12:45 pm **Session 3:** ***NEW TOOLS FOR OVERCOMING DISEASE MODELING CHALLENGES***

Chair/Moderator: **Bree Aldridge, PhD, Tufts University School of Medicine**

Vivek Kumar, PhD, The Jackson Laboratory
The JAX Digital In Vivo Initiative for scalable advanced mouse phenotyping

Ayan Paul, PhD, Northeastern University College of Engineering
Mechanistic Modeling of RNA Binding Proteins Regulating Alternative Splicing

Alternative splicing is a fundamental feature of eukaryotic organisms, and genetic variation that causes pathologic splicing is an important cause of human diseases. The role of alternative splicing in driving proteome diversity is well established but the complex regulatory logic by which RNA Binding Proteins (RBP) regulate alternative splicing is not well understood. Detailed mechanistic models of how RBPs regulate alternative splicing can lead to a better understanding of the biology of splicing and identify opportunities for therapeutic interventions that can correct aberrant, disease-causing splicing. We combine eCLIP and RNA-seq data from ENCORE (ENCODE) along with GENCODE annotations to build graphs representing individual splicing events and show how RBP cooperativity can be assessed and pave a path towards building interpretable machine learning models to understand the regulation of alternative splicing by RBPs

Samia Ali, Tufts University School of Medicine
Single Nuclei RNA Sequencing Analysis of mybpc-3-associated HCM to identify common pathological mechanisms in Human, Feline, and Murine Hearts

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiovascular disease characterized by unexplained hypertrophy, often associated with left ventricular outflow tract (LVOT) obstruction, ventricular tachyarrhythmias, diastolic heart failure, and sudden cardiac death. Mutations in mybpc3 are the most common genetic mutations associated with human and feline HCM. To understand how mutations in mybc3 causing sarcomere dysfunction result in the development of non-myocyte phenotypes such as fibrosis, mitral valve anomalies, and microvascular occlusion across species, we generated single nuclei RNA-sequencing datasets from feline, human and murine heart tissue carrying mybpc3 variants. Thus, identifying common and species-specific disease-promoting pathways in HCM tissue that will allow identification of conserved disease mechanisms that may be targeted in both human and feline disease and will facilitate an understanding of the relevance of mouse models.

Sheng Li, PhD, The Jackson Laboratory
Spatial and temporal multi-omics phenotyping of cancer evolution in an aged ecosystem

Cancer is a disease of aging, with its evolution resulting from selection acting on cell-to-cell genetic and epigenetic heterogeneity over time. Through spatial and temporal multi-omic phenotyping of cancer evolution in an aged ecosystem, we are unifying the guiding principles to study aging and cancer initiation, linking across disciplines, laying the foundation for developing 'evolution-blocking' strategies to prevent cancer in global high-risk aging populations.

Amanda Martinot, DVM, MPH, PhD, Tufts University Cummings School of Veterinary Medicine
Searching for Suppression: using spatial biology to understand Tuberculosis pathology

Peter Robinson, MD, MSc, The Jackson Laboratory
HPO, GA4GH Phenopackets, and OMOP to study mental health and disease in EHR

Joseph Gormley, Tufts CTSI

Computational Methods to Increase Information Yield and Guide Laboratory Experiments

Effective integration of machine learning, predictive analytics and biochemical informatics is the new frontier in life science and healthcare modeling and analysis. This presentation will demonstrate the Tap Discovery Platform and workflow in support of biomarker discovery and drug development.

2:15 pm **CLOSE**