The Duchossois Family Institute

"Harnessing the Microbiome and Immunity for Human Health"

INVESTIGATIVE TEAMS, GOALS, AND DIRECTIONS

2022

A Note from the Institute Director

The Duchossois Family Institute was established in 2017 with the goal of enhancing human health by investigating the microbiome and its impact on the immune system. Humans are colonized by a vast array of microorganisms, including viruses, bacteria, and fungi, but our understanding of these complex microbial populations and their impact on health and disease has, until recently, been limited. Interest in this topic is not new to the University of Chicago. In the 1950s, researchers Marjorie Bohnhoff and C. Phillip Miller demonstrated that innocuous bacterial populations residing in the gut provide resistance against intestinal pathogens such as Salmonella. Technical, bioinformatic, and computational advances have led to amazing strides in our understanding of the microbes colonizing the skin, mouth, vagina, and intestines of humans and other mammals. Clinical studies have correlated the microbiome with human diseases and disease resistance. In 2022, it is fair to say we know a lot about the bacteria that colonize humans and we continue to learn about the metabolites they produce. Still, much remains to be discovered about the interactions between bacteria within these populations and their diversity.

DFI investigators Laurie Comstock, Sam Light, and Arjun Raman are conducting experimental studies to learn how commensal bacteria both compete and cooperate in tight spaces, such as the human intestine, how they break down complex molecules to generate energy and metabolites beneficial to the host, and how we can use bioinformatic and statistical tools to design bacterial populations or consortia for therapeutic purposes. Molecular engineers like Mark Mimee in UChicago's Department of Microbiology, are developing genetic tools to modify commensal bacterial species while microbial geneticists, such as Sampriti Mukherjee in the Department of Genetics and Cell Biology, are identifying and characterizing molecular mechanisms by which bacteria communicate.

While the microbiome field continues to spin off discoveries that impact human health, the major challenge is translating these discoveries into therapies that will enhance the health of individuals and human populations. Clinical studies at the University of Chicago have demonstrated that patients undergoing organ transplantation, patients with severe liver disease, and patients requiring intensive care hospitalization often have highly abnormal microbiome compositions. With the goal of optimizing microbiomes, the DFI has positioned itself to translate scientific advances into clinical therapies by establishing a current Good Manufacturing Practices (cGMP) facility, enabling the manufacture of specific commensal bacterial populations for clinical trials at the University of Chicago Medical Center. We are excited that the DFI and its cGMP facility will enable novel and groundbreaking clinical trials that will move the academic microbiome field from an investigational/descriptive posture into an interventional/therapeutic position.

Eric G. Pamer, MD
Director

Laurie Comstock, PhD
Professor, Department of Microbiology

The Comstock lab studies bacteria of the order Bacteroidales, which are abundant bacterial members of the human gut microbiota. Studies in the lab focus on understanding how these bacteria interact with each other both cooperatively and antagonistically to form health-promoting microbial communities. The lab uses basic microbiological, genetic, biochemical, and gnotobiotic mouse analyses, combined with genomic, metagenomic, and computational analyses to understand these complex interactions. They have discovered several classes of new antimicrobial proteins that these bacteria use to compete in their ecosystem, and are studying their mechanisms of action, ecological properties, and how those molecules can be translated for human health benefits. Another focus of the Comstock lab is the evolution of microbes in the human gut and how genetic elements horizontally transferred between bacterial species personalize each individual's gut microbiota and the phenotypes and community benefits conferred by these shared genetic elements.
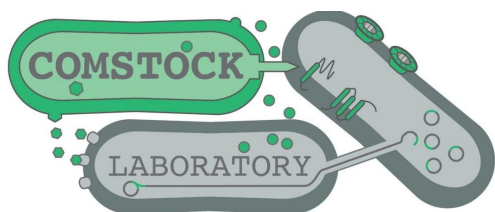
Sam Light, PhD
## Assistant Professor, Department of Microbiology

