

DIABETES RESEARCH DAY VIRTUAL SYMPOSIUM PRESENTERS

November 12, 2020

2 Breakout Q&A Sessions : 1) 10 am – 11 am, 2) 11 am – 12 pm

BETA CELL FUNCTION

Samantha Adamson, MD, PhD, Medicine/Endocrinology (Basic Science)

Mentor: Jing Hughes, MD, PhD

Title: *Aberrant Calcium Signaling in Beta Cells that Lack Primary Cilia*

- Beta cells without primary cilia have decreased insulin secretion.
- Beta cells without primary cilia have altered calcium signaling in response to high glucose.
- Beta cells without primary cilia do not respond normally to somatostatin.

Rie Asada, PhD, Medicine/Endocrinology (Basic Science)

Mentor: Fumihiko Urano, MD, PhD

Title: *Therapeutic Development for Wolfram Syndrome with High Frequency Variant in Ashkenazi Jewish Population*

- Molecular characterization of pathogenic variants is essential for therapeutic exploration in wolfram syndrome.
- We found that a product of a unique variant of the WFS1 gene, WFS1 p.R558C, shows a protein stability less than normal WFS1 and causes a mild form of wolfram syndrome.
- Treatment with a combination drug of chemical chaperones improved the protein instability and physiological dysfunction caused by WFS1 p.R558C in stem cell-derived pancreatic beta cells.
- This study provides the insight critical for therapeutic application of the chemical chaperones in wolfram syndrome with WFS1 p.R558C.

Punn Augsornworawat, MS, Medicine/Endocrinology (Basic Science)

Mentor: Jeffrey Millman, PhD

Title: *Interrogating Beta Cell Maturation in Stem Cell Derived Islets using Single-Cell Technologies*

- Islets can be generated from pluripotent stem cells.
- Stem-cell derived islets resemble human islets after transplantation.
- Maturation of Beta cells is associated with increased function in vivo.
- Single-cell technologies reveal key genes and pathways associated with Beta cell maturation.

Amy Clark, DO, Pediatric Endocrinology (Basic Science)

Mentor: Maria Remedi, PhD

Title: *High Fat Diet Prevents Autoimmune Diabetes in NOD Mice*

- Determining the contribution of high fat diet (HFD) upon the development of type 1 diabetes is important as it will help delineate if the rise in childhood obesity may be fueling the increased incidence of type 1 diabetes.
- Non-obese diabetic (NOD) mice, a model of type 1 diabetes, fed with HFD demonstrated significant weight gain, impaired glucose tolerance, and developed insulin resistance at 10 weeks of age.
- Despite having an initially worse metabolic phenotype, HFD fed NOD mice paradoxically exhibited reduced islet immune cell infiltration, increased T regulatory cells, increased beta cell mass and insulin secretion resulting in protection from the development of diabetes.
- This study shows that HFD induces an immune tolerant state protecting NOD mice from the development of diabetes and further mechanistic studies may lead to novel therapies for patients with type 1 diabetes.

Guifang Dong, PhD, Medicine/Endocrinology (Basic Science)

Mentor: Clay F. Semenkovich, MD

Title: *Inactivation of Acyl-Protein Thioesterase 1, a Major Mediator of Depalmitoylation Promotes Insulin Secretion and Beta Cell Failure*

- APT1 is a major mediator of depalmitoylation recently implicated in diabetic vascular disease, but the physiological role of APT1 in type 2 diabetes, a disorder characterized by insulin hypersecretion followed by beta cell failure, remains unknown.
- Two independent animal models on a chow diet, global and islet-specific APT1 KO mice, have enhanced glucose tolerance and increased insulin levels, in concert with increased glucose stimulated insulin secretion under static and dynamic conditions without effects on beta cell morphometrics.
- Global APT1 KO db/db mice develop more pronounced hyperglycemia and hypoinsulinemia compared to littermate db/db mice with intact APT1, islet-specific APT1 knockout mice on a high fat diet also develop impaired glucose intolerance and hypoinsulinemia compared to control mice on a high fat diet, and both models have decreased beta cell area with APT1 deficiency.
- Knockdown of APT1 in human islets increases insulin secretion, and APT1 enzyme activity is decreased in human islets cultured in high glucose, suggesting that APT1 may represent a specific mediator of glucotoxicity in the clinical evolution of human type 2 diabetes.

Feyza Engin, PhD, Univ of Wisconsin - Biomolecular Chemistry (Basic Science)

Mentor: N/A

Title: *The Role of Ormdl3 in Beta Cells and Obesity*

- Islets of overweight/obese human donors display markedly reduced ORMDL3 expression, whereas Ormdl3 expression is significantly upregulated in the islets of ob/ob mice.
- Leptin treatment markedly reduced Ormdl3 expression in the islets of ob/ob mice.
- Fumonisin B1 restores increased apoptotic marker levels induced by Ormdl3 silencing.
- Deletion of Ormdl3 in beta cells, leads to elevated glucose levels.

Jeong Hun Jo, PhD, Medicine/Endocrinology (Basic Science)

Mentor: Jing Hughes, MD, PhD

Title: *Primary Cilia Mediate WNT Signaling in Pancreatic Islets*

- Primary cilia modulate Wnt responsiveness of islet beta-cells, which is a novel observation.
- Wnt4-Wnt3 antagonism is a key component of cilia-mediated Wnt regulation.
- Cilia-dependent Wnt signaling exhibits sexual dimorphism in mouse islets.
- In both mouse and human islets, cilia-dependent Wnt modulation is crucial to beta-cell function, including insulin secretion, beta-cell identity, and paracrine signaling.

Santhosh Karanth, PhD, Univ of Utah - Nutrition & Integrative Physiology (Basic Science)

Mentor: N/A

Title: *Utilizing Foxn3 Mediated Liver-Alpha Cell Cross-Talk to Make GRA Therapies Safer for Glucose Control in Type 1 Diabetes*

- Understanding the factors and cellular mechanisms controlling alpha cell mass and function is critical for developing new therapies to treat type 1 diabetes mellitus (DM1) that mitigate Glucagon receptor antagonism's (GRA) adverse reactions.
- We propose that FOXN3 is an integrator of glucagon's actions on amino acid metabolism in the liver. FOXN3 is stabilized by GRA, leading to amino acids accumulating in blood and driving alpha cell hyperplasia.
- In mice and zebrafish lacking foxn3 in liver, the number of alpha cells in the principal islet is decreased, while zebrafish over-expressing human FOXN3 in the liver have increased alpha cells counts.

