Washington University in St. Louis
SCHOOL OF MEDICINE

John T. Milliken Department of Medicine
Division of Endocrinology, Metabolism & Lipid Research
Diabetes Research Center

Diabetes Day Symposium – November 9, 2023
Eric P. Newman Education Center (EPNEC)

Abstracts and Presenters

Abdulsattar, Dahlia, MS, *Department of Surgery, Division of Vascular Surgery*
Mentor: Mohamed Zayed

Abdulsattar DA, Roberts SH, Malik H, Zaghloul MS, Arif B, Alhamad T, Remedi MS, Lin Y, Zayed MA. Quantification of Viability of Human Pancreatic Islets Encapsulated in Alginate Beads over a 5-Week Period. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Islet area to bead area ratio has an impact on islet viability over time. Encapsulation of Islets prevents islets from fragmenting over a period of time. Fragmentation of Islets over time decreases their viability. Islets with a smaller diameter tend to have better viability over time (50% viability up to 15 weeks).

Alexander, Caroline, PhD, *Oncology, University of Wisconsin-Madison*

Nick Riley, Ildiko Kasza, Julian Michaud, Dudley Lamming, Greg Barrett-Wilt, Raghav Jain, Judi Simcox, Eric Yen, Ormond MacDougald, Caroline Alexander. Skins are the largest target of dietary lipid, and diet becomes reflected in the insulating properties of skin. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Only 3 days of feeding of high fat diet to mice induces a more insulating skin phenotype, suggesting that skin could exacerbate or signal the changes in metabolism that accompany obesogenesis. Radiotracer studies show that dietary lipid is taken up primarily into skin (both epidermis and dermal white adipose tissue), and remains there for weeks after administration. This is confirmed by the appearance of a Western diet "signature" of milk fat proteins in serum, epidermis and sebome. Anti-obesogenic paradigms such as low-isoleucine containing diets work rapidly to increase heat loss across skins. These diets have molecular lipidomic signatures which appear in both epidermis and sebome, and include the neutral lipid class of wax diesters. Sebocytes are indicated to be the critical cell type acting as modifiers of energy expenditure.

Asadi, Farzad, PhD, *Department of Cell Biology and Physiology*
Mentor: David Piston

Asadi F, Piston DW. A simple and applied protocol for ablation of β-cells in murine dispersed islet cells to enrich α-cell populations for glucagon secretion studies. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> The protocol is novel, simple, inexpensive, and universally achievable. The protocol can be run with low numbers of isolated islets. The protocol yields in enriched α-cells, which demonstrate linear glucose-dependent glucagon secretion. The protocol provides enriched α-cells that keep the phenotype of glucagon secretion for more than 7 days.

Bekele, Bayu Begashaw, PhD, *Department of Surgery*
Mentor: Ying, Liu
Bekele, BB, Liu Y, Lian M. The Impact of Diabetes on Breast Cancer Treatment among Low-Income Women. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> More than one-fifth of breast cancer women had coexisting diabetes. Diabetes significantly hampered the quality utilization of adjuvant breast cancer treatment among Medicaid-registered low-income women. Radiation therapy initiation and delay were significantly lower among diabetic than diabetes-free breast cancer women. Chemotherapy initiation and completion were significantly lower among diabetic than diabetes-free breast cancer women.

Borrego Alvarez, Aluet, MSc, *Department of Pediatrics, Division of Endocrinology & Diabetes*
Mentor: Stephen Stone

Borrego Alvarez A, Millman JR, Buchser W, Baldridge D, Stone SI. Precision Modeling of Genetic Variants in Atypical Diabetes. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> As our understanding of the pathophysiology of diabetes evolves, we increasingly recognize many patients may have a form of diabetes that does not neatly fit with a diagnosis of either type 1 or type 2 diabetes. The discovery and description of these forms of "atypical diabetes" have led to major contributions to our collective understanding of the basic biology which drives insulin secretion, insulin resistance, and islet autoimmunity. A critical gap in the field of precision medicine for diabetes is that there are no established in vitro or in vivo methods to determine the functional pathogenicity of specific genetic variants found by sequencing. We can generate iPS derived adipocytes to study the effect of variants of uncertain significance in the adipose tissue lineage. We can generate iPS derived beta cells to study the effect of variants of uncertain significance in the pancreatic beta cell lineage.

Bradley, Kameron, MEng, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Jeffrey Millman

Bradley KW, Schmidt M, Est C, Moore C, Millman JR. Investigating Genetic Pathways of Hypoxia-Induced β Cell Death and Dysfunction. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Primary and SC-islets are susceptible to death and dysfunction caused by hypoxic conditions, limiting their efficacy as cell replacement therapies. Transcriptional profiles show hypoxic islets switch to anaerobic glycolysis, potentially impacting β-cell glucose sensing. Surprisingly, these islets maintain high glucose-induced insulin secretion while also increasing secretion at low glucose levels compared to normoxic islets. Further research is needed to understand this unexpected GSIS behavior. We have created a pipeline for SC-islet-based CRISPR screens to engineer hypoxia resistant islet cells. Our hypoxia selection step and NGS sample preparation must be further optimized for our CRISPR screens to work properly.

Bryan, Melanie, MD, *Department of Pediatrics, Division of Endocrinology & Diabetes*
Mentor: Ana Maria Arbelaez

Bryan MM, Bockstruck M, Sicard M, Danis N, Markley B, Patton L, Glover-Jones L, Nelson C, Arbelaez AM. Improving Pediatric Diabetes and Obesity Care Access Through a School-Based Mobile Clinic. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Despite notable advancements in therapeutic strategies, a substantial proportion of pediatric diabetes patients under the care of the Washington University Pediatric Endocrinology clinics do not achieve goal glycemic control. While this outcome may be attributed to a multitude of factors, the role of social determinants of health is increasingly recognized as a crucial factor impacting diabetes outcomes. One social determinant of health that holds potential for modification is access to healthcare. School-based health centers are a well-established model for enhancing healthcare delivery to the adolescent demographic. However, a fixed, school-based clinic would be an inefficient use of resources given the limited number of patients with diabetes in each school and district. In response to this challenge, the mobile diabetes clinic was conceived in partnership with Healthy Kids Express as a solution to delivering diabetes care within a school-based framework. By enhancing the accessibility of healthcare for patients and their families, this approach seeks to facilitate the completion of recommended screenings, development of individualized treatment plans, and the encouragement of self-management among a high-risk pediatric diabetes population. Subsequent to the successful implementation of a pilot program in spring 2023, eight school districts enrolled for the 2023-2024 school year. We are tracking clinical outcomes for participating patients, including metrics related to glycemic control, appointment adherence, hospital admissions, and emergency department visits. Our hypothesis is that this model of care delivery will improve measures of glycemic control and reduce high-cost healthcare utilization.

