**Epicutaneous Tolerance: A Novel Treatment for Inflammatory Bowel Diseases**

Crohn’s disease (CD) and ulcerative colitis are collectively known as inflammatory bowel disease (IBD). The incidence of CD in both adults and children has increased in the past 60 years, especially in adolescents and children under 10 years of age. CD is believed to result from a failure to develop tolerance to normal gut bacteria in genetically predisposed individuals. Treatment depends on the use of therapies that suppress aspects of the immune system including: glucocorticoids, immune-suppressants, tumor necrosis factor antagonists, integrin inhibitors and, more recently, antibody to interleukin 12/23. The drawbacks of these agents include an increased risk of infection and cancer and limited efficacy. Resistance or intolerance to treatment is also common, with up to 18% of children requiring surgery within 5 years from disease onset. As a result, there is an urgent need to develop new therapies with different mechanisms of action.

Under normal conditions, tolerance to food and microbiota is actively mediated by regulatory T-cells. Immune tolerance has been investigated as a treatment for autoimmune diseases such as rheumatoid arthritis, diabetes and demyelinating neuropathies by inducing antigen-specific regulatory T-cells to control inflammation. Regulatory T-cells specific to bystander antigens can also suppress inflammation. This is useful when the triggering antigen is unknown, as is the case with CD. Studies utilizing oral tolerance induction in rodent models of colitis have shown some success in ameliorating disease. However, one rodent study failed to show induction of oral tolerance but demonstrated that nasal tolerance induction was more efficacious for treating colitis. Despite the efficacy shown in murine studies, oral tolerance is unlikely to work in humans given that patients with CD have an inherent defect in the ability to form tolerance via the gut. Thus, alternative routes of tolerance induction may better induce regulatory T-cells and suppress inflammation.

David Dunkin, MD and his laboratory investigate the induction of tolerance through the skin, its mechanism, and its potential use as a novel method to treat colitis in an antigen-nonspecific manner via bystander suppression. Their initial work has shown that the skin is a highly active immune organ capable of inducing effector cells, as well as immune tolerance. Immunization by skin application of antigen has mainly been previously investigated as vaccines and immunotherapy for food allergens. Dr. Dunkin’s lab has demonstrated that tolerance induction can be achieved by epicutaneous ovalbumin exposure to the same extent as when induced orally, and is dependent on TGF-β, a regulatory cytokine. Significantly, they demonstrate that epicutaneous tolerance induction abrogates colitis and ileitis via bystander suppression in murine models. Thus, epicutaneous tolerance induction has the potential as a novel treatment for IBD. Future work translating their work to human disease will test other antigens, such as bacterial antigen, CBir, which ~50% of Crohn’s patients have antibodies against. Research will focus on determining the appropriate antigen to utilize and translate into a novel therapy for treating IBD.

A representation of the experiments to determine if epicutaneous tolerance induction can treat colitis and ileitis in murine models of IBD: Antigen applied to the skin is taken up by dendritic cells and presented to T cells. Regulatory T cells to the antigen (Foxp3+, IL10+ or LAP+) migrate to the intestines where they may suppress inflammation. These regulatory T cells may be activated by oral antigen. Testing will occur in a colitis and an ileitis model.
Research Advancements: Medical Practices

The Medication Level Variability Index (MLVI)—A Behavioral Biomarker Assessing Patients’ Medication Adherence