- The overarching goal for these studies is to provide a pre-clinical proof-of-concept demonstration that GRA can be made safe for DM1 patients by lowering hepatic FOXN3 expression.

Shuntaro Morikawa, MD, PhD, Medicine/Endocrinology (Basic Science)

Mentor: Fumihiko Urano, MD, PhD

Title: *A Soluble Endoplasmic Reticulum Factor as Regenerative Therapy for Wolfram Syndrome*

- Wolfram syndrome is characterized by juvenile-onset diabetes, optic nerve atrophy, and neurodegeneration due to ER stress-mediated cell death. Since there is no treatment that can stop or even slow the progression of this syndrome currently, developing the novel treatment has been an urgent task.
- Mesencephalic astrocyte-derived neurotrophic factor (MANF), a neurotrophic factor secreted from ER stressed cells, activates the proliferation of human primary islets.
- MANF prevents ER stress-mediated beta cell death and enhances beta cell proliferation in cell and mouse models of Wolfram syndrome.
- The molecular pathways regulated by MANF are promising therapeutic targets for regenerative therapy of ER stress-related disorders, including diabetes and Wolfram syndrome.

Margaret Nalugo, MD, Vascular Surgery (Clinical/Translational)

Mentor: Mohamed Zayed, MD, PhD

Title: *Transplantation of Stem-Cell Derived Beta Cell Clusters into Porcine Arteriovenous Graft*

- Over 29 million people are living with diabetes in the US. This is about 1 in every 11 people and this number is projected to continue to increase. Cell replacement therapy may provide new opportunities insulin treatments to cure diabetes.
- In our study set we constructed a modified arteriovenous graft platform to facilitate transplantation of stem-cell derived beta cell clusters.
- We demonstrated arteriovenous graft patency in a porcine host, as well as beta cell xenograft viability despite no use of immunosuppression.
- Our experiments highlight the feasibility of using an arteriovenous graft platform for transplantation of beta cells, which provides new opportunities for treatment of diabetes.

Xue Wen Ng, PhD, Cell Biology & Physiology (Basic Science)

Mentor: David Piston, PhD

Title: *Role Of Complexin II In the Regulation of Islet Cell Physiology*

- We seek to identify the mechanistic pathways of Complexin II in regulating insulin and glucagon secretion at the secretory vesicle level in mouse islets via phosphorylation by Protein Kinase A (PKA) which is in turn regulated by somatostatin paracrine signaling.
- Using islets from Complexin II knockout mice, we demonstrate that both glucagon and insulin output increased despite a concomitant increase in somatostatin secretion.
- Further, using transgenic mice islets that express GCaMP6 specifically in alpha cells, we observe that Complexin II is necessary for the paracrine inhibition of alpha cell calcium activity by somatostatin.
- Overall, Complexin II plays an important role in regulating islet cell secretory activities which is influenced by somatostatin paracrine signaling.

Nathaniel York, PhD, Cell Biology & Physiology (Basic Science)

Mentor: Colin Nichols, PhD

Title: *Control of KATP Conductance in Diabetes and Hyperglycemia*

- Recently it has been demonstrated that elevated glucose levels can reduce KATP activity in-vitro by decreasing channel density in the membrane, an effect which is further amplified by activation of the channel with diazoxide.

- Decreased KATP density, leading to stimulation of secretion, may represent a mechanism of beta-cell adaptation to hyperglycemia resulting from insufficient glucose-stimulated insulin secretion (GSIS).
- For the first time I examine this phenomenon in-vivo, using mouse and zebrafish models of KATP gain-of-function induced diabetes and remission.
- Understanding the potential of such adaptation could have a significant impact on future therapies for many diabetic patients.

CARDIOVASCULAR COMPLICATIONS AND PERIPHERAL NEUROPATHY IN DIABETES

Jared Elenbaas, MS, Medicine/Cardiology (Clinical/Translational)

Mentor: Nathan Stitzel, MD, PhD

Title: *The Metabolic Impact of SVEP1, a Novel Human Disease Locus*

- Generating novel therapeutic approaches to cardiometabolic disease is critical given the substantial residual risk despite current therapies.
- SVEP1 is causally associated with type II diabetes, coronary artery disease, and hypertension in humans, as determined by genome wide association and Mendelian Randomization studies.
- Depletion of SVEP1 appears to abrogate metabolic dysfunction in a mouse model of diet-induced obesity.
- These data suggest that SVEP1 modifies cardiometabolic disease risk and that targeting SVEP1 may be therapeutically beneficial.

Connor Engel, BS, Vascular Surgery (Basic Science)

Mentor: Mohamed Zayed, MD, PhD

Title: *CEPT1 Mediated Postpholipogenesis Regulates Endothelial Cell Function and Ischemia-induced Angiogenesis*

- A growing body of evidence demonstrates that disruption of CEPT1 is associated with a variety of human conditions including diabetes, but a complete understanding of the effect of CEPT1 expression on endothelial cells is lacking.
- Our study demonstrates that CEPT1 expression in the arterial intima is increased in the setting of type 2 diabetes, and is essential for endothelial cell function, viability, and lipid synthesis.
- Furthermore, CEPT1 is essential for ischemia-induced micro-vascular angiogenesis, ischemic hind limb perfusion, and skeletal muscle recovery.
- Our experiments highlight the importance of CEPT1 in endothelial cells and provide further insight into the role of phospholipogenesis in peripheral arterial ischemia.

Zhen Guo, PhD, Medicine/Cardiology (Basic Science)

Mentor: Ali Javaheri, MD, PhD

Title: *Apolipoprotein M Drives Myocardial Autophagy to Prevent Doxorubicin Cardiotoxicity and Mortality*

- Apolipoprotein M (ApoM) is a secreted, hepatic lipoprotein that is associated with mortality risk across all major subtypes of human heart failure, but whether ApoM plays a role in doxorubicin cardiotoxicity is unknown.
- Doxorubicin reduces ApoM, while ApoM overexpression attenuates doxorubicin-induced mortality and cardiotoxicity by driving autophagic flux in the myocardium.
- Administration of ApoM prevents doxorubicin-induced reductions in transcription factor EB (TFEB), a master regulator of autophagy that is required for proper cardiac function in ApoM overexpressing mice.
- Our studies provide a mechanistic link between ApoM, a hepatic lipoprotein, and TFEB-dependent myocardial autophagy.