We are currently limited in our understanding of the ecological strategies by which diverse microbes colonize the gut microbiome. With the goal of establishing context to inform the interpretation and manipulation of microbiome states, the lab's research is focused on defining the microbes and/or genes that enable colonization of distinct ecological niches within the gut. Current projects primarily focus on elucidating the basis of metabolic specialization within the gut microbiome and take three separate approaches: (1) As part of an unbiased discovery approach, the lab is performing high-throughput microbial enrichments to elucidate novel modes of metabolic specialization. (2) As part of a bioinformatically driven approach, they are applying genome mining-based analyses to evaluate the distribution of broad enzyme classes and to generate testable hypotheses about the microbes responsible for particular types of metabolic specialization. (3) As a final metabolite-inspired approach, the lab is working backwards from biomedically relevant metabolites to identify the microbes and energy metabolisms that produce them.
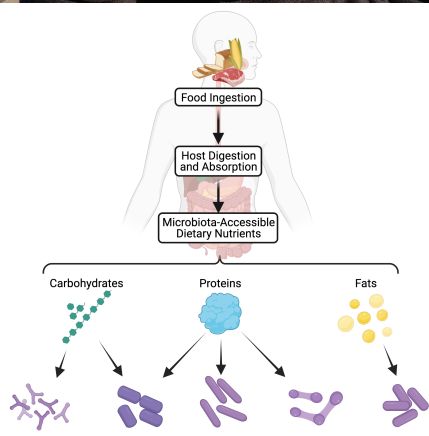
Mark Mimee, PhD
Assistant Professor, Department of Microbiology
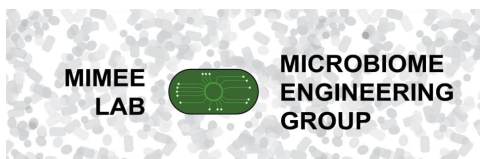
The Mimee Lab leverages synthetic biology to engineer the microbiome, exploring strategies to modify commensal bacteria and bacteriophage for diagnostic and therapeutic applications. By genetically manipulating commensal microbes, they seek to create living devices that can serve as biosensors to probe the structure and function of the microbiome and as cell-based therapeutics for infectious and inflammatory disease. Additionally, they develop approaches to augment the natural properties of viruses that infect bacteria, called bacteriophage, to create novel therapies for antibiotic-resistant bacterial infections. Mimee's long-term vision is to implement these synthetic biology technologies to chart new basic and translational studies to exploit the microbiota for human health.

MIMEE LAB — MICROBIOME ENGINEERING GROUP

Sampriti Mukherjee, PhD
Assistant Professor, Department of Molecular Genetics & Cell Biology
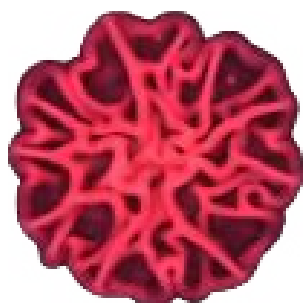
Bacterial responses to self-generated and environmental stimuli influence their survival, persistence in particular niches, and lifestyle transitions between individual and collective behaviors. How the information encoded in multiple sensory inputs is extracted and integrated to control collective behaviors is largely mysterious. To address this knowledge gap, the Mukherjee lab focuses on two research areas: 1. Photo sensory signal transduction. Although light is a ubiquitous environmental stimulus and photoreceptors have been well-studied in the context of photosynthetic organisms, the function of photosystems in non-photosynthetic bacteria are mostly unknown. They have identified an entire photo-sensing cascade in the human pathogen Pseudomonas aeruginosa — enabling crucial insight into light-driven control of bacterial behaviors relevant to human disease. The lab is characterizing the photo-sensing signaling system, defining the physiological role of light, and exploring the possibility of using light as an antibacterial therapeutic. 2. Convergence of sensory signaling pathways. It is imperative that bacteria integrate varied sensory cues to make key behavioral transitions; however, the mechanisms by which they do so are poorly understood. Mukherjee's goal is to identify the molecular mechanisms by which information from different sensory signaling pathways are combined in the control of bacterial behaviors. She and her lab are currently studying how photo-sensing, quorum-sensing, and nutrient-sensing cues are integrated into the regulation of collective behaviors.

Eric Pamer, MD
Professor, Department of Medicine

The Eric Pamer laboratory studies interactions between pathogenic and beneficial bacteria and their mammalian hosts. His laboratory's research focuses on a wide range of commensal bacteria that have been characterized at the genomic, proteomic and metabolomic level and they are using gnotobiotic mice to test assembled commensal consortia for their ability to enhance resistance against pathogenic bacteria. Using these platforms, they have identified mechanisms of antimicrobial resistance that can be exploited to reduce the risk of infection by highly antibiotic-resistant pathogens.