Medications can’t work if patients don’t take them. Indeed, nonadherence to medications (not taking the medicines as prescribed) is one of the most important reasons leading to poor patient outcomes in the developed world. But we do not know how to tell whether a given patient is taking her or his medications as prescribed; the “Achilles heel” of adherence research is that there is no gold standard way to measure adherence, and each of the proposed methods has serious shortcomings. For example, subjective methods such as patient reports tend to be unreliable – patients often fail to provide accurate information about their adherence. Clinicians sometimes use the presence of poor outcomes as an indication of nonadherence (for example, poor diabetes control); this approach is not only inaccurate, but also means that poor outcomes must occur before suspicion is aroused. Medication refill rates are indirect measures of adherence (refilling a prescription is not the same as taking a pill) that cannot be used when automatic refill plans are in place. Other objective methods, such as pill counts or electronic monitoring, impose additional burden on the patient, and require patient cooperation and significant logistic support. Increased patient burden matters because nonadherent patients, by definition, are not likely to cooperate with a procedure that increases their burden. If a patient finds it hard to take the medications as prescribed, she or he will also find it hard to bring the pill bottle to clinic, or to use an electronic monitor. Thus, because of resource-allocation barriers as well as due to selection bias against the very segment of the population that should be monitored, few clinics or clinical trials use a robust adherence monitoring plan. There is, therefore, particular interest in personalizing care delivery via the use of a simple, objective method that would allow efficient targeting of at-risk patients via algorithms built into standard care.

We defined and studied an innovative method to detect nonadherence to medications that uses existing clinical data without additional patient burden: computing the standard deviation (SD) of consecutive blood levels of a medication over time. The resulting variable, the Medication Level Variability Index (MLVI), reflects the degree of fluctuation between the levels. A higher MLVI means less consistent medication adherence. The MLVI has been studied in pediatric and adult organ (liver, kidney, heart, and lung) transplant recipients, but it can be applied more broadly, in clinical contexts where medication levels are reflective of exposure to a medication. One of very few validated markers of human behavior, the MLVI may guide interventions that target nonadherent patients, as has been shown in our pilot studies. Consistent with widely applied measurement theory, MLVI monitoring can inform a personalized patient-centered paradigm in which patient care is stratified based on a biological marker of behavioral risk.

Eyal Shemesh, MD
Associate Professor, Pediatrics
Associate Professor, Psychiatry
Division Chief, Developmental and Behavioral Pediatrics
Project Title: “Identifying the Regulatory Mechanisms Underlying an Accurate Asthma Biomarker?”

Investigators: Supinda Bunyavanich, MD, MPH, MCHDI Investigator and Assistant Professor of Genetics and Genomic Sciences and Pediatrics; Gaurav Pandey, PhD, Assistant Professor of Genetics and Genomic Sciences; Madhan Malisamani, PhD, MCHDI Investigator and Associate Professor of Pediatrics

Abstract: Asthma is a chronic respiratory disease that affects 9.5% of US children, with mild/moderate asthma especially difficult to diagnose given fluctuating symptoms. Under-diagnosis of asthma contributes to significant healthcare costs globally. Thus, there is high potential impact of improved diagnostic tools on reducing morbidity from asthma. Using a machine learning pipeline applied to RNA sequence data generated from a cohort that we recruited, we recently identified a nasal brush-based asthma gene panel that accurately differentiates subjects with and without mild/moderate asthma. In independent subjects, our nasal brush-based panel performed with positive predictive value 1.00, negative predictive value 0.96, ROC AUC 0.994. Testing in 7 external data sets confirmed the panel’s robust performance. Although our panel provides accurate classification of asthma, potential biological mechanisms for its performance remain unexplored. We need to better understand the regulatory mechanisms underlying its predictive ability to (1) discover what the panel genes can inform on asthma pathophysiology, and (2) identify secondary endpoints for translational and clinical trials next needed to bring this novel asthma biomarker closer to clinical use. We propose the following aims to identify the regulatory mechanisms underlying our asthma gene panel’s predictive ability: Aim 1: Construct a regulatory network that captures potentially non-linear transcription factor-target gene relationships relevant to asthma; Aim 2: Analyze the network to identify transcription factors that regulate asthma panel genes; Aim 3: Experimentally validate panel-regulatory transcription factors. Completion of this pilot study will (1) advance child health by elucidating regulatory mechanisms underlying asthma, the most common chronic disease of childhood; and (2) position the investigators to successfully apply for extramural funding for translational and clinical trials needed to bring this novel asthma biomarker to clinical practice. Children are most likely to benefit from successful implementation of this asthma biomarker.