Hyo-Jung Jeong, MS, Movement Science/Physical Therapy (Clinical/Translational)

Mentor: Mary Hastings, MD

Title: *Midfoot and Ankle Motion During Heel Rise and Gait are Related in People with Diabetes and Peripheral Neuropathy*

- Movement dysfunction is identified as midfoot and ankle dorsiflexion at peak heel rise.
- Midfoot and ankle motions of heel rise and push-off of gait are positively related.
- Dorsiflexed motion at heel rise is replicated as increased dorsiflexion during gait.
- A heel rise task may help with assessment of the movement dysfunction of gait.

Jin Vivian Lee, BA, Vascular Surgery (Clinical/Translational)

Mentor: Mohamed Zayed, MD, PhD

Title: *A Pilot Randomized Controlled Trial Of N-Acetyl-Cysteine (NAC) for Healing of Amputation Stumps in the Setting of Peripheral Arterial Disease*

- Patients with critical limb ischemia (CLI) and diabetes are at increased risk of poor major amputation site healing.
- Preclinical studies have demonstrated that the antioxidant N-acetyl-cysteine (NAC) can augment tissue perfusion, arteriogenesis, and healing of ischemic amputation stumps in rodents. However, no clinical trials have investigated the feasibility of NAC as a therapeutic agent in the setting of peripheral arterial disease (PAD).
- In a randomized prospective, double-blinded, placebo-controlled, pilot clinical trial, we demonstrate that peri-operative NAC administration may improve amputation stump healing and perfusion in patients with CLI and amputation stump perfusion defects at baseline.
- Intraoperative LAFA may help identify patients with decreased stump perfusion who can benefit from early therapeutic intervention.

Kartik Mani, MD, Medicine/Cardiology (Basic Science)

Mentor: Abhinav Diwan, MD

Title: *Abnormal Proteostasis in the Pathogenesis of Lipotoxic Cardiomyopathy*

- Diabetes mellitus is associated with abnormal proteostasis and increased protein aggregation in cardiac tissue, even without evidence of reduced systolic function.
- We demonstrate that the myh6-ACSL1 transgenic model of diabetic cardiomyopathy is associated with cardiac myocyte protein aggregate accumulation similar to human diabetic patients.
- Preventing protein aggregate accumulation by knocking out cardiac myocyte expression of p62 does not prevent cardiomyopathy.
- Augmenting overall proteostasis by intermittent fasting as well as TFEB overexpression improves outcomes and rescues cardiomyopathy, thus suggesting that abnormal proteostasis, and not just protein aggregate accumulation, is a critical target in treating a lipotoxic model of diabetic cardiomyopathy.

Shirli Tay, MPHS, Vascular Surgery (Clinical/Translational)

Mentor: Mohamed Zayed, MD, PhD

Title: *Serum Circulating Fatty Acid Synthase and Diabetes are Independently Associated with Chronic Limb-Threatening Ischemia*

- Identifying serum-based early predictive diagnosis of chronic limb-threatening ischemia (CLTI) is essential to prevent amputation and premature death.
- We demonstrate that CLTI is significantly associated with higher levels of serum circulating fatty acid synthase (cFAS) content, independent of diabetes and smoking.
- Furthermore, using serum cFAS content, diabetes, and smoking as predictors provide moderate-to-high accuracy in distinguishing patients with CLTI.
- This study serves as a background for further studies evaluating serum cFAS content as a potential diagnostic and prognostic serum biomarker for peripheral artery disease.

Carla Valenzuela Ripoll, MD, Medicine/Cardiology (Basic Science)

Mentor: Ali Javaheri, MD, PhD

Title: *Sodium Glucose Co-Transporter 2 Inhibition Improves Cardiac Function, Prevents Endothelial Leak, and Increases Apolipoprotein M in Lipopolysaccharide Treated Mice*

- Beyond their clinical cardioprotective and nephroprotective effects, pre-clinical studies have recently identified that sodium glucose co-transporter 2 inhibitors (SGLT2i) improve survival in sepsis, although no mechanism has been identified.
- We observed that the SGLT2i dapagliflozin improves cardiac function and reduces endothelial leak in a lipopolysaccharide (LPS) mouse model.
- Dapagliflozin pretreatment prevented LPS-induced reductions in apolipoprotein M, which is known to improve survival in sepsis and promote endothelial integrity.
- Dapagliflozin improves endothelial integrity likely by increasing apolipoprotein M, which highlights a novel mechanism of action of SGLT2i.

Rong Mei Zhang, MD, Medicine/Endocrinology (Clinical/Translational)

Mentor: Carlos Bernal-Mizrachi, MD

Title: *Effect of Acute Hyperglycemia on Monocyte Cholesterol Metabolism in Type 2 Diabetes*

- Acute hyperglycemia increases monocyte total cholesterol, free cholesterol, and cholesterol ester after 2 and 6 hrs in vitro.
- Acute hyperglycemia increases monocyte oxidized-LDL uptake after 2 and 6 hrs in vitro.
- Acute hyperglycemia does not have an effect on monocyte cholesterol efflux or synthesis after 2 and 6 hrs in vitro.
- Acute hyperglycemia promotes formation of monocytes enriched with cholesterol which are capable of delivering this cholesterol to plaques and contribute to nascent plaque formation.

Xiangyu Zhang, PhD, Medicine/Cardiology (Clinical/Translational)

Mentor: Babak Razani, MD, PhD

Title: *Dietary Protein Activates Monocytes and Macrophage mTOR Signaling and Downstream Proatherogenic Effects in Humans*

- Identifying the atherogenic effect of high protein diet is essential to prevent cardiometabolic disorders.
- We demonstrate that high protein smoothie leads to an acute increase of serum amino acid concentration and activated mTORC1 signaling in circulating monocytes from volunteers, while low protein smoothie only causes a minimal increase on serum amino acid concentration and monocyte mTORC1 activation.
- In vitro studies also confirm a dosage dependent mTORC1 activation and correlating atherogenic effect of amino acids on human monocyte derived macrophages, including significant increase in inhibition on mitophagy, mitochondria dysfunction and apoptosis.
- This study serves as a background for further studies evaluating the connections between uptake of specific amino acids and atherosclerosis.

CLINICAL DIABETES

Katrina Han, MD, Medicine/Endocrinology (Clinical/Translational)

Mentor: Carlos Bernal-Mizrachi, MD

Title: *Comparing Inpatient and Outpatient Insulin Requirements in Patients Taking U-500 Regular Insulin*

- To reduce the risk of hypoglycemia and potential dosing errors associated with the use of U-500 insulin, conversion to U-100 insulin is often preferred during hospitalization; however, there is no formal guideline to describe the best method of making this transition.