Arjun Raman, MD, PhD
Assistant Professor, Department of Pathology
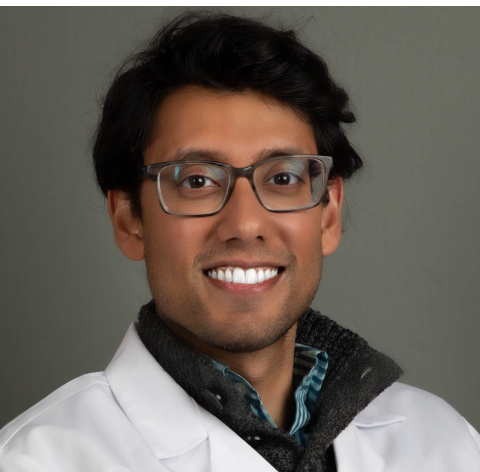
Understanding engineered systems comprised of many parts is predicated on robust physics-based theories. Understanding natural systems is challenging because such systems have come from a completely different design process—iterative variation and selection. Thus, we do not have access to a 'wiring diagram' of biological systems. The Raman laboratory is focused on two questions: (1) What is a strategy for inferring the architecture of interactions for evolved systems? (2) Why is the architecture the way it is? Using bacteria as a model, the lab has shown that hierarchical patterns of protein interactions, i.e. the emergence of pathways from individual proteins, can be derived purely from the statistics of evolutionary variation.

Ongoing work in the laboratory is comprised of three directions. First, how general is their strategy? With ever-increasing high content biological data, the generality of their statistical approach across different systems can be tested. Second, what influences the pattern of interactions defining an evolved system? As evolved systems interact with the environment, they are testing whether environmental structure may drive system structure. Finally, can statistical variance enable the creation of synthetic systems? Raman's lab is using statistical potentials derived from their approach to create complex consortia of bacteria designed to perform specific functions.
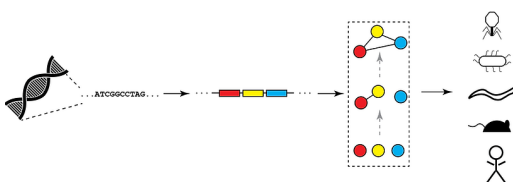
DFI Employees