Supinda Bunyavanich, MD, MPH
Associate Professor, Genetics and Genomic Sciences
Associate Professor, Pediatrics

Project Title: “Gene-environment interaction in defects of forebrain and facial patterning: potential role of THC?”

Investigators: Robert Krauss, PhD, MCHDI Investigator and Professor of Developmental and Regenerative Biology; Yasmin Hurd, PhD, Professor of Psychiatry, Neuroscience, and Pharmacological Sciences

Abstract: Holoprosencephaly (HPE) is a common developmental defect caused by failure to define the midline of the forebrain and/or midface. HPE is associated with heterozygous mutations in Sonic hedgehog (Shh) pathway components. However, clinical presentation is highly variable, and many mutation carriers are unaffected. It is therefore thought that such mutations must interact with more common modifiers, genetic and/or environmental. Little is known about environmental agents that promote human HPE, and their identification is in its infancy.

We have modeled the complex etiology of HPE in mice. Cdon encodes a Shh coreceptor, and CDON mutations have been found in HPE patients. Cdon−/− mice have a largely subthreshold defect in Shh signaling and are sensitive to genetic and environmental modifiers that result in a broad spectrum of HPE phenotypes. Cdon−/− mice are therefore a useful system for discovery of potential HPE risk factors. Environmental modifiers likely include naturally occurring Shh pathway inhibitors. Such factors could work with a heterozygous pathway mutation to depress signaling below a threshold level required for successful patterning of the forebrain and midface. The activity of the critical Shh pathway component Smoothened (Smo) is modulated by numerous small molecules; among these are naturally occurring teratogens. It was recently reported that phytocannabinoids, including A9-tetrahydrocannabinol (THC), are inhibitors of Shh signaling, working via inhibition of Smo. This raises the possibility that Cannabis exposure in utero may promote HPE, particularly in genetically susceptible individuals. The aim of this proposal is to determine if in utero exposure to THC induces HPE in wild type and/or genetically sensitized mice, and whether this occurs via combined inhibition of Shh signaling. If so, the implications for public health are substantial, as environmental risk factors represent targets of prevention.

Robert Krauss, PhD
Professor, Cell, Developmental & Regenerative Biology

Pilot Projects, continued on next page
Faculty Highlights

Pilot Projects: 2016-2017 Awardees, continued

Project Title: “Does chronic metabolic stress in childhood accelerate the aging of young pancreatic beta cells?”

Investigators: Donald K. Scott, PhD, MCHDI Investigator and Professor of Medicine; Adolfo Garcia-Ocaña, PhD, MCHDI Investigator and Associate Professor of Medicine; Martin J. Walsh, PhD, MCHDI Investigator and Associate Professor of Pediatrics, Structural & Chemical Biology, and Genetics and Genomics Sciences;

Abstract: Childhood obesity and childhood onset Type 2 diabetes are emerging public health issues. Little is known about the molecular mechanisms of the onset of the disease, though epigenetics likely plays an important role. Type 2 diabetes occurs when insulin-producing beta cells fail to secrete enough insulin to compensate for insulin resistance. Young mice, and probably young humans, normally adapt to a metabolic stress [like a high fat diet (HFD)] by expanding beta cell mass through proliferation of existing beta cells to meet the demand for insulin. Old beta cells do not respond to mitogenic stimuli. Young beta cells have an open chromatin phenotype with minimal DNA methylation of proliferative and metabolic genes allowing proliferation and adaptive expansion of beta cell mass. Old beta cells display proliferative/metabolic genes that are hypermethylated, with more closed chromatin, correlating with a decreased capacity to proliferate. Our preliminary data show that a HFD inhibits beta cell proliferation, and that a HFD causes hypermethylation of key hepatic genes. This proposal will test the hypothesis that a HFD turns young beta cells into old beta cells: we hypothesize that a HFD alters DNA methylation leading to decreased expression of genes involved in beta cell proliferation/metabolism. The resulting change in chromatin availability results in a restricted ability to adaptively expand to the increased insulin demand of a HFD. Thus, a chronic hypercaloric diet phenocopies aging islets, and increases the likelihood of childhood diabetes. The aims are 1): to analyze the impact of obesity on the beta cell phenotype, DNA methylation pattern (Methylseq) and transcriptional signature (RNAseq and ATACseq) in islets from young mice and adult mice fed acutely and chronically with a HFD; and 2) to compare the metabolic signature of islets from adult and young mice fed with a standard chow or a high fat diet.