Castelblanco, **Esmeralda,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Maria Remedi

Castelblanco E, Mrad M, Ramirez-Sotero I, Bambouskova M, Remedi M. Autophagy is Impaired in Pancreatic Islets at Early Stages of Type 1 Diabetes Pathogenesis. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Endoplasmic reticulum stress and pro-inflammatory cytokines are increased in islets from the NOD mouse model of autoimmune T1D before diabetes onset. TFEB, the master regulator of lysosomal biogenesis, gene expression and perinuclear localization, increased at the early stages of T1D pathogenesis, suggesting activation of autophagy. LC3II, a gold standard marker of autophagosome formation, increased in islets of NOD mice at the early stages of T1D pathogenesis but significantly decreased as diabetes progressed. Lack of further increase in LC3II upon chloroquine injection (inhibits autophagosome-lysosome fusion) and decreased LC3II CQ/Saline ratio in islets from NOD mice indicate autophagosome accumulation and impaired autophagy flux in T1D.

Castro, Daniel, PhD, *Department of Radiology*

De Gregorio D, Stephanie Xian, Melena B, Kong C, Piston D, Hughes J, Castro DC. Endogenous opioids regulate glucose homeostasis and ingestive behaviors. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Mu opioid receptors influence ingestive behaviors across the light/dark cycle. Mu opioid receptors augment insulin secretion. Mu opioid receptors modulate glucose tolerance. Mu opioid receptors directly act on pancreatic islets.

Chan, Mandy, BS, *Department of Pathology and Immunology*

Mentor: Joel Schilling

Chan MM, Daemen S, He L, Yang BQ, Fu C, Park AC, Beatty W, Razani B, Schilling JD. Enhancing lysosomal lipid metabolism in Kupffer Cells prevents cell death and reduces pathology in metabolic dysfunction-associated steatotic liver diseases. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Using a mouse model of metabolic dysfunction-associated steatotic liver diseases (MASLD), we uncovered that liver-resident macrophages develop phagolysosomal pathology, characterized by reduced phagocytic capability, limited lipid droplets, and abnormally active lysosomes. To devise a strategy for KCs to counter these cellular abnormalities triggered by MASLD, we generated an in vivo model in which Tfeb, a master transcriptional regulator of lysosomal biogenesis and lipid metabolism, is overexpressed in KCs (KC-Cre-TFEBTg). KC-Cre-TFEBTg mice preserve their KCs and have reduced infiltration of inflammatory MdMs into the livers upon MASLD-inducing diet feeding. Overexpression of Tfeb in KCs also reduces liver steatosis and injury. These Tfeb-overexpressing KCs harbor large lipid droplets in their endolysosomal compartments and have active lipid metabolic gene reprogramming. In vivo and in vitro systems further showed that Tfeb-overexpressing macrophages readily take up exogenous free fatty acid and lipoproteins.

Chatterjee Basu, **Gargi,** PhD, *Department of Medicine, Nutritional Science & Obesity Medicine*
Mentor: Nada Abumrad

Chatterjee Basu, G, McIntee, Farron L, Peche, Vivek S, Morris, Edward, Pietka, Terri, Kuda, Ondrej, Sosa, Mariam J, Abumrad, Nada A. Brain metabolic remodeling associates with altered behavior. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Defects in Fatty acid uptake in brain Defects in mitochondrial function. Impaired membrane remodeling. Impaired neurogenesis and altered behavior in mouse.

Cho, Jung Hoon, PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Jing Hughes

Cho JH, Hughes JW. Wnt4 in beta-cells induces sexual dimorphism on insulin secretion. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Beta-cell-specific Wnt4 knockout female mice show a mild impact on glucose homeostasis. Loss of Wnt4 in beta cells displays sexual dimorphism on in vivo insulin secretion. Wnt4 in beta cells is required for insulin biosynthesis in a sex-independent manner. Depletion of Wnt4 in beta cells escalates a canonical Wnt signaling target c-Myc, which has pivot roles in beta cell proliferation and function.

Dabill, **Lila,** BA, *Department of Medicine, Division of Bone and Mineral Diseases*
Mentor: Erica Scheller

Dabill, Lila, Shen Ivana, Zhang Xiao, DiAntonio Aaron, Scheller Erica. Conditional knockout of neural Sarm1 improves body mass and metabolic health with high fat diet. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Over the 24-week study period, Sarm1-cKO male mice fed HFD gained 20% less body mass than controls (20.8g mass gain on average in cKO vs 26g mass gain in control mice). Female Sarm1-cKO mice on HFD showed a complete prevention of weight gain.Subcutaneous inguinal fat, but not visceral gonadal fat, was

preferentially reduced by 26% in Sarm1-cKO male mice on HFD. Both fat types were reduced in the female Sarm1-cKO HFD mice. Insulin tolerance testing (ITT) results show that both male and female Sarm1-cKO mice on HFD were more sensitive to insulin than controls. Behavioral assays such as tail flick and electronic von Frey show trending evidence that Sarm1-cKO male and female HFD mice have improved peripheral nerve response compared to controls with temperature or mechanical stimuli.

Dong, **Guifang,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Clay Semenkovich

Dong G, Adak S, Ng X W, Zhang W, Spyropoulos G, Feng C, Yin L, Speck S, Remedi M, Wei X. APT1 (Acyl-Protein Thioesterase 1) overexpression in pancreatic islets preserves β cell function. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

APT1 is a major mediator of depalmitoylation recently implicated in the progression of T2D since we found that APT1 KO in mice causes hyperinsulinemia that leads to β cell failure. Whether APT1 overexpression (OE) can ameliorate the progression of T2D is unknown. APT1 OE on chow diet does not affect body weight or insulin sensitivity. However, female mice with APT1 islet OE on chow diet have increased C-peptide during GTTs, suggesting that APT1 islet OE may promote insulin secretion. Mice with APT1 islet OE on HFD appear to have improved β cell function and preserved functional β cell mass. This may occur by decreasing the β cell senescence associated protein p53BP1 and altering expression of SASP relevant genes such as IGF1R and Ctsb implicated in cellular senescence, aging and inflammation. Mice with APT1 islet OE in the db/db model show enhanced glucose tolerance and higher levels of insulin and C-peptide during GTTs compared to controls at 1-2 months following induction of APT1 overexpression. These findings suggest that APT1 islet OE may preserve β cell function in obesity-associated diabetes.