Host Microbiome Metabolomics Facility

Ashley Sidebottom, PhD
Director

Jessica Cleary, PhD
Senior Staff Scientist

Michael Mullowney, PhD
Senior Staff Scientist

David Moran
Research Core Team Lead

William Leiter
Senior Research Technician

Mary McMillin
Senior Research Technician

Amber Rose
Research Technician

Host Microbiome Metagenomics Facility

Anitha Sundararajan, PhD
Director

Rita Smith
Senior Research Technician

Ashish Yalavarthi
Senior Research Technician

Victoria Burgo
Research Technician

Carolyn Metcalfe
Research Technician

Che Woodson
Research Technician

Symbiotic Strain Bank

Bidisha Barat, PhD
Director

Emily Waligurski
Research Specialist

Steven Medina
Research Technician

Jake Mostad
Research Technician

Lauren Paddock
Research Technician

Bioinformatics

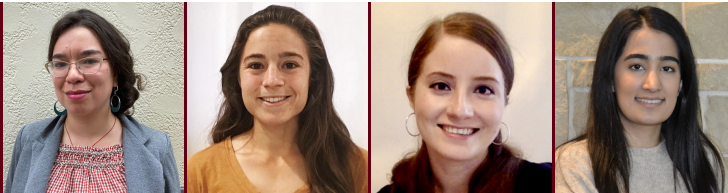Mark D'Souza
Bioinformatic Specialist

Nicholas Dylla
Bioinformatic Specialist

Huaiying (Eddi) Lin
Bioinformatic Specialist

Ramanujam Ramaswamy
Bioinformatician

Dinanth Sulakhe
Bioinformatic Specialist

Clinical Research

Emerald Adler
Manager

Jaye Boisierre
Coordinator

Jackelyn Cantoral
Coordinator

Maryam Khalid
Coordinator

Administrative & Support

Ingrid Leiner
Center Manager

Noreen Bentley
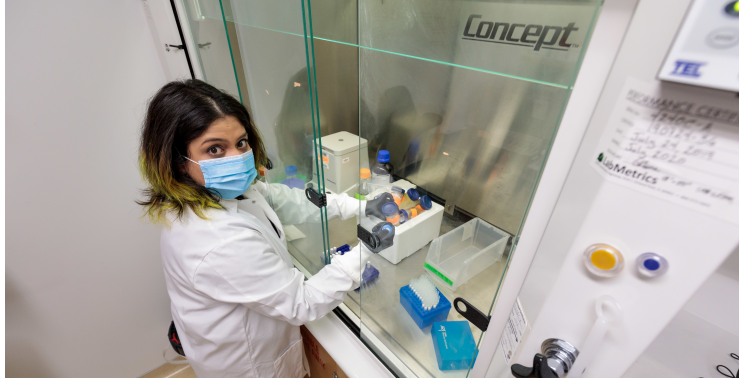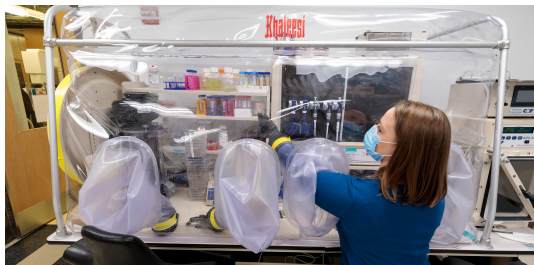Administrative Assistant
to Dr. Eric Pamer

Aubrey Nielsen
Administrative Coordinator

Lorena Marmolejo
Technical Research Assistant

DISSEMINATION, COMMERCIALIZATION, AND SUSTAINABILITY

Ken Onishi, PhD
Associate Manager for
Business Development-
Microbiome

DFI Research Platforms

Microbiome Metagenomics

The DFI Microbiome Metagenomics Facility (MMF) provides bacterial 16S ribosomal RNA gene and shotgun metagenomic sequence analyses on intestinal contents and other samples containing complex microbial populations. The MMF works with investigators to analyze microbiota sequence data from experimental and clinical samples. Analysis tools are available to classify bacterial sequences down to the genus level (and to the species level when possible) to determine both community membership and structure.

Host-Microbe Metabolomics

The DFI's Host-Microbe Metabolomics Facility (HMMF) provides resources to measure, characterize, and identify the metabolites produced or modified by microbes to better understand how these molecules function in microbe-microbe and host-microbe interactions/communication and how these processes influence human health and disease. The HMMF uses mass spectrometry to test each sample for 200 different metabolites, a number that will increase as more metabolites are identified.

Bioinformatics

Supporting the MMF and HMMF are a team of bioinformaticians who provide comprehensive computational data analyses, including genome assembly and annotation, using computation software programs to analyze microbial genome sequences and characterize their metabolite utilization and secretion to better understand how commensal bacteria impact human health.

Symbiotic Strain Bank

The Symbiotic Bacterial Strain Bank contains more than 2000 bacterial strains, isolated from healthy human fecal donors, that have been anaerobically cultured and characterized and are available to the research community.

Clinical Research Studies

The DFI's Clinical Research Support Team supports our ongoing clinical studies by obtaining patient consent, collecting samples and preparing them for analysis, and assisting in the development and design of projects.

Dissemination, Commercialization, & Stability

The DFI and Polsky Center recruited Ken Onishi to work exclusively with DFI faculty members to build partnerships with companies and to help researchers transform their ideas and discoveries into intellectual property licenses, services, and startups.

DFI Multidisciplinary Grants Awarded

The goal of the DFI Multidisciplinary Research Grant is to facilitate productive research collaborations between clinical investigators studying patients in whom the microbiome and immune system are contributing to disease states and laboratory investigators focusing on mechanisms of immune and microbiome-mediated disease resistance. Grantees are awarded up to $250,000 per project.
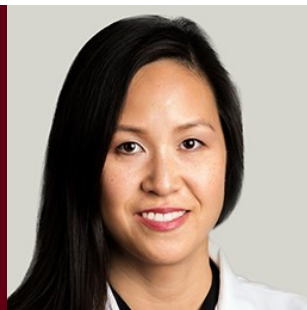
2022 Awardees

Project Title:

"Metabolomic Profiling as a Marker for Rejection in Heart Transplantation"

Maria-Luisa Alegre, MD, PhD
Professor
Department of Medicine
Section of Rheumatology

Ann Nguyen, MD
Assistant Professor
Department of Medicine
Section of Cardiology

Bohdan Khomtchouk, PhD
Pathways to Independent Instructor
Department of Medicine
Section of Computational Biomedicine
and Biomedical Data Science