Trainee Highlights

Evan Bardot is a PhD candidate in the laboratory of Nicole Dubois, PhD, within the Cell, Developmental and Regenerative Biology Department. He was the winner of the Young Investigator’s predoctoral division at the annual retreat this past November 2016. His thesis work is focused on identifying and characterizing cardiac progenitor populations in order to elucidate how the heart forms during embryonic development. These studies will help us understand how congenital heart defects arise and may improve our ability to generate cardiomyocytes in vitro for therapeutic purposes.

Diana Guallar, PhD was previously a postdoctoral fellow in the laboratory of Jianlong Wang, PhD in the department of Cell, Developmental and Regenerative Biology. She was the winner of the Young Investigator’s postdoctoral division at the annual retreat. Her work focused on modulation of Tet2 function through RNA targeting which may present new avenues for therapeutic strategies.
Shelley H. Liu, PhD
Shelley H. Liu, PhD is an Assistant Professor in the Center for Biostatistics within the Department of Population Health Science and Policy. She received her undergraduate degree in Biological Sciences, with a concentration in Physiology, and Statistics, from Northwestern University in 2011. She completed her PhD thesis in 2016 at Harvard University under advisor Brent Coull, where she developed Bayesian statistical methods for children’s environmental health research. Specifically, she developed new models to study how time-varying exposures to chemical mixtures affect neurodevelopment, and identified critical time windows of exposure. She also studied the interaction and effect modification of co-exposures. During her PhD, she also developed a method to account for missing data in HIV viral genetic linkage analysis. Since joining the Icahn School of Medicine at Mount Sinai, she is interested in children’s health research and environmental epidemiology.

Recent Publications:

Minji Byun, PhD
Minji Byun, PhD is a tenure-track Assistant Professor in the Department of Medicine, Division of Clinical Immunology, and a member of the Precision Immunology Institute. She received her undergraduate degree in Life Science from POSTECH, South Korea, where she studied 3D structures of peptidoglycan recognition proteins by X-ray crystallography. She completed her PhD thesis at Washington University in St. Louis on poxvirus-encoded immune evasion mechanisms targeting the MHC class I antigen presentation pathway. She then performed her postdoctoral studies at The Rockefeller University, where she made the novel finding that pediatric Kaposi sarcoma is associated with primary immunodeficiency and mapped the disease cause down to the single gene level. She also ascertained the molecular mechanisms behind the immune defects caused by these mutations. In 2014, she joined as faculty at the Washington University in St. Louis, with a research focus on genetic and immunological mechanisms underlying susceptibility to rare immune disorders. In 2017, she was recruited to Icahn School of Medicine at Mount Sinai to join the Precision Immunology Institute. Her current research focus includes Kawasaki disease, an acute systemic vasculitis primarily affecting children, and idiopathic multicentric Castleman disease, a rare lymphoproliferative disorder affecting people of all ages. She hypothesizes that rare high-impact variants – inborn or acquired – underlie susceptibility to these disorders. Her laboratory uses various cutting-edge human genetics tools to identify candidate morbid variants, which are then investigated for their pathogenic roles in patient-derived cells as well as in vivo animal models.

Recent Publications:

Shelley H. Liu, PhD
Assistant Professor, Population Health Science and Policy

Minji Byun, PhD
Assistant Professor, Medicine
Genomic instability…Egli D.

plasma membrane.

by mediating FGF receptor trafficking to the


Li J, Miao L, Zhao C, Shaikh Qureshi WM, Shieh

2017 Jan 20;120(2):400-6.

Li J, Miao L, Zhao C, Shaikh Qureshi WM, Shieh


Y, Cleaver O, Fan ZC, Wu M.