Dusso, **Adriana,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Carlos Bernal-Mizrachi

Dusso AS, Castelblanco E, Ivancovich JJ, McNerney K, Kutz G, Stone P, Oh J, Larson D, Stokes J, Bernal-Mizrachi C Vitamin D Supplementation During Pregnancy Reduces the Increments in Offspring SD-BMI during a Critical Time Period for Subsequent Obesity Risk—the VDAART Study. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Maternal vitamin D (VD) supplementation (4000 IU/daily, initiated in the 2nd trimester) decreases their offspring BMI from age 4 to 8 to levels compatible with a lower risk of obesity in early adulthood. Piecewise mixed model analysis identified years 2 to 4 after birth as the critical period in which a high dose of maternal VD supplementation markedly reduced the increments in their offspring SD-BMI compared to those achieved in children from mothers receiving conventional VD supplementation. The capacity of intrauterine VD supplementation to reduce the increments in offspring SD-BMI between ages 2 to 4 is more significant in males from white mothers. Maternal obesity blunts vitamin D-driven reductions in offspring' SD-BMI between age 2 and 4.

Ferguson, **Daniel,** PhD, *Department of Medicine, Nutritional Science & Obesity Medicine*
Mentor: Brian Finck

Ferguson D, Jarasvaraparn CJ, Chan MM, Daemen S, Eichler SJ, Schilling JD, Finck BN. Loss of Macrophage Mitochondrial Pyruvate Carrier Attenuates Metabolic Disease. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Obesity is associated with many metabolic comorbidities including metabolically associated steatotic liver disease (MASLD) and type 2 diabetes (T2D). Importantly, metabolic disease is associated with an increase in macrophage number, as well as a shift towards a pro-inflammatory phenotype. Macrophage polarization is tightly linked to metabolic rewiring of macrophage mitochondrial metabolism and a central player in mitochondrial metabolism is the mitochondrial pyruvate carrier (MPC), which transports pyruvate into the mitochondrial matrix where it can enter the TCA cycle. We hypothesized that macrophage-specific MPC deletion would reduce diet-driven metabolic disease in mice. To test this, we crossed Mpc2fl/fl mice to Cx3cr1-Cre transgenic mice (Cx3cr1MPCKO) to generate macrophage-specific MPC deficient mice. To induce MASLD, we placed mice on a diet high in fat, fructose, and cholesterol for 4 months. Cx3cr1MPCKO mice had a significant decrease in F4/80lo/MHCIIlo monocytes that were Ly6Chi, which are typically associated with a pro-inflammatory state. Additionally, Cx3cr1MPCKO mice had lower plasma ALT levels, a surrogate marker of liver damage, and decreased expression of genes associated with hepatic stellate cell activation, relative to wild-type (WT) littermates. When placed on a high fat diet (HFD, 60% kcal fat), Cx3cr1MPCKO mice were protected from diet-induced weight gain, had reduced fat mass, improved glucose tolerance, and increased energy expenditure compared to WT. Lastly, we observed reduced inflammatory gene expression in white adipose tissue in Cx3cr1MPCKO mice. Collectively, these data suggest that Cx3cr1MPCKO mice are more protected from diet-induced MASLD, obesity, and glucose intolerance. Our studies also contribute to the understanding of the role of mitochondrial metabolism in macrophage function during the development of metabolic disease.

Gallardo Pinera, **Juan,** BS, *Department of Pathology and Immunology*; *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Fumihiko Urano

Gallardo Pinera JJ, Hummel H, Gurram V, Urano F. CRISPR Prime Editing for Visual Acuity Restoration in Wolfram Syndrome Mutant Mice. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

The pathogenic variant can be corrected in vivo with Prime Editing in juvenile mouse models. Correction of WFS1 in iPSCs differentiated into RGC organoids may demonstrate reversal of disease phenotype in terms of ER stress, calcium dysregulation, and cell viability. Correcting the pathogenic variant may restore visual acuity in WFS mouse models and, potentially, in human patients. If effective in the eye, this genome editing therapy could be systemically administered to address all symptoms of the disease.

Guo, Zhen, PhD, *Department of Medicine, Division of Cardiovascular Research*
Mentor: Ali Javaheri

Guo Z, Ma P, Margulies KB, Lavine KJ, Javaheri A. Single nuclear RNA sequencing identifies unique features of anthracycline cardiomyopathy. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Anthracycline-induced cardiomyopathy remains a significant problem for cancer survivors. Despite extensive studies, the mechanistic underpinnings of anthracycline (such as doxorubicin, Dox) cardiomyopathy remain incompletely understood. We hypothesized that end-stage Dox cardiomyopathy represents a unique phenotype with distinguishing features compared to end-stage non-ischemic cardiomyopathy. End-stage doxorubicin cardiomyopathy exhibits unique transcriptional features, compared to end-stage non-ischemic cardiomyopathy including evidence of increased fibroblast activation, and reduced markers of macrophage phagocytosis. Increased expression of the “don’t-eat-me signal” CD47 may account for reduced macrophage phagocytosis of activated fibroblasts.

Gurram, **Venu,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Fumihiko Urano

Zhang W, Brown C, Skinner G, Gurram V, Urano F. Characterizing novel mouse model for Wolfram Syndrome. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> These Wfs1 Q670STOP mice show severe diabetic phenotype as early as at 4 months of age. Both Males and females showed diabetic phenotypes They also show significant weight loss irrespective of gender. These mice also show neurological defects which could potentially enable us to study wolfram syndrome in these model in detail.

Habibi, **Mohammad,** PhD, *Department of Medicine, Nutritional Science & Obesity Medicine*
Mentor: Brian Finck

Habibi M, Ferguson D, Eichler SJ, Chan MM, Shew TM, He M, Schilling JD, Cho KY, Patti GJ, Finck BN. Mitochondrial Pyruvate Carrier Inhibition Attenuates Hepatic Stellate Cell Activation and Liver Injury in a Mouse Model of Metabolic Dysfunction-associated Steatotic Liver Disease. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Mitochondrial pyruvate carrier (MPC) inhibition reduces pyruvate-derived TCA cycle metabolites leading to lower activation of hepatic stellate cells. Lack of MPC reduces the stabilization of hypoxia inducible factor 1 alpha (HIF1α) via lower mitochondrial alpha ketoglutarate (α-KG) synthesis in activated hepatic stellate cells. The mitochondrial glutamate-pyruvate transaminase 2 (GPT2) plays a key role in maintaining mitochondrial metabolism under the lack of MPC. Genetic deletion of MPC2 attenuates MASH and liver fibrosis in mice models of MASH.

