2009 Pilot & Feasibility Award Recipients

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Malcolm J. Avison, Ph.D.
Professor, Department of Radiology and Radiological Sciences

"Functional Brain Imaging in Mouse Genetic Models of Obesity and Diabetes"

Functional neuroimaging is now widely employed in human studies to identify functional phenotypic correlates of genetic polymorphisms and epi-genetic variability. Conversely, genetically manipulated mouse models are increasingly used to test (and to generate) novel hypotheses related to the genetic basis of variability in behavior. Both approaches are gaining increased attention in the area of obesity and diabetes research, as recognition of the importance of understanding the central mechanisms regulating food intake (and behaviors therein) in developing effective strategies for managing obesity. However significant gaps remain in linking molecular and cellular consequences of genetic manipulations to systems-level effects on CNS circuitry in mice, and in identifying the specific molecular and cellular pathways mediating the (epi-)genetic influences on brain function in humans. The present proposal seeks to address this by bringing together experts in neuroimaging, obesity and diabetes research, and mouse genetic models of obesity and diabetes. Specifically, we propose to address a significant gap in technology (human and rat imaging have progressed rapidly), to develop core methodology for functional imaging of brain circuitry in genetically modified mice. The research will focus on developing a toolbox of techniques for acquisition and analysis of the neural correlates of neuro-genetic manipulations, and will validate them in well characterized mouse models of obesity and diabetes. Specifically, we will: 1. Translate and extend existing functional imaging methods developed in rats to mice; 2. Develop novel computational tools for the identification of systems/circuit level effects of cell-type specific genetic manipulation.

Wenbiao Chen, Ph.D.
Assistant Professor, Department of Molecular Physiology and Biophysics

"Nutrient Regulation of Beta Cell Mass in the Zebrafish"

Intrauterine malnutrition, manifested as low birth weight, is strongly associated with type 2 diabetes. Another hall marker of intrauterine malnutrition is the decreased mass of pancreatic beta cell. In rodent models, this decrease of beta cell mass is irreversible late in life, predisposing the animal to type 2 diabetes. The mechanism of malnutrition-induced decrease of beta cell mass is not clear. We have demonstrated that zebrafish fries experience a marked expansion of beta cell mass during the first 4 days of free feeding and food withholding during the period completely abolish the expansion. In the proposed pilot and feasibility studies, we will determine whether the diminishment of beta cell mass is irreversible as in rodents, and whether the nutrient-sensing mTOR pathway is involved in food-induced beta cell growth in this model. Lastly, we will develop a transgenic fish that fluorescently labels the membrane and nucleus of beta cells for precise measurement of beta cell size and number. The transgenic line should facilitate screens for the identification of genes and compounds that alter this nutrient response. Since nutrient sensing and beta cell biology are largely conserved in vertebrates, studies in the zebrafish should provide relevant insights in humans.

Charles R. Flynn, Ph.D.
Assistant Professor

"Diacylglycerols and Insulin Action in Skeletal Muscle upon Caloric Restriction"

Insulin resistance in skeletal muscle is a characteristic abnormality of obesity and type 2 diabetes (T2DM). Although the mechanisms responsible for this pathophysiology remain unclear, the intramuscular accumulation of lipids is crucial. Current evidence points towards dyslipidemia-induced DAG accumulation and inflammation as a consequence of a high fat diet as contributory. In this project, we will test the hypothesis that in skeletal muscle, molecular species of DAGs enriched in palmitate, a reactive oxygen species
(ROS) promoting fatty acid will be decreased preferentially in both short- and long-term caloric restriction, but that the decrement will be greater in the morbidly obese cohort. We also anticipate that DAG species rich in oleate, a protective fatty acid, will remain unchanged in both groups during the short-term but will increase with long term caloric restriction in the morbidly obese. Lipid extracted from skeletal muscle biopsies obtained both before and after short-term and long-term caloric restriction will be analyzed using mass spectrometry-based lipidomics approaches to monitor molecular DAG species accumulation. The hyperinsulinemic-euglycemic clamp technique will be used to assess insulin-stimulated glucose disposal activity. The differential expression of lipids in muscle will be correlated with circulating and tissue resident markers of inflammation, fibrosis and macrophage infiltration. We expect data from our proposed studies will provide new insight into mechanisms underlying insulin resistance.