- We demonstrate that on average, the inpatient total daily dose of insulin on admission is about 35-40% lower compared to outpatient total daily dose for patients taking U-500 regular insulin.
- Prior to discharge, the average reduction in total daily dose was 36% compared to outpatient dose. With this reduction, more patients had blood glucose maintained under 250 mg/dL, and only one patient had blood glucose under 70 mg/dL which was an improvement compared to the first 24 hours of admission.
- This serves as a background for further studies which are still needed to help design inpatient treatment algorithms for patients taking U-500 regular insulin.

Jennifer Powers Carson, PhD, Medicine/Endocrinology (Clinical/Translational)

Mentor: N/A

Title: *Alternate Biomarkers for Predicting Adverse Neonatal Events in Pregnant Women with Diabetes*

- Published studies from Japan and China have shown the effective use of percent glycated albumin (%GA) in plasma as an effective predictive marker of adverse neonatal events in pregnant women with diabetes.
- We examined the use of %GA and total glycated serum proteins (GSP) in a population not previously studied (>50% Black, median BMI 34).
- Using trimester 2 data, receiver-operator curve AUC was 0.934 for %GA and 0.950 for GSP, but much lower for trimester 3 data. Cut-offs do not need to be adjusted based on BMI.
- Additional data will allow us to finalize a cut-off to be used and determine whether or not lipid biomarkers may also represent a useful approach.

Judith Simcox, PhD, Univ of Wisconsin – Biochemistry (Clinical/Translational)

Mentor: N/A

Title: *Discovering Circulating Lipid Biomarkers for Diabetes in African American Populations*

- Circulating HDL and triacylglycerol levels are poor predictors of metabolic disease in African American populations.
- Using global lipidomics from the Midlife in the US (MIDUS) and Survey of the Health of Wisconsin (SHOW) population studies we identified over 300 lipids that correlate with metabolic syndrome factors.
- Analysis of the global lipidomics results with machine learning algorithms identified 72 lipids that are predictive of metabolic disease.
- Lipids that promote inflammation were correlated with metabolic disease in both African American and Caucasian populations.

Drishti Sinha, AB, Medicine/Endocrinology (Clinical/Translational)

Mentor: Cynthia Herrick, MD

Title: *Barriers and Facilitators to Postpartum Diabetes Screening and Prevention for Low-Income Women with Gestational Diabetes: A Qualitative Study of Provider and Staff Perspectives*

- Among healthcare providers and staff, prominent barriers and facilitators to postpartum diabetes screening and prevention were found across societal, healthcare system, and interpersonal environments of the socio-ecological model, with some factors like distrust in medicine crossing multiple environments.
- Among societal barriers identified, health insurance issues and employment struggles were frequently cited. Providers and staff noted that facilitators such community-based organizations and governmental programs existed, but patients were often unaware of these programs.
- The most commonly cited healthcare system barriers included issues with care fragmentation between specialties, between medical centers, and within care teams, although instances of care coordination, such as home health nursing, were also noted.

Within the interpersonal environment, providers and staff sometimes noted difficulty accommodating cultural differences and perceived patient motivation as a key determinant of outcome.

COGNITIVE FUNCTION IN DIABETES

Sarah Eisenstein, PhD, Psychiatry (Clinical/Translational)

Mentor: N/A

Title: *Neuroinflammation and Cognition in Obesity*

- Application of the novel diffusion basis spectrum imaging (DBSI) technique on MRI-based diffusion tensor images (DTI) allows for non-invasive measurement of whole-brain neuroinflammation in humans, in whom brain mechanisms underlying cognitive dysfunction in obesity, a risk factor for diabetes and Alzheimer disease, are not fully understood.
- We replicate our recent findings from a retrospective study in which DBSI metrics of neuroinflammation related to body mass index (BMI) and cognitive function across normal-weight and obese humans.
- Further, we demonstrate that DBSI metrics of neuroinflammation relate to BMI and cognitive function in a sample of normal-weight and obese humans rigorously screened for co-morbid disease and diabetes in this prospective study using state-of-the-art MR imaging techniques optimized for DBSI and the well-validated NIH Toolbox Cognition Battery.
- The results of this pilot study serve as preliminary data for a grant proposal to test whether obesity-associated neuroinflammation and cognitive dysfunction are reversible by weight loss or exacerbated by weight gain over time, and whether neuroinflammation mediates the relationship between adiposity and cognitive function.

Mary Katherine Ray, PhD, Psychiatry (Clinical/Translational)

Mentor: Tamara Hershey, PhD

Title: *Optimization of a Smartphone Application to Assess In-The-Moment Cognitive Function in Youth with Type 1 Diabetes*

- Understanding whether fluctuating glucose levels alter in-the-moment cognitive function in the everyday lives of youth with type 1 diabetes (T1D) is significant as it could lead to improved academic accommodations and treatment recommendations for this vulnerable population.
- Tools to assess in-the-moment cognitive function in the daily lives of youth are currently limited. This study aims to optimize a novel smartphone application (Ambulatory Research in Cognition; ARC app) to test dynamic cognitive functions (e.g., working memory, processing speed, associative memory) in youth with T1D.
- In a lab setting, participants completed cognitive testing on the ARC app 5 times, completed cognitive tasks previously validated to measure the same cognitive domains (i.e., working memory, processing speed, associative memory), and completed an experiential interview about the app's usability.
- Results demonstrated that youth understood how to use the app, found the cognitive tasks entertaining, performed similarly on the well-established tests, and had reliable scores across testing sessions. Further validation is ongoing in real-world settings in youth with and without T1D; analyses will integrate continuous glucose monitoring data to determine if glucose fluctuations predict cognitive function variability in daily life.

CYSTIC FIBROSIS

Andrea Granados, MD, Pediatric Endocrinology (Clinical/Translational)

Mentor: Ana Maria Arbelaez, MD

Title: *The Association Between Body Composition, Leptin Levels and Glucose Dysregulation in Youth with Cystic Fibrosis*

- Limited reports addressing the relationship between body composition and leptin levels with glucose dysregulation in youth with Cystic Fibrosis (CF) have had inconsistent results.
- This study aims to evaluate the relationship between body composition, particularly body fat content, leptin levels, and the degree of glucose intolerance, in clinically stable youth with CF compared to healthy controls.