Hu, **Donghua,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Irfan Lodhi

Hu D, Tan M, Lu D, Kleiboeker B, Liu X, Lodhi IJ. TMEM135 Links Peroxisomes to the Regulation of Brown Fat Mitochondrial Fission and Energy Homeostasis. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> TMEM135 is localized in peroxisomes and mitochondria. TMEM135 expression is enriched in brown adipose tissue and increases with cold exposure. TMEM135 plays a key role in brown adipocyte mitochondrial dynamics and metabolism. TMEM135 promotes thermogenesis and protects against diet-induced obesity and insulin sensitivity.

Hummel, **Devynn,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Fumihiko Urano

Asada R, Hummel D, Skinner G, Ustione A, Urano F. Dual role of NPTN in insulin secretion and inflammation of pancreatic b-cells. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> NPTN deficiency increases glucose-stimulated insulin secretion (GSIS) and b cell mass. NPTN stabilizes PMCA2 by the protein-protein interaction to regulate cytosolic Ca2+ homeostasis in b cells. NPTN

deficiency inhibits inflammation induced by cytokines treatment via TRAF6-NFkB axis b cell-specific Nptn KO mice are resistant to STZ-induced diabetes mellitus.

Ishahak, **Matthew,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Jeffrey Millman

Matthew Ishahak, Mason Schmidt, Ed Sanchez-Castro, Punn Augsornworawat, Jeffrey R. Millman. Comparative and Integrative Single Cell Analysis Identifies Gene Regulatory Networks that Drive Cell Identity in Stem Cell-derived Islets. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Stem cell-derived beta cells are transcriptionally more similar to adult rather than fetal beta cells. Stem cell-derived beta cells express progenitor and neuronal gene regulatory networks. Multiomic map of stem cell-derived islet differentiation reveals critical stages of fate decision. In silico transcription factor knockout simulations identifies potential regulators of off-target cell fate

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Jia, **Wentong,** PhD, *Department of Pathology and Immunology*
Mentor: Jonathan Brestoff

Jia W, Giwa R, Moley J, Abousaway O, Smith GI, Petersen M, Field RL, Klein S, Diamond MS, Brestoff JR. Matrix remodeling associated 8 (MXRA8) drives pathologic adipose tissue remodeling and promotes obesity pathogenesis. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

MXRA8 is most highly expressed in pre-adipocytes and mature adipocytes and its expression is upregulated in white adipose tissue (WAT) in obese patients and high fat diet (HFD)-induced obese mice. MXRA8-deficient mice protect from HFD-induced obesity, which is strictly dependent on the thermogenic protein Uncoupling protein 1 (UCP1). The antiangiogenic protein thrombospondin 1 (TSP1) binds MXRA8 and elicits p38 MAPK phosphorylation in 3T3 cells in a MXRA8-dependent manner. Administration of soluble MXRA8 to neutralize endogenous TSP1 was associated with preservation of the vascular bed in brown fat and protection from HFD-induced weight gain.

Kong, **Chen,** MD, *Department of Cell Biology and Physiology*
Mentor: David Piston

Kong C, Piston D. Opioid receptor-dependent modulation of glucagon-release in pancreatic alpha-cells. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Islet alpha cells-specific deletion of OPRM1 gene in GCGCrefl/fl mouse mode was generated. Validation and glucose phenotype of mice were investigated. Alpha cell OPRM1 KO mice develop abnormal glucose intolerance and glucagon secretion induced by feeding a high-fat diet. OPRM1 regulates glucagon secretion in vitro by a post-KATP mechanism.

Lee, Jeongmin, BS, *Department of Cell Biology and Physiology*
Mentor: David Piston

Lee J, Piston DW. Investigating the Large Brown Adipocyte Secreted proteins for Implications for Type 1 Diabetes Management: Reversing Hyperglucagonemia and Beyond. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> 100kDa brown adipocyte secreted proteins (CB-100) injection to T1D mouse model promotes the long-term recovery of euglycemia and reverses the hyperglucagonemia. The attainment of euglycemia by CB-100 is associated with the enhanced thermogenic activity and browning of adipose tissue, and enhanced glucose uptake of skeletal muscle. CB-100 Suppresses Glucagon Secretion in Both Mouse and Human Pancreatic Islets. CB-100 modulates Glucagon Secretion in pancreatic alpha Cells via the Insulin Receptor, Impacting Intracellular messengers (cAMP and calcium)

Li, Zhaolong Adrian, BA, *Department of Psychiatry*
Mentor: Tamara Hershey

Li ZA, Sanders AFP, Ray MK, Cai Y, Gu Y, Hershey T. Longitudinal associations between weight indices and basal ganglia microstructure in children. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> We studied the longitudinal links between BMI and waist circumference and MRI-assessed brain microstructure in 4036 children from 9-10 to 12-13 years. In both girls and boys, greater BMI and waist circumference at baseline predicted larger increase in basal ganglia cellularity, suggesting possible obesity-related neuroinflammation and/or accelerated subcortical neurodevelopment. In girls only, greater basal ganglia cellularity at baseline predicts larger weight gain, suggesting potential sex and/or puberty-specific brain mechanisms on eating and obesity. Future work incorporating functional MRI and more data waves can help clarify links between brain structure, function, and weight status across child and adolescent development.

Liu, **Katie, BS, and Gobble, McKinlee, BS,** *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Stephen Stone

Liu K*, Gobble M*, Phan NH, Borrego Alvarez, A, Ornitz, DM, Stone, SI. Adipose Tissue Dysfunction in a Murine Model of Insulin Mediated Pseudoacromegaly. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Insulin mediated pseudoacromegaly (IMPA) is a rare severe insulin resistance syndrome, related to pathogenic variants in the FGF21 signaling pathway (FGFR1 and KLB). Female (but not male) transgenic mice expressing pathogenic variants in FGFR1 and KLB demonstrate increased weight gain and fat mass when placed on a high fat diet. White adipose tissue isolated from these female FGFR1 / KLB mutant mice demonstrate decreased lipolysis and inflammation. Brown adipose tissue isolated from these female FGFR1 / KLB demonstrates increased lipid accumulation and decreased Ucp1 expression.

Liu, **Xuejing**, PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor:

Xuejing Liu, Anyuan He, Dongliang Lu, Donghua Hu, Min Tan, Brian Kleiboeker, Clay F. Semenkovich, Irfan J. Lodhi. Futile Metabolism of Branched Chain Fatty Acid in Peroxisomes Promotes UCP1-Independent Adipose Thermogenesis. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Gene expression of proteins involved in BCFA b-oxidation and synthesis increases in brown and beige adipocytes in response to thermogenic stimuli. FASN translocates to peroxisomes in response to thermogenic stimuli and mediates BCFA synthesis in brown adipocytes. Acox2 is a peroxisomal protein involved in β-oxidation of BCFA in brown adipocytes. Acox2 incativation impairs thermogenesis and promotes diet-induced obesity and insulin resistance.