Project Title:

"Human Mucosal Lymph Node Compartments as Local Responders to the Microbiome"

Daria Esterhazy, PhD
Assistant Professor
Department of Pathology

Maria Lucia Madariaga, MD
Assistant Professor
Department of Surgery

Project Title:

"Understanding the Relationship of Gut Microbiome and Immune Response in Critically Ill Patients"

Savas Tay, PhD
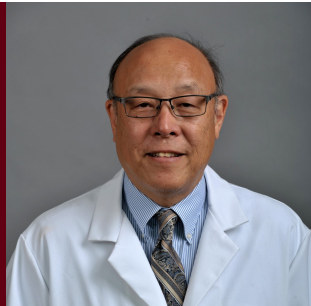Professor
Department of Molecular
Engineering

Krysta Wolfe, MD
Assistant Professor
Department of Medicine
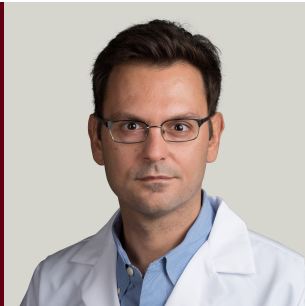Section of Pulmonary and
Critical Care

2021 Awardees

Project Title:

"Gut Dysbiosis After Acute Brain Injury: Profiling and Associations with Clinical Trajectories and Neurologic Outcomes"

Eugene Chang, MD
Professor
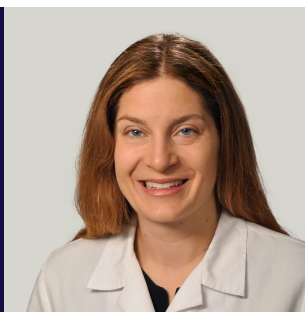Department of Medicine
Section of Gastroenterology

Christos Lazaridis, MD
Associate Professor
Department of Neurology

Project Title:

"The Effect of Fiber Supplementation on Oral Immunotherapy Outcomes in Children with Peanut Allergy"

Cathryn Nagler, PhD
Professor
Department of Pathology

Christina Ciaccio, MD
Associate Professor
Department of Pediatrics
Section of Allergy & Immunology

Project Title:

"Gut Microbiota-Mediated Modulation of Abeta Deposition and Microglial Phenotypes in Mouse Models"

Sangram Sisodia, PhD
Professor
Department of Neurobiology

James Mastrianni, MD, PhD
Professor
Department of Neurology

DFI Fellowship Grant

The DFI Fellowship Grant, awarded in 2021, was limited to clinical fellows focusing on the impact of the microbiome and/or the immune system on clinical outcomes in patients receiving care at the University of Chicago. The award totaled $125,000.

Recipient

Project Title:

"Understanding Microbial Factors that Influence CD4+FOXP3+IL17+ T-cells and Their Role in Tumorigenesis in Primary Sclerosing Cholangitis"

Ariel Stromberg, MD

Chicago Scholars Fellowship

The Chicago Scholars Fellowship Grant, awarded to post-doctoral researchers, funds 2 years of salary plus $10,000 per year for research.

2022-2024

Project Title:

"Identifying Essential Colonization Factors for Anti-Inflammatory Clostridial Members of the Gut Microbiota"

Deepti Sharan, PhD

2021-2023

Project Title:

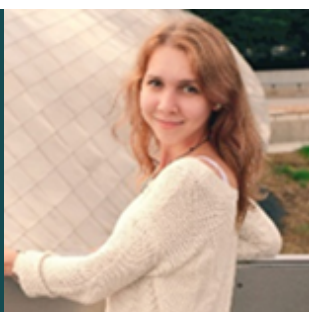"Role of Innate and Adaptive Immune Mechanisms in Shaping Intestinal Microbiota"
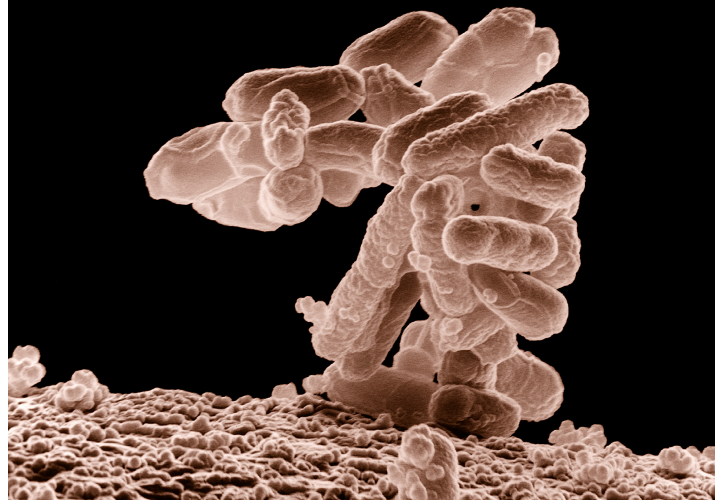
Helen Beilinson, PhD