- Overall, CF patients had lower fat mass, leptin levels and diminished indices of insulin secretion than healthy controls. The strong correlation between low leptin concentrations and diminished insulin secretion in the CF patients suggest that leptin may play a role in glucose dysregulation in this population. These findings resemble similar metabolic changes occurring in conditions with low leptin levels, and postulate a potential therapeutical role for leptin in these patients.
- This study highlights the impact of body composition and leptin concentrations in early glucose abnormalities in subjects with CF. Fat mass depletion and low leptin levels in those patients with lower insulin secretion, as observed in our study, may represent an early manifestation of a cascade for metabolic derangements that may ultimately result in negative clinical outcomes in patients with CF.

Emily Siegler, BS, Medicine/Endocrinology (2020 Summer NIDDK Student) (Clinical/Translational)

Mentor: Marina Litvin, MD

Title: *Unique Challenges in Treating Cystic Fibrosis-Related Diabetes in Pregnancy*

- Pregnancy is an insulin resistant state that may uncover underlying insulin deficiency in patients with Cystic Fibrosis, resulting in Cystic Fibrosis-Related Diabetes (CFRD)/Gestational Diabetes Mellitus.
- Compared to patients with insulin-dependent diabetes, patients with CFRD, at least early on in disease, tend to have low basal insulin requirements or they risk developing nocturnal and fasting hypoglycemia; however, due to their high carbohydrate diet, they benefit from rapid-acting insulin to cover meals and snacks per carb ratio.
- Patients with CF and diabetes in pregnancy benefit from diabetes technologies, such as insulin pumps and continuous glucose monitors (CGMs). Such devices can improve glycemic control and communication between physicians and patients with CFRD, particularly during pregnancy, and have the potential to reduce disease burden, increase time in appropriate glycemic range, and improve quality of life.

DIABETIC NEUROPATHY

Steven Funk, PhD, Medicine/Nephrology (Basic Science)

Mentor: Jeffrey Miner, PhD

Title: *Probing Effects of Albumin and Albumin Free Fatty Acid Cargo in Models of Proteinuric Kidney Diseases: Alport Syndrome and Laminin Beta2 Mutant Mice*

- The role of albumin in kidney injury due to proteinuria, the increased leakage and exposure of renal epithelium to blood proteins, in diabetes and general kidney diseases is confused by inconsistent quality, species mis-match, and usage of exogenous albumin sources.
- To clarify the role of albumin in renal injury, we tested the effects of albumin knockout in the proteinuric contexts of Alport syndrome mice and laminin beta2 mutant mice.
- Albumin loss delayed injury onset and prolonged lifespan similarly in both Alport syndrome mice and the heavily proteinuric, long lived laminin beta2 mutant mice.
- Ongoing studies are aimed at determining the role of albumin in injury-driven gene expression through parabiosis-mediated albumin repletion, and identification of albumin-borne free fatty acids that might contribute to renal injury in these proteinuric contexts through lipid mass spectrometry.

Eirini Kefalogianni, PhD, Medicine/Nephrology (Basic Science)

Mentor: Andreas Herrlich, MD, PhD

Title: *Roles of Cell-Surface and Soluble TNFR1 and TNFR2 In Diabetic Nephropathy*

- Circulating soluble sTNFR1/2 serum levels are very strong predictors of kidney disease progression in type 1 and type 2 diabetes but their roles in disease progress remain unknown.

- Using mice that cannot release the transmembrane cell-surface receptor TNFR1 (mutant receptor), and drugs that neutralize soluble TNF, we show that soluble TNF signaling via TNFR1 is injurious, and/or that production of circulating soluble TNFR1, as occurs after kidney injury, is protective.
- In vivo comparison of a drug that binds only soluble TNF versus a drug that binds both membrane and soluble TNF, suggests that membrane TNF (possibly via the cell-surface receptor TNFR2) has repair/protective functions after kidney injury.
- We have begun to dissect the contribution of cellular and soluble components of TNF - TNFR1/2 pathways to diabetic nephropathy progression using human samples and plan to also use mouse models of the disease.

Nirupama Ramkumar, MD, Univ of Utah - Medicine/Nephrology & Hypertension (Basic Science)

Mentor: N/A

Title: *Renoprotective Effect of Targeting Endothelin and SGLT2 In Type 2 Diabetes*

- This proposal evaluates if dual therapy with inhibition of endothelin and SGLT2 signaling confer synergistic/additive protection in diabetic kidney disease in Type 2 diabetes.

Hani Suleiman, MD, PhD, Medicine/Nephrology (Basic Science)

Mentor: N/A

Title: *Glomerular Basement Membrane Composition and Architecture in Diabetic Nephropathy*

- Increased GBM thickness is an early sign of diabetic nephropathy.
- Genome-Wide Association Study of diabetic kidney disease highlights biology involved in COL4A3 in the progression of the disease: Two variants in COL4A3, two different outcomes: 1) Diabetic patients with Asp(D) 326 (COL4A3) develop DN. 2) Diabetic patients with Tyr(Y) 326 (COL4A3) are protected from DN.
- Using CRISPR/Cas9 technology, we generated two KI mouse models for COL4A3 mutations D326 (COL4A3-D) and Y326 (COL4A3-Y). We crossed the mice to the diabetic mouse model OVE26 to study the effect of these two COL4A3 mutations on the disease outcome.
- So far, at the baseline, ~24 weeks-old mice appear normal with no clear difference in the GBM thickness in the COL4A3-D/D compared to the COL4A3-Y/Y. Next, we will analyze the COL4A3-D/D; OVE26 and COL4A3-Y/Y; OVE26 diabetic mice.

Parker Wilson, MD, PhD, Pathology & Immunology (Basic Science)

Mentor: Benjamin Humphreys, MD, PhD

Title: *Integration of Single Nucleus RNA and ATAC Sequencing Identifies Signaling Pathways that Promote Gluconeogenesis in the Diabetic Proximal Tubule*

- Single cell profiling in the diabetic kidney captures cell-specific pathways in the diabetic kidney.
- Single cell assay for transposable accessible chromatin identifies open chromatin areas.
- Cell-specific open chromatin implicates transcription factors and cis-regulatory interactions that regulate transcription.
- Germline variation influences allele specific expression and may be regulated by distal intergenic enhancers.

Haojia Wu, PhD, Medicine/Nephrology (Basic Science)

Mentor: Benjamin Humphreys, MD, PhD

Title: *Mapping the Response of Murine Diabetic Nephropathy to Therapy at Single-Cell Resolution*

- This is the first comprehensive single cell transcriptional atlas of the effects of diabetic nephropathy treatments in a mouse model.
- Cell types were prioritized on the basis of their molecular response to diabetic nephropathy and drug treatments.
- Drug specific and overlapping gene expression patterns were identified.
- The results should help elucidate cell-specific mechanisms of therapeutic benefit.