Lu, **Dongliang,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Irfan Lodhi

Lu D, Tan M, Hu D, Liu X, Goodarzi P, Lodhi IJ. Liver-Derived ether lipids are required for maintenance of BAT mitochondrial function. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Adipose tissue specific knockout of GNPAT is not sufficient to affect plasmalogen level and mitochondria function in mice BAT. GNPAT deficiencies in vitro led to decreased plasmalogen and elongated mitochondria of BAT adipocytes. GNPAT-LKO mice have dysfunctional BAT with lower plasmalogen level in mitochondria. Plasmalogen increase mitochondria supercomplexes through regulating DHODH activity.

Lugar, **Heather,** MA, *Department of Psychiatry*
Mentor: Tamara Hershey

Lugar HM, Letourneau-Freiberg L, Greeley S, Hershey T. KCNJ11 mutation-related diabetes related to early differences in cortical volume and thickness in humans; a pilot study. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Neonatal diabetes can be caused by mutations in the KCNJ11 or ABCC8 subunits of the KATP channel. Some forms of KCNJ11-related diabetes are associated with cognitive and behavioral deficits, but it is unknown whether brain structure is also altered in this condition. We analyzed a small set of MRIs in individuals with KCNJ11-related diabetes, early-onset type 1 diabetes (T1D), and non-diabetic controls to determine if there are alterations in brain structure in the KCNJ11 group. We found that the KCNJ11 group had widespread lower cortical gray matter volume and thickness, but little to no differences in white matter or subcortical gray matter compared to T1D and non-diabetic groups.

Maestas, **Marlie,** *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Jeffrey Millman

Augsornworawat P, Veronese Paniagua DA, Velazco-Cruz L, Maxwell K, Marquez E, Millman JR. Veling islet stress response through cell-type-specific transcriptional analysis. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Cell type specific stress response. Reduced apoptosis in SC-islets alpha, beta and ductal cells respond to stress the most. BFA induces the largest response in cell types.

Meyer, **Gretchen,** PhD, *Program in Physical Therapy*

Shen, Karen C, Collins, Kelsey H, Guilak, Farshid, Meyer, Gretchen A. Myofiber "Lipotoxicity" Does Not Disrupt Cellular Biophysical Properties. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Large accumulation of intramyocellular lipid does not impact active or passive properties of permeabilized muscle fibers in mice with hyperlipidemia but without obesity. Intramyocellular lipid accumulation is associated with reduced active force generation in human fibers from individuals with type 2 diabetes. In humans, this relationship is likely not caused by changes to the myofilament or cytoplasmic viscoelastic properties as passive properties of the permeabilized fibers were unaffected by type 2 diabetes. Pre-diabetes and type 2 diabetes have different parameters of lipid accumulation in muscle fibers.

Mrad, **Marguerite,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Monika Bambouskova

Mrad M, Porubska B, Wigge NM, Molgora M, Gilfillan S, Colonna M, Bambouskova M. Myeloid cell interplay in the adipose tissue and diet-induced obesity. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

High dimensional analysis of combined immune and metabolic markers shows adipose tissue macrophages (ATM) undergoing most prominent metabolic remodeling in obese adipose tissue (AT). Metabolic remodeling of ATMs in obese AT correlates with decline in AT eosinophil population. Blocking the obesity-associated remodeling in ATM leads to retention and phenotypic changes in eosinophils in obese AT. These data indicates a novel pathway mediating communication between ATMs and eosinophils in AT.

Mukherjee, **Sandip,** PhD, *Department of Medicine, Nutritional Science & Obesity Medicine*
Mentor: Brian Finck

Mukherjee Sandip, Shew Trevor M., Pietka Terri A., Crewe Clair L., Khan Usna, Markan Kathleen R., Yoshino Jun, Finck Brian N. Adipocyte NAMPT and the regulation of Cav1 expression and function. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Adipocyte specific overexpression (Ad-OV) of the NAD+ biosynthesis pathway enzyme nicotinamide phosphoribosyltransferase (NAMPT) protected mice from diet induced insulin resistance. NAMPT overexpressing mice have reduced adipose tissue inflammation and improved adipocyte metabolism. NAMPT regulates the expression of Caveolin-1, a key constituent of caveolae, which are flask-shaped plasma membrane invaginations that serve as an important signaling hub for plasma membrane receptors and transporters. NAMPT is also essential for sustaining Caveolin-1 oligomer structure and increased its interaction with caveolin-2 and Cavin. Overall, these protein interactions form a high molecular weight functional caveolae complex.

Ozcan, Mualla, MD, *Department of Medicine, Division of Cardiovascular Research*
Mentor: Ali Javaheri

Ozcan Mualla, Valenzuela Ripoll Carla, Guo Z, Diab Ahmed, Lotfinaghsh Aynaz, Ataran Anahita, Javaheri A. Optimizing Fasting Strategies to Mitigate Doxorubicin-Induced Cardiac Toxicity and Aging. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Cancer survivorship comes with the burden of accelerated aging. Doxorubicin (Dox)-induced toxicity exacerbates aging phenotypes, including frailty and cardiac dysfunction. Because caloric restriction and fasting strategies have the potential to prevent aging in lower organisms, we tested if alternate-day

fasting (ADF) can attenuate Dox cardiotoxicity (DoxTox) in mice. In contrast to our prior work on sustained fasting, Dox administration during refeeding prevents cardiac toxicity and aging, and preserves lean body mass. However, when fasting is started after Dox chemotherapy, fasting potentiates cardiac and skeletal muscle loss, and increases brown adipose mass. Our human proteomic studies of patients with Dox cardiomyopathy identified a regulator of brown adipogenesis that we also found to be increased by fasting and Dox, suggesting that browning may drive cachexia and aging after Dox in humans and mice. In summary, fasting prior to Dox chemotherapy can blunt cardiotoxicity and aging, with implications for future cancer survivorship care. Moreover, our data suggests a novel potential role for brown adipose tissue thermogenesis in Dox-induced toxicity.

Palaniappan, **Nila,** *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Fumihiko Urano

Evan Lee, Nila Palaniappan, Megha Verma, William An, Emiko Pope, Cris Brown, Stacy Hurst, Bess Marshall, Tamara Hershy, Sammie Lee. Genotype and Clinical Characteristics of Patients with Wolfram Syndrome and WFS1-related Disorders. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Diabetes mellitus and optic atrophy demonstrated a dose-effect of number of non-sense/frameshift variants with respect to age of onset. Number of in-frame variants which were transmembrane demonstrated a statistically significant dose-effect on age of onset of diabetes mellitus and optic atrophy. In patients with one in-frame variant and one nonsense/frameshift variant, an in-frame variant in a transmembrane position had statistically significant earlier onset of diabetes mellitus. A greater number of variants correlates with earlier onset and a more severe presentation of Wolfram.