2020-2022

Project Title:

"The Role of Lymph Node Macrophages in Sensing the Local Gut Milieu"

Aliia Fatkhullina, PhD

Clinical Research Studies

Heart Transplant

For heart transplant patients, one of the most common complications is cardiac allograft vasculopathy (CAV). In CAV, fibers grow down the inside of the cardiac artery wall, thickening the vessels. Transplant specialists like Ann Nguyen, MD, suspected that CAV results from an attack not by the body's immune cells, but by immune proteins - antibodies - circulating in the blood. The presence of those antibodies can increase the odds of a failed heart graft fivefold. Nguyen and cardiology fellow Mark Dela Cruz, MD, are interested in understanding how a patient's individual microbiome might affect the production of donor-specific antibodies and the outcomes patients experience after heart transplants.

Working with the DFI, they designed an observational clinical study that monitors patients' stool samples before and for months after heart transplant. The stool samples enable the DFI team to assess the patient's microbiome before surgery and track any changes after transplant. They will correlate what they learn about each patient's microbiome with the progress of the cardiac transplant for at least the first two years after the patient's surgery.

Liver Transplant

Aalok Kacha, MD, PhD, Associate Professor of Anesthesia and Critical Care, and Christopher Lehmann, MD, Adult and Pediatric Infectious Disease Fellow are spearheading an investigation into the impact of microbiome composition on liver function and metabolism following transplantation. End-stage liver disease patients who are chronically ill have often been treated with multiple antibiotics pre-transplant, wreaking havoc on their microbiome. In conjunction with the DFI, they look at the patient's microbiome before, during, and after the transplant, hoping to correlate complications with changes in the microbiome.

Intensive Care Unit

Patients admitted to the ICU have a wide range of microbiome composition: some are normal, while others have been devastated by antibiotics and sedation. Just how imbalanced microbiomes affect long-term outcomes is unclear.

John Kress, MD, Director of the University of Chicago Medicine's medical intensive care unit, and fellow Matthew Stutz, MD, have partnered with the DFI to study the microbiomes of patients in sepsis or respiratory failure. Through the study, patients' stool samples are collected throughout their stay. The samples are analyzed for their diversity and their metabolomic profile, with the hopes of understanding whether any particular microbe is associated with mortality or readmission to the ICU.

Many ICU patients suffer from physical, emotional and cognitive dysfunction long after leaving the ICU, and the researchers hope to find a correlation to outcomes in the microbiome.