CDC42 is required for epidermal and pro-epidermal differentiation by mediating FGF receptor trafficking to the plasma membrane. Development. 2017 May 1;144(9):1655-1647.


Supinda Bunyavanich, MD, MPH, American Academy of Allergy, Asthma, and Immunology 2017 Annual Meeting, American Academy of Pediatrics Section on Allergy and Immunology Outstanding Pediatric Abstract Award

Shelley H. Liu, PhD, ENAR International Biometric Society, Distinguished Student Paper Award

Shelley H. Liu, PhD, American Statistical Association, Biometrics Section Student Paper Award

Shelley H. Liu, PhD, American Statistical Association, Section in Epidemiology Travel Award

Ruth J.F. Loos, PhD, Thomson Reuters, 2016 Thomson Reuters Highly Cited Researcher

Nadia Micali, MD, MRCpsych, PhD, FAED, Christina Barz lecture, Christina Barz foundation, & German Society for Psychiatry and Psychology

Donald K. Scott, PhD, American Diabetes Association, Basic Science Innovation Award, Targeting the ChREBP-Nrf2 axis to expand functional beta cell mass

Faculty Highlights

Awards/Honors

Dusan Bogunovic, PhD, Top 10 Innovations, 2016 Scientific American

Supinda Bunyavanich, MD, MPH, American Academy of Allergy, Asthma, and Immunology 2017 Annual Meeting, American Academy of Pediatrics Section on Allergy and Immunology Outstanding Pediatric Abstract Award

Shelley H. Liu, PhD, ENAR International Biometric Society, Distinguished Student Paper Award

Shelley H. Liu, PhD, American Statistical Association, Biometrics Section Student Paper Award

Shelley H. Liu, PhD, American Statistical Association, Section in Epidemiology Travel Award

Ruth J.F. Loos, PhD, Thomson Reuters, 2016 Thomson Reuters Highly Cited Researcher

Nadia Micali, MD, MRCpsych, PhD, FAED, Christina Barz lecture, Christina Barz foundation, & German Society for Psychiatry and Psychology

Donald K. Scott, PhD, American Diabetes Association, Basic Science Innovation Award, Targeting the ChREBP-Nrf2 axis to expand functional beta cell mass

Grants

Chenleng Cai, PhD, NHLBI, R01, “T-box transcription factor Tbx2 in coronary vascular development and disease”

Donald K. Scott, PhD, NIDDK, R01, “ChREBP Isoforms in Pancreatic Beta Cells”

Hirofumi Morishita, MD, PhD, NEI, R21, “Structure-Function Relationships of Experience-Dependent Spine Plasticity”

Ruth J.F. Loos, PhD, NIDDK, R01, “Study of coding variants in human obesity and their functional characterization using human iPSC-derived cellular models”

Ruth J.F. Loos, PhD, NHLBI, X01, “The BioMe Biobank at Mount Sinai: a diverse ancestry biobank to map biomedical traits and elucidate health disparities”

Rupangi Vasavada, PhD, JDRF, Innovative Award, “Characterization of Extracellular Vesicles From Human and Rodent Type 1 Diabetes Serum”

Publications


Faculty Highlights

Publications, continued


Bello GA, Arora M, Austin C*, Horton MK, Wright RO, Jennings C. Extending the distributed lag model framework to handle chemical mixtures. Environ Res. 2017 Mar 31;156:253-64.


Darvish H, Azcona LJ, Tafakori A, Ahmadi M, Ahmadifard A, and Puisán-Ruiz C. Whole genome sequencing identifies a novel homozgyous exon deletion in the NT5C2 gene in a family with intellectual disability and spastic paraplegia. NPJ Genomic Medicine. [In press]


Faculty Highlights

Publications, continued


*Denotes MCHDI trainee authors

Events / Announcements

5th Annual MCHDI Retreat

Save the Date
5th Annual MCHDI Retreat

Date: November 28, 2017
Time: TBA
Location: Harmonie Club
Ballroom, 1st Floor
4 E 60th St, New York, NY 10022