GLUCOSE METABOLISM AND INSULIN RESISTANCE

Guifang Dong, PhD, Medicine/Endocrinology (Basic Science)

Mentor: Clay F. Semenkovich, MD

Title: *Acyl-Protein Thioesterase 1 Deficiency in Skeletal Muscle Promotes Glucose Intolerance in Mice*

- APT1 is responsible for removal of palmitate from a large number of lipid-modified proteins, but its role in glucose metabolism has not been defined.
- On a chow diet, skeletal muscle-specific APT1 deficient mice have the same body weight, body composition, fasting plasma glucose, fasting insulin, insulin tolerance, and glucose tolerance as compared to control littermates.
- On a high fat diet, skeletal muscle-specific APT1 deficient mice also have the same body weight as control littermates, but they have impaired glucose tolerance in the setting of normal insulin tolerance, elevated fasting plasma glucose levels, and decreased fasting insulin levels, strongly suggesting an effect on beta cell function.
- Palmitoylation proteomics identified ten potential candidate substrates, including Vdac family members (known to be altered in type 2 diabetes), in skeletal muscle from muscle-specific APT1 KO mice, suggesting potential mediators of the hyperglycemic phenotype in these mice.

Kyle McNerney, MD, Pediatric Endocrinology (Clinical/Translational)

Mentor: Carlos Bernal-Mizrachi, MD, PhD

Title: *Neonatal Vitamin D Deficiency and Insulin Resistance*

- Vitamin D deficiency in mothers may lead to insulin resistance or diabetes in the offspring.
- We demonstrate that maternal vitamin D deficiency remains highly prevalent in newborns and their mothers despite maternal report of prenatal vitamin administration.
- Monocytes isolated from vitamin D deficient newborns induce insulin resistance in co-cultured 3T3-L1 cells, and this effect appears mediated by miR-106b.
- This study provides evidence of adverse metabolic effects on offspring of mothers with low maternal vitamin D status, which will be further studied through interventional trials of antenatal vitamin D supplementation.

John Moley, BSc, Pathology & Immunology (Basic Science)

Mentor: Jonathan Brestoff, MD, PhD

Title: *Rubicon Regulates White Adipose Tissue Function, Inflammation, and Glucose Homeostasis*

- High fat diet-induced obesity is associated with increased expression.
- Rubicon in white adipose tissue Rubicon-deficient mice fail to store lipids in white adipose tissue and develop severe non-alcoholic fatty liver disease (NAFLD).
- Rubicon is required to restrain inflammation in white adipose tissue in the setting of a high fat diet.
- Rubicon-deficient mice exhibit severe glucose intolerance and insulin resistance.

Sarah Speck, BA, Medicine/Endocrinology (Basic Science)

Mentor: Clay F. Semenkovich, MD

Title: *Depalmitoylation in The Murine Liver Regulates Glucose Metabolism*

- Palmitoylation has been shown to regulate adipose glucose metabolism, but the role of palmitoylation cycling in hepatic glucose metabolism and the development of diabetes is unclear.
- Deletion of the depalmitoylating enzyme, APT1, from the livers of female mice leads to insulin resistance.
- Palmitoyl-proteomics identified potential hepatic substrates of APT1, including mitochondrial proteins as well as those involved in amino acid metabolism.
- Future experiments will explore the proteins mediating hepatic insulin resistance in APT1LKO mice.

George Spyropoulos, MD, Medicine/Endocrinology (Basic Science)

Mentor: Clay F. Semenkovich, MD

Title: *Acyl-Protein Thioesterase 1 Deficiency In Adipose Tissue Promotes Insulin Resistance In Mice*

- Acyl-Protein Thioesterase 1 (APT1) mediates removal of palmitate from cysteines, but little is known about the role of palmitoylation/depalmitoylation cycling in insulin resistance.
- Adipose-specific APT1 deficiency is associated with increased lean and fat tissues in mice fed a high fat diet, suggesting that APT1 in adipose tissue affects energy homeostasis.
- Mice with adipose-specific APT1 deficiency have increased insulin resistance but no glucose intolerance on a high fat diet, in concert with decreased fasting plasma glucose levels and elevated fasting insulin levels.
- Adipose-specific APT1 deficient mice fed a chow diet for more than one year have insulin resistance and, unexpectedly, enhanced glucose tolerance, suggesting that the adipose palmitoylation/depalmitoylation cycling is linked to pancreatic beta cell regulation.

Stephen Stone, MD, Pediatric Endocrinology (Basic Science)

Mentor: David Ornitz, MD, PhD

Title: *FGF-21 Receptor Variants Demonstrate Severe Insulin Resistance In a Mouse Model of Insulin Mediated Pseudoacromegaly*

- Insulin-mediated pseudoacromegaly is a rare insulin resistance syndrome leading to tall stature, overgrowth, acromegalic features, and extremely high insulin levels.
- Individuals with insulin-mediated pseudoacromegaly may harbor digenic mutations in the FGF21 signaling pathway (FGFR1/KLB).
- Female mice harboring mutations in FGFR1 and KLB treated with a high fat diet demonstrate increased weight gain, fat mass, and insulin resistance (as measured by intraperitoneal insulin tolerance test).
- Mice harboring mutations in FGFR1 and KLB demonstrate increased hepatic steatosis and adipose inflammation.

Nicole K.H. Yiew, PhD, Medicine/Nutritional Sciences (Basic Science)

Mentor: Brian Finck, PhD

Title: *Renal and Hepatic Gluconeogenesis: Role of the Mitochondrial Pyruvate Carrier*

- Increased glucose production from gluconeogenic substrates by kidney and liver contributes to hyperglycemia in diabetes, but the mechanisms involved are incompletely understood.
- We demonstrated that the loss of mitochondrial pyruvate carrier (MPC) in the kidney and liver lowered plasma glucose concentrations but did not lead to frank hyperglycemia.
- We predicted that loss of MPC and block in mitochondrial pyruvate import might trigger compensatory responses to maintain normoglycemia by activating gluconeogenesis from glycerol, but glucose production from glycerol also seemed to be reduced.
- These data demonstrate an important role for MPC in regulating kidney and liver glucose production and may suggest that glycerol fluxes through pyruvate to enter the gluconeogenic pathway.