Good Manufacturing Practice Facility

Baback Kohanpour, MSEE
Director

The 4,978 square foot Duchossois Family Institute GMP facility will be open by the end of 2022. Located on the 6th floor of the University of Chicago Hospital Rubloff building, the facility will have the capacity to produce anaerobic bacteria, enabling the manufacturing of live biotherapeutics by culturing and preparing symbiotic bacterial strains FDA approved for clinical trials.
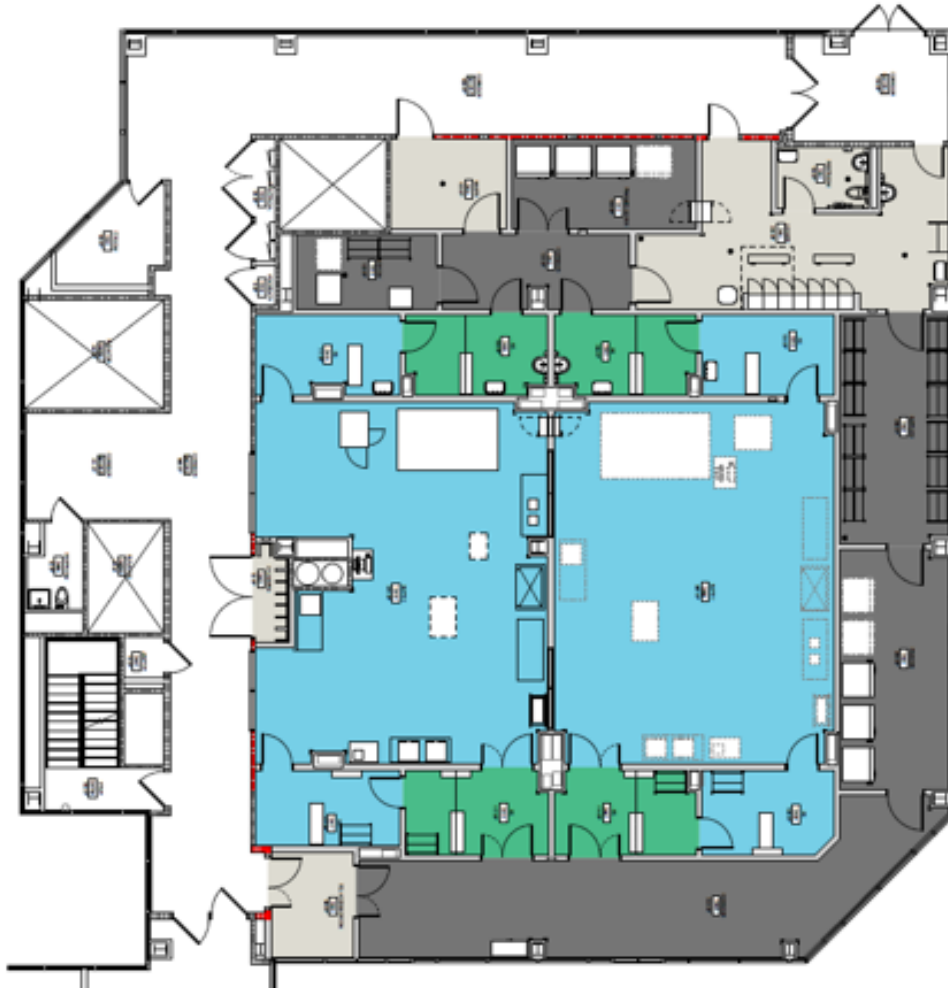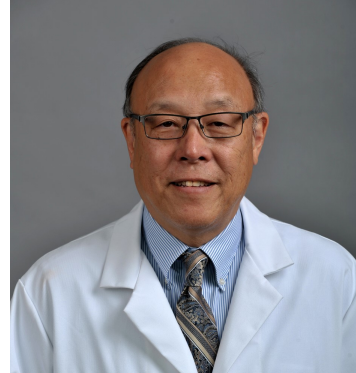
DFI Advisory Boards
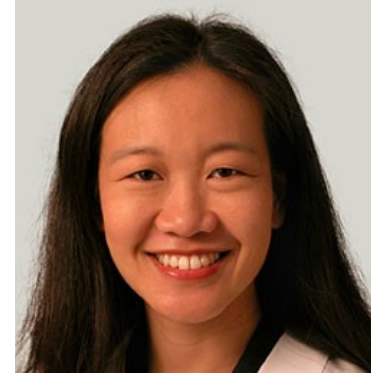
Internal Advisory Board

Eric G. Pamer, MD
Director

John Alverdy, MD
Department of Surgery

Eugene Chang, MD
Department of Medicine

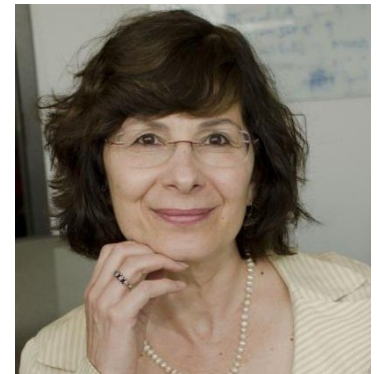Erika Claud, MD
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Thomas Gajewski, MD, PhD
Department of Pathology

T. Conrad Gilliam, PhD
Dean for Basic Science

Tatyana Golovkina, PhD
Department of Microbiology

Bana Jabri, MD, PhD
Department of Medicine

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Stanford University

Julie Segre, PhD
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National Institutes of Health

Jeffrey Gordon, MD
Professor
Washington University
in St. Louis

2022