Park, **Christopher,** *Department of Medicine, Division of Cardiology/Cardiovascular Diseases*
Mentor: Joel Schilling

Park CC, Chan MM, Schilling JD, Fu CF. Investigating the Role of Nlrp3 and Irg1 on MASH Pathogenesis. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Kupffer cell-specific deletion of Nlrp3 does not impact Kupffer cell loss or inflammatory/fibrotic markers in a mouse model of MASH. Loss of Irg1 from macrophages enhances IL-1b release in a macrophage subtype-specific manner. Deficiency of Irg1 in macrophages does not impact tissue pathology in a mouse model of MASH.

Patel, **Sumit,** MS, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Maria Remedi

Patel SP, Zihan Y, Remedi MS. Intermittent Fasting Improves diabetes and Protects Beta-cell Mass and Function in Polygenic Mouse Models of T2DM. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Chronic hyperglycemia induces β-cell dysfunction, loss of β-cell mass/identity, and β-cell dedifferentiation. Intermittent fasting reduced blood glucose and plasma insulin levels, decreased body weight gain, reduced plasma triglycerides and cholesterol, and improved insulin sensitivity. Intermittent fasting enhanced expression of the β-cell transcription factors: PDX1 and NKX6.1, and decreased

expression of dedifferentiation marker: ALDH1a3 suggesting protection from loss of β-cell identity. Intermittent fasting increased glucose stimulated insulin secretion in islets from polygenic mouse models of T2DM, demonstrating improved β-cell function.

Petersen, **Max,** MD, PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Samuel Klein

Petersen MC, Yoshino M, Smith GI, Shulman GI, Klein S. Effect of weight loss on skeletal muscle bioactive lipids in people with obesity and type 2 diabetes. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Marked (>15%) weight loss in adults with obesity and type 2 diabetes was associated with an approximately 2-fold increase in skeletal muscle insulin sensitivity. Improved muscle insulin sensitivity after weight loss was associated with a decrease in mitochondrial C18 ceramide content, but no change in sarcolemmal sn-1,2-DAG content or sarcolemmal C18 ceramide content. These results suggest a decrease in muscle mitochondrial C18 ceramide content could contribute to the therapeutic effect of weight loss on skeletal muscle insulin sensitivity.

Porubska, **Bianka,** *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Monika Bambouskova

Porubska B, Mrad M, Wigge NM, Frankfater Ch, Hsu FF, Bambouskova M. IκBζ acts as a key regulator of metabolic rewiring of activated Mϕ. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

IκBζ is important for metabolic switch after different TLR stimulations, mostly pronounced after activation of TLR7/8. Metabolic differences in IκBζ KO macrophages associate with different cytokine profile. IκBζ is transiently expressed after TLR4 but remains up-regulated after TLR7/8 activation. IκBζ is down-regulated in TRIF-dependent manner.

Prifti, **Kevin,** BS, *Department of Obstetrics and Gynecology*
Mentor: Antonina Frolova

Prifti KK, McCarthy R, England SK, Frolova AI. Mice with diet-induced obesity (DIO) have decreased uterine contractility in vivo and alterations in the uterine metabolomic profile. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

DIO mice have higher rates of labor dystocia. DIO mice have impaired uterine contractility in vivo. Untargeted metabolomic profiling of uterine tissue reveals dysregulation of multiple metabolomic pathways in DIO uteri. These data suggest a dysregulated uterine energy fuel homeostasis in the setting of obesity.

Ray, **Mary Katherine,** PhD, *Department of Psychiatry*
Mentor: Ana Maria Arbelaez

Ray MK, Bryan M, Hershey T, Arbelaez AM. Engaging Youth with Type 1 Diabetes from Underrepresented Communities in Research: Lessons Learned. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Youth from racial/ethnic minority, low income, and rural populations are often underrepresented in diabetes research, and unique engagement strategies are needed to reach these communities. Lesson 1: A collaborative approach is necessary to reach these communities and Washington University and St. Louis Children's Hospital have numerous resources to promote this effort including the Center for Diabetes Translational Research, Center for Community Health Partnership and Research, and the Healthy Kid Express Mobile Diabetes Treatment Unit. Lesson 2: A mixed method approach that includes qualitative input from youth with Type 1 Diabetes and their caregivers is invaluable for determining what methods and outcomes should be considered for studies aimed at better understanding diabetes in youth. Lesson 3: Additional consideration is needed to ensure youth from low resource communities have the materials needed to engage in diabetes research such as providing continuous glucose monitors to assess glycemic control.

Sanchez-Castro, **Enrique E.,** MSc, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Jeffrey R. Millman

Sanchez-Castro EE, Ishahak M, Millman JR. In silico transcription factor perturbations unravel candidates to enhance protocols for stem cell-derived islet generation. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Multiomic data of several time points of Stem Cell-derived Islets across the differentiation protocols allows the simulation of transcription factor knock out to unravel fate drivers. Top transcription factor candidates to inhibit in order to block the off-target like-enterochromaffin cells specification (ARID2 and ZEB1) are related with chromatin remodeling activity. Stage 5 day 5 (at the middle of the pancreatic progenitor stage) is the critical time point from where the specific pancreatic cell types and the like-enterochromaffin cells arise. Both Beta cells and like enterochromaffin cells share a common progenitor. In fact, based on transcriptomic and chromatin accessibility data, they are closer related to each other than to other cell types such as alpha or delta cells.

Symons, **J David,** PhD, *Nutrition and Integrative Physiology, University of Utah*

Symons J, Mookherjee S, Wilkerson J, Holland W, Summers S, Denorme F, Campbell R. Defining the contribution from endothelial cell ceramide accrual to outcomes of acute ischemic stroke. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Ceramides associate with the prevalence and severity of acute ischemic stroke in humans. We evoke acute ischemic stroke (AIS) in mice via transient middle cerebral artery (MCA) occlusion (tMCAO). 60-min tMCAO + 23 h reperfusion heightens brain ceramides in mice. In preliminary studies, serine palmitoyl transferase (SPT) inhibition improves cerebral infarct volume, neurobehavioral, and motor outcomes of acute ischemic stroke (AIS) in mice. However, SPT inhibitors have gut toxicity and cannot be used. Here we test the hypotheses that : (i) dihydroceramide desaturase 1 (DES1) inhibition improves cerebrovascular, neurobehavioral, and motor outcomes of AIS; and (ii) amplifying endothelial cell ceramides worsens, whereas (iii) inhibiting endothelial cell ceramides mitigates, AIS outcomes.