HYPOGLYCEMIA

Wei Wang, MD, PhD, Pediatric Endocrinology (Clinical/Translational)

Mentor: Ana Maria Arbelaez, MD

Title: *Brain Resting State Functional Connectivity During Hypoglycemia and after Recurrent Hypoglycemic Episodes*

- Antecedent hypoglycemia causes defective glucose counter-regulation and hypoglycemia unawareness to a second episode of hypoglycemia, known as hypoglycemia-associated autonomic failure (HAAF). This lack of responses puts patients at risk for dead-in-bed syndrome and the precise mechanisms are unknown.

- The current study aims to study the neural mechanism of HAAF by examining brain functional connectivity in healthy individuals and in patients with T1DM undergoing study-induced hypoglycemia.
- Recurrent hypoglycemia in healthy individuals caused an attenuation of hypoglycemic symptoms and counterregulatory responses, similar to that of T1DM. Following the same pattern, recurrent hypoglycemia also caused an attenuation of functional connectivity values during hypoglycemia in healthy individuals after repeated hypoglycemia.
- Repeated hypoglycemic episodes induced a HAAF-like response in healthy individuals. This was accompanied by altered brain functional connectivity, which approximated that of T1DM during hypoglycemia. These findings suggest that impaired brain functional connectivity is associated with poor glucose counter-regulation and hypoglycemia unawareness, potentially causing HAAF.

OBESITY

Suba Gunawardana, PhD, Cell Biology & Physiology (Basic Science)

Mentor: David Piston, PhD

Title: *Insulin-Independent Reversal of Type 1 Diabetes with Brown Adipose Tissue Transplants; Role of IGF-1*

- In an attempt to develop better therapeutic approaches for type 1 diabetes (T1D), we investigate the mechanisms of insulin-independent glucose regulation following brown adipose tissue (BAT) transplants.
- Subcutaneous transplantation of embryonic BAT produces long-term euglycemia in mouse models of T1D, with no apparent contribution from endogenous insulin. Euglycemia correlates with increased levels of insulin-like growth factor 1 (IGF-1) in plasma, and expression of IGF-1 in adipose tissue.
- While adult BAT transplants alone cannot correct T1D, temporary administration of exogenous IGF-1 enables adult BAT transplants to reverse T1D in NOD mice, leading to rapid and long-lasting euglycemia.
- These data confirm the importance of IGF-1 in BAT transplant function, and provide a possible path for clinical translation of this approach.

Donghua Hu, PhD, Medicine/Endocrinology (Basic Science)

Mentor: Irfan Lodhi, PhD

Title: *TMEM135 Regulates Mitochondrial Dynamics and Metabolism in Brown Adipocytes*

- Previous studies suggest that adipose-specific knockout of the peroxisomal biogenesis factor Pex16 (Pex16-AKO) in mice impairs thermogenesis and decreases energy expenditure due to inhibition of cold-induced mitochondrial fission. To elucidate the underlying molecular mechanism, we performed proteomics analysis of mitochondria isolated from BAT of Pex16-AKO and control mice. Our results that show that transmembrane 135 (TMEM135) was the most dramatically decreased protein in Pex16-AKO mice with no change in its gene expression.
- TMEM135 is localized in peroxisomes and mitochondria. Its expression is enriched in brown adipose tissue and increases with cold exposure.
- TMEM135 plays a key role in brown adipocyte mitochondrial dynamics. TMEM135 knock down decreases mitochondrial copy number and results in elongated mitochondria networks. In contrast, overexpression of TMEM135 increases mitochondrial copy number and results in fragmented mitochondria.
- TMEM135 knock down decreases oxygen consumption rate (OCR) in brown adipocytes, suggesting that it plays an important role in mitochondrial metabolism.

Lex Kravitz, PhD, Psychiatry (Basic Science)

Mentor: N/A

Title: *Neural Adaptations Underlying Persistent Obesity*

- Dieting often results in short-term weight loss in humans that usually lasts ~6-24 months before reversing. A similar phenomenon occurs in laboratory animals, where the term “persistent obesity” has been used to describe animals that are resistant to losing weight after becoming obese.
- The goal of our project is to determine why obesity is so persistent, which is critical for making meaningful progress against the obesity epidemic.
- We hypothesize that obesity causes long-lasting disruptions in neurons that control food intake, leading to persistent over-eating and obesity.
- We propose to quantify the link between neural activity in the hypothalamus and related structures, and weight loss.

Heather Lawson, PhD, Genetics (Basic Science)

Mentor: N/A

Title: *Brown Adipose Expansion and Diabetic Remission in Obese SM/J Mice*

- High-fat-fed SM/J mice initially develop poor glucose homeostasis relative to controls. Strikingly, their glycemic dysfunction resolves by 30 weeks of age despite persistent obesity.
- The mice dramatically expand their brown adipose depots as they resolve glycemic dysfunction. This occurs naturally and spontaneously on a high-fat diet, with no temperature or genetic manipulation.
- Removal of the brown adipose depot impairs insulin sensitivity, indicating that the expanded tissue is functioning as an insulin-stimulated glucose sink.
- We have identified Sfrp1 (secreted frizzled-related protein 1) as a compelling candidate gene that may underlie this phenomenon.

Bridget Matikainen-Ankney, PhD, Psychiatry (Basic Science)

Mentor: Alexxai (Lex) Kravitz, PhD

Title: *Investigating Obesity-Linked Cortico-Accumbal Plasticity Mechanisms Underlying Enhanced Hedonic Feeding*

- Following weight loss after obesity, our data show that formerly obese mice exerted increased effort to obtain palatable foods, and had increased rates of weight re-gain upon re-exposure to obesogenic diets.
- In vivo fiber photometry recordings revealed that during food seeking, a population of neurons associated with motivation exhibited enhanced activity in formerly obese mice relative to lean controls.
- We hypothesized this reflected increased corticostriatal connectivity, and used in vivo electrophysiology and optogenetic stimulation to reveal that long-term synaptic depression (LTD) was occluded in obese mice.
- This reveals a mechanism likely underlying sustained brain circuit changes during and after obesity and potentially leading to obesity-linked persistent increases in hedonic feeding.

Julie Pendergast, PhD, Univ of Kentucky – Biology (Basic Science)

Mentor: N/A

Title: *How the Liver Tells Time on High-Fat Diet: Pathway to Obesity*

- The timing of metabolic processes, and sex differences in timing, are critical (and often ignored) variables in understanding homeostatic mechanisms and diet-induced obesity.
- In our pilot project, our first goal is to determine the physiological consequences of high-fat diet disruption of the liver circadian clock that occurs in males but not females.
- Our second goal is to determine why the liver circadian clock is protected from disruption by high-fat feeding in females.
- Discovering the mechanisms that protect the liver circadian clock in females may elucidate novel therapeutic strategies for obesity and insulin resistance.