Talati, **Khushi,** *Department of Medicine, Division of Gastroenterology*
Mentor: Devesha Kulkarni

Kulkarni DH, Rusconi B, Floyd AN, Joyce EL, Talati KB, Kousik H, Harris DL, Newberry EP, McDonald KG, Newberry RD. Gut microbiota induces weight gain and inflammation in the gut and adipose tissue independent of

manipulations in diet, genetics, and immune development. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Gut microbiota from obese human samples, independent of obesogenic diet and genetics, was sufficient to drive significant weight gain in mice with a normal immune system. The microbiota was also sufficient to drive significant systemic inflammation, independent of other manipulations; the microbiota drove the accumulation of inflammatory immune cells in the small intestine and adipose tissue but did not promote intestinal barrier leak. Obese donor microbiota, but not lean donor microbitoa induced gene expression that promoted caloric uptake and harvest but was less effective at inducing genes associated with mucosal immune responses. Dysbiotic gut microbes from individuals with obesity, affects intestinal epithelial goblet cells and inhibit goblet cell functions.

Townsend, **Shannon,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Jing Hughes

Townsend SE, Li ZA, Cho JH, Hughes JW. Investigating β-cell ciliary involvement in the modulation of β-cell endoplasmic reticulum stress. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Primary cilia are sensory cellular organelles located on the surface of cells and disruption in the functioning of primary cilia leads to many diseases, some of which include symptoms such as obesity and diabetes. Loss of primary cilia on β cells leads to dysregulated hormone secretion in α, β, and δ cells. Lack of primary cilia on β cells results in increased expression of the endoplasmic reticulum (ER) stress markers calreticulin and calnexin. During basal conditions, βCKO (β-cell cilia knockout) islets express several ER stress markers more highly than wild-type islets, which is further exacerbated by treatment with the ER stressor thapsigargin.

Usala, **Sister Grace Miriam,** MD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Erica Scheller

Usala RL, Shen I, Mohseni M, Mitchell D, Bouxsein M, Scheller EL. Adolescent girls with type 1 diabetes develop changes in bone prior to evidence of clinical neuropathy. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

> Adolescent girls with type 1 diabetes mellitus (T1D) develop changes in bone prior to evidence of clinical neuropathy. In the tibia, cortical volumetric bone mineral density increases, and cortical porosity decreases in our population of adolescent girls with T1D. We hypothesize girls with type 1 diabetes mellitus are exposed to exogenous insulin (a growth hormone that promotes density) and also dysregulated counterregulatory hormones (which compromise bone remodeling especially in weight-bearing bone). Despite changes in bone microarchitecture, bone mineral density (BMD) and estimated failure load in adolescent girls with T1D does not differ from controls. Also, neuropathy was not identified on clinical testing in adolescent girls with T1D. Because BMD is used for bone health screening and clinical bedside exam is not sensitive for subclinical neuropathy, emerging bone disease and neuropathy in patients with T1D is likely missed. Bone microarchitectural changes in the tibia (weight-bearing bone) are more pronounced than in the radius (non-weight-bearing bone). This suggests some contribution of the skeletal response to biomechanical load in diabetic bone disease.

Ustione, **Alessandro,** PhD, *Department of Cell Biology and Physiology*
Mentor: David Piston

Ustione A, Piston DW. The ongoing efforts to develop a high-throughput assay to study glucagon secretion. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

The regulation of glucagon secretion is important for euglycemia and for proper management of diabetes. Intrinsic heterogeneity of islet cells is an obstacle to scaling up glucagon secretion assay. Minitaturization and automation are necessary to establish a reliable high-throughput assay to measure glucagon secretion. Luminescence and fluorescence can be both be used to engineer genetically encoded reporters of proglucagon processing.

Verma, **Sonam,** PhD, *Department of Medicine, Division of Allergy and Immunology*
Mentor: Peggy Kendall

Verma S, Cohen SL, Olin RI, Kendall LP. Akkermansia muciniphila acts synergistically with Btk-deficiency to prevent Type 1 Diabetes. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Gnotobiotic monocolonization of Btk-/-/NOD with A. muciniphila protected significantly against T1D compared to germ-free or monocolonized WT NOD mice. High FOXP3/CD4 ratio in Btk-/-/NOD and Btk-/-/NOD with A. muciniphila suggests the role of Tregs in protection from T1D. Transmission electron microscopy (TEM) of the small intestine and MUC2 staining showed dense mucus layer and unexpected presence of free active mitochondria in the intestinal lumen of Btk-/-/NOD mice as compared to WT NOD. The insulitis score at the early time point of 9-10 weeks was reduced in Btk-/-/NOD mice compared to WT NOD mice, but A. muciniphila did not affect this outcome in either genotype.

Veronese-Paniagua, **Daniel,** BA, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Jeffrey Millman

Veronese-Paniagua DA, Hernandez-Rincon DC, Augsornworawat P, Tse H, Millman JR. Coxsackievirus b infection invokes unique cell-type responses in a heterogenous pancreatic organoid model. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

There are cell type-specific responses to viral infection within the various islet cell populations. Transcriptional and functional assays indicate a decrease in mitochondrial function in coxsackievirus infected islets. Alpha, beta, and ductal cells have the strongest immune responses whilst delta cells are virtually transcriptionally unaffected by viral infection. Genetically modified human stem cell-derived islets elucidate the role of MIR7-3HG, a novel islet gene, in viral infection and replication.

Wasserman, **Henry,** *Department of Pediatrics*
Mentor: Brian DeBosch

Wasserman HD, Higgins CB, Adams JA, Joshi H, Sun J, Zhang Y, Kelly S, Morley SC, DeBosch BJ. Hepatocyte L-Plastin is Induced in NASH and Mediates Lipid Accumulation. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

L-plastin is present in hepatocytes during NASH. L-Plastin knockout reduced body weight gain in a mouse model. L-Plastin mediates cell-autonomous LPS-induced inflammation in hepatocytes. L-Plastin mediates lipid accumulation in the liver in vivo.