Wei Zou, MD, PhD, Pathology & Immunology (Basic Science)

Mentor: Steven Teitelbaum, MD

Title: *Ablation of Fat Cells in Adult Mice Induces Massive Bone Gain*

- Postnatal fat ablation induced by DT/DTRADQ profoundly increases systemic bone mass.
- Loss of peripheral adipose tissues has no impact on osteogenesis.
- Marrow adipocytes negatively regulate bone growth by altering BMPR activation.
- Cooperative activation of BMP and EGFR stimulates osteoblast growth and differentiation

OBESITY AND FATTY LIVER

Mandy Chan, BS, Medicine and Pathology & Immunology (Basic Science)

Mentor: Joel Schilling, MD, PhD

Title: *Phagolysosomal Dysfunction of Kupffer Cells during Non-Alcoholic Fatty Liver Disease*

- Liver resident macrophage Kupffer cells are lost during the development of NAFLD.
- During NAFLD, Kupffer cells develop phagolysosomal dysfunction.
- Kupffer cell-specific overexpression of TFEB drives increased expression of lysosomal and lipid metabolic genes which may be a strategy to improve KC function.
- Mice with Kupffer cell-specific overexpression of TFEB develop normally and have normal KC appearance and distribution at baseline.

Sabine Daemen, PhD, Medicine/Cardiology (Basic Science)

Mentor: Joel Schilling, MD, PhD

Title: *Recruited Monocyte-Derived Macrophages Regulate Hepatic Crown-Like Structure Formation and Liver Fibrosis in NASH*

- Monocyte-derived macrophages localize at and are essential for hepatic crown-like structures (hCLS) in NASH.
- Loss of monocyte-derived macrophages prevents hCLS formation and increases liver fibrosis.
- Monocyte-derived macrophages form tight interactions with hepatic stellate cells at the site of hCLS which regulates stellate cell activation.
- Macrophages isolated from the NASH liver regulate stellate cell organization ex vivo.

Daniel Ferguson, PhD, Medicine/Nutritional Sciences (Basic Science)

Mentor: Brian Finck, PhD

Title: *Inhibition of the Mitochondrial Pyruvate Carrier to Treat Nonalcoholic Fatty Liver Disease*

- Nonalcoholic fatty liver disease (NAFLD) is a leading cause of liver disease throughout the world but there are no pharmacological therapies approved for this condition.
- Deletion of the mitochondrial pyruvate carrier (MPC) specifically in hepatic stellate cells, the primary cell type facilitating liver fibrosis, reduces the activation of stellate cells in vitro and in vivo.
- Furthermore, newly identified MPC inhibitors also show efficacy in decreasing in vitro stellate cell activation.
- Collectively, our studies demonstrate that inhibition of MPC may be a therapeutic target in treating patients with NAFLD.

Katsu Funai, PhD, Univ of Utah - Molecular Medicine & Physical Therapy (Basic Science)

Mentor: N/A

Title: *Mitochondrial Membrane Lipids in Non-Alcoholic Fatty Liver Disease (NAFLD)*

- Oxidative stress is a hallmark in the progression of NAFLD.
- Inefficiency in mitochondrial oxidative phosphorylation may increase oxidative stress.
- Mitochondrial membrane lipid compositions alters with various models of NAFLD.

- Changes in mitochondrial membrane lipid composition is sufficient to promote NAFLD

Yongjia Li, PhD, Anatomic & Molecular Pathology (Basic Science)

Mentor: Steven L. Teitelbaum, MD

Title: *Hepatic Lipids Promote Liver Metastasis*

- Obesity predisposes to cancer and a virtual universality of nonalcoholic fatty liver disease (NAFLD), however, the impact of hepatic steatosis on liver metastasis is enigmatic.
- We find that while control mice were relatively resistant to hepatic metastasis, those which were lipodystrophic or obese, with NAFLD, had a dramatic increase in breast cancer and melanoma liver metastases.
- NAFLD promotes liver metastasis by reciprocal activation initiated by tumor-induced triglyceride lipolysis in juxtaposed hepatocytes.
- Given the similar histological features of lipid distribution in human metastasis-bearing liver, there is a reasonable likelihood that our observations will translate to patients.

Elizabeth Newberry, PhD, Medicine/Gastroenterology (Basic Science)

Mentor: Nicholas Davidson, MD

Title: *Liver Specific Deletion of Tm6sf2 Promotes Both Hepatic Fibrosis and Hepatocellular Cancer*

- Tm6sf2 LKO mice develop steatosis on a chow diet, and increased steatosis and fibrosis on a high fat diet.
- Tm6sf2 LKO hepatocytes secrete smaller VLDL particles that contain less triglyceride.
- Tm6sf2 LKO mice display increased tumorigenesis using two models of hepatocellular carcinoma (STAM and Diethylnitrosamine).
- Delivery of exogenous Tm6sf2 protein via AAV reduced hepatic steatosis, fibrosis and tumor formation.

Michael Thompson, MD, PhD, Pediatric Endocrinology (Basic Science)

Mentor: Nicholas Davidson, MD

Title: *Mechanisms of Altered Bile Acid Homeostasis in Offspring Exposed to Maternal Obesogenic Diet*

- Maternal obesogenic diet exposure leads to altered bile acid homeostasis in offspring, but the mechanisms for these changes are unclear.
- We show that bile acid production is increased in offspring exposed to maternal high fat high sucrose diet exposure, but bile acid excretion and cholesterol absorption are unchanged.
- Furthermore, the gut microbiome is altered in offspring exposed to maternal high fat high sucrose diet and transplantation of the microbiome to antibiotic treated mice replicates the changes in bile acid homeostasis observed.
- This study provides evidence that bile acid production is increased in offspring exposed to maternal obesogenic diet and vertical transmission of the microbiome from dam to offspring is one mechanism by which bile acid homeostasis is altered.

Yiming Zhang, BS, Pediatric Gastroenterology (Clinical/Translational)

Mentor: Brian DeBosch, MD, PhD

Title: *Leveraging Hepatocyte Arginine Catabolism to Treat Metabolic Diseases*

- Arg2 activation represents a TRACTABLE fasting-induced therapeutic pathway against insulin resistance, NAFLD, and NASH.
- Arginine catabolism through ADI-PEG 20 treatment recapitulates the therapeutic effects of hepatocyte Arg2 overexpression.
- The therapeutic effects of Arg2 and ADI-PEG 20 are at least in part due to induction of hepatic autophagic flux.