Williams, **Rashaun,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Maria Remedi

Rashaun A Williams, Esmeralda Castelblanco, Sumit Patel, Jeongmin Lee, Davis Piston, Maria S Remedi. Reduced incretin signaling in pancreatic β-cells from KATP-GOF diabetic mice can be restored by GLP1R/GIPR agonists. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

KATP gain-of-function mutations (KATP –GOF) cause Neonatal diabetes. KATP –GOF mice developed severe diabetes due to lack of insulin secretion, reiterating the features of the human disease. As diabetes progresses, KATP –GOF mice show loss of insulin content, increased islet oxidative and ER stress, reduced ER calcium and distended ER, and deteriorated mitochondria. Single Cell RNA seq showed downregulation of GLP1 and GIP receptors in β-cells from KATP –GOF mice, consistent with decreased GLP1R and GIPR proteins by western blot analysis. Islets from KATP –GOF mice did not show increase in calcium or cAMP in response to high glucose, but both calcium and cAMP increased in response to Exenatide (GLP1R agonist) or Forskolin (AC activator); suggesting that GLP1R/GIPR agonist therapy can restore incretin signaling in KATP –GOF mice.

Woodson, **Reilly,** BS, *Department of Molecular Microbiology*
Mentor: Christina Stallings

Woodson R, Mayer Bridwell AE, Brestoff JR, Castelblanco E, Remedi MS, Stallings CL. Investigating the effects of diabetes on Mycobacterium tuberculosis pathogenesis. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Neutrophils in diabetic mouse models respond differently to Mycobacterium tuberculosis infection. Mouse models of Type 1 and Type 2 diabetes are more susceptible to Mycobacterium tuberculosis infection. Host genetic background influences the susceptibility of Type 1 diabetes mouse models to Mycobacterium tuberculosis infection.

Wu, **Feixuan,** *School of Pharmacy, University of Kentucky*
Mentor: Lingjun Li

Wu FX, Tabang DN, Chiang HY, Li ZH, Lu K, Zhu ZX, Odorico JS. Li LJ. A Mass Spectrometry-Enabled Multiomic Investigation of Pancreatic Islets in Diabetes. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Characterize the matrisome of the peri-islet and intra-islet regions in human pancreas. MALDI-MS imaging of pancreas tissues and islets Characterize human islet peptide hormone production in diabetes. Characterize human islet post-translational modifications (PTMs) and their changes in diabetes.

Xue, **Jeffrey,** BA, *Department of Ophthalmology and Visual Sciences*
Mentor: Rithwick Rajagopal

Xue JL, Zhang S, Rajagopal R. A Novel Tool for Investigating Loss of Rod-Photoreceptor De Novo Lipogenesis in Post-Developmental Tissues. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Fatty Acid Synthase (FAS) is a key enzyme in de novo lipogenesis, and its loss in retinal tissue results in profound neurodegeneration. In prior studies, we used genetic tools that caused FAS loss in the developing retina. Though our studies suggest that the phenotype occurred in post-developmental stages, we aimed to create a more reliable tool to study FAS manipulation in the adult retina. In this study, we designed and validated a tamoxifen-inducible mouse line, with rod-photoreceptor specificity. The tamoxifen-inducible line was tested using reporter gene assays.

Yiew, Nicole, PhD, *Department of Medicine, Nutritional Science & Obesity Medicine*
Mentor: Brian Finck

Yiew NKH, Deja S, Ferguson D, Cho K, Jarasvaraparn C, Jacome-Sosa M, Lutkewitte AJ, Mukherjee S, Fu X, Singer JM, Patti GJ, Burgess SC, Finck BN. Effects of hepatic mitochondrial pyruvate carrier deficiency on de novo lipogenesis and glycerol-mediated gluconeogenesis. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Rates of de novo lipogenesis were impaired by the loss of hepatic mitochondrial pyruvate carrier (MPC), but this did not reduce intrahepatic lipid content. Metabolomics analyses revealed that the loss of hepatic MPC: enhanced glycerol conversion into blood glucose via the direct cytosolic pathway; decreased glycerol conversion into TCA cycle metabolites and glucose via the indirect mitochondrial pathway. Interestingly, suppression of glycerol metabolism did not affect glucose concentrations in mice with liver-specific MPC deficiency. Glycerol-mediated gluconeogenesis and glucose production by kidney and intestine may compensate for MPC deficiency in the liver.

Zhang, **Xiaohua Douglas,** PhD, *Biostatistics, University of Kentucky*

Zhang XD, Nikolajczyk BS, Saraswat S, Fisher SJ, Kern PA. Development of Analytic Methodology and Software for Using Cytokine Profiling and Continuous Glucose Monitoring in Diabetes. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Analytic software for analyzing cytokine profiling and continuous glucose monitoring (CCGM) data. Workflow of data analysis for cytokine profiling and CGM studies. Quality control using biologically meaningful cutoffs.

Zhang, **Wei,** PhD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Clay Semenkovich

Zhang W, Wei XC, Yin L, Feng C. Dong GF, Adak S, Debnath A. Wang YX, Singamaneni S, Semenkovich CF. Depalmitoylation inhibition improves glucose tolerance by promoting insulin transcytosis across the endothelium. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Endothelial cell-specific knockout of de-palmitoylase APT1 improves the glucose tolerance of diet-induced obese mice. Using the in vivo plasmonic fluor-linked immuno-microneedle patch technique, Endothelial APT1 KO mice showed increased insulin concentration in interstitial fluids. Inhibition of APT1 in endothelial cells promotes insulin transcytosis through dynamin and flotillin-1-related transport pathways. APT1 overexpression in endothelial cells inhibited insulin transcytosis.

Zhang, Rong Mei, MD, *Department of Medicine, Division of Endocrinology, Metabolism & Lipid Research*
Mentor: Carlos Bernal-Mizrachi

Zhang RM, Oh J, Kutz G, Dusso AS, Bernal-Mizrachi C. Acute Hyperglycemia Induces Human Podocyte Apoptosis by Increasing Monocyte Release of TNF□□through ER stress/ROS Activation of ADAM17/iRhom2 Expression. Poster session presented at: Diabetes Day 2023. Washington University School of Medicine. 2023 November 9. St. Louis, MO

Acute moderate hyperglycemia mimics frequent episodes of acute hyperglycemia in podocyte- driven microalbuminuria through distinct mechanisms. An acute episode of moderate hyperglycemia cannot induce podocyte apoptosis directly, but it is sufficient to induce the release of TNFα by normal human monocytes to levels that drive podocyte apoptosis. In normal human monocytes, acute hyperglycemia-induces TNFα release through ROS- and ER stress- activation of ADAM17/iRhom2 expression. During acute hyperglycemia, GLP1 activation of monocyte GLP1 receptor downregulates ADAM17/iRhom2 expression, thereby decreasing TNFα release and podocyte apoptosis. This uncovers a novel anti-inflammatory role for GLP1 receptor agonists in attenuating renal disease progression.

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