Sabina B. Gesell, Ph.D.
Research Assistant Professor
Department of Pediatrics

"Building Social Networks to Prevent Postpartum Weight Retention"

Obesity is highly associated with type 2 diabetes. Inspired by the seminal work of Christakis and Fowler that demonstrated the power of social network phenomena on the development of obesity and cessation of smoking, this project sets the groundwork for examining whether social networks can play a significant role in preventing postpartum weight retention on a population-level. The goal of this proposal is to conduct feasibility pilot work to 1) establish recruitment and retention rates of pregnant Latinas who are recent immigrants and at high risk of developing obesity; 2) develop and manualize a culturally-tailored intervention program that increases ties among participants and with community resources; and 3) test tools to accurately capture social network information that allow for social network analysis, and parameter estimation to inform future power calculations. A within-subjects repeated measure design will be used investigate to the effect of a social network enhancement intervention on change in social network attributes. We estimate being able to recruit 30 lower income pregnant Latinas > 18 years who will receive a 12-week social networking intervention during pregnancy with the goal of influencing postpartum outcomes. Primary outcomes of interest are various network attributes; secondary outcomes are postpartum body mass index and body composition. Data will be collected at baseline, at completion of the intervention, at 1 moth postpartum and 6 months postpartum. Recruitment and retention rates will be calculated (Aim 1) and patterns of missing data will be examined (Aim 2). Stage one of the social network analysis will include assessing the degree and nature of network formation by examining the creation of dyadic ties, the formation of subgroups in the network, and by measuring changes in the overall density of the network (Aim 3). Stage two will treat individual-level network-related characteristics as independent variables predicting intervention-related outcomes.

Todd M. Hulgan, M.D., M.P.H.
Assistant Professor
Department of Medicine

"Adipokines and Oxidant Stress in Diabetic and Non-Diabetic HIV-Infected Subjects"

Human immunodeficiency virus (HIV) infection and the resulting acquired immunodeficiency syndrome (AIDS) is one of the greatest public health challenges in history. Antiretroviral therapy (ART) has dramatically reduced morbidity and mortality due to HIV/AIDS, but remains limited by long-term complications. These complications include mitochondrial toxicities due primarily to nucleoside reverse transcriptase inhibitors (NRTI), and metabolic complications attributed to the non-NRTI (NNRTI) and protease inhibitor (PI) drug classes. These ART complications mirror the metabolic syndrome, with insulin resistance (and overt type 2 diabetes mellitus), dyslipidemia
(predominant hypertriglyceridemia), and lipodystrophy (including abdominal obesity). Not surprisingly, excess cardiovascular disease (CVD) and myocardial infarction rates have been reported in association with ART exposure. Mechanisms of metabolic complications in HIV infection and its treatment are poorly understood, and appear to differ by drug class. NRTI have adverse effects on mitochondrial and cellular energetics. Some NRTI have direct effects on insulin sensitivity, and have been associated with development of insulin resistance and diabetes in cohort studies. PI influence cellular lipid and glucose metabolism, leading to hypoleptinemic and hypoadiponectinemic states. The additional influence of chronic inflammation due to HIV infection is unknown. Much remains to be learned about the effects of HIV and ART on fundamental processes of oxidant stress, inflammation, and adipogenesis in HIV-infected patients, especially as they relate to ART-associated fat redistribution, obesity, insulin resistance, and diabetes. The overarching hypothesis of the proposed studies is that in HIV-infected persons, adiponectin will be negatively correlated with F2-isoprostanes (a urine biomarker of oxidant stress and CVD risk), but this correlation will be influenced by ART exposure, fat content (total, trunk, limb) by dual-energy X-ray absorptiometry, and by the presence of insulin resistance by homeostasis model assessment and/or diabetes mellitus. This hypothesis will be tested through the determination of fasting adipokine levels in stored specimens from an ongoing cohort study of HIV-infected, chronically ART-treated, non-diabetic subjects (N=50), and in prospectively enrolled, chronically HIV-infected, ART-naÃ¯ve, non-diabetic (N=30) and ART-treated diabetic subjects (N=30). We will then determine correlations between adipokines and urine eicosanoid biomarker data, adjusted for regional fat content and the presence of insulin resistance or diabetes mellitus.

Stacey S. Huppert, Ph.D.
Assistant Professor
Department of Cell and Developmental Biology

"Requirement of Notch Signaling for Beta Cell Neogenesis"

Development of safe and effective therapeutic options for diabetes mellitus requires a thorough understanding of the genetic components governing pancreatic development, maintenance, and injury responses. Transplantation of islet cells has been successfully performed, relieving patients with type I diabetes of symptoms for extended periods of time. This suggests that diabetes can be treated by replenishing deficient ÃŸ cells. ÃŸ cell mass is normally dynamic, responding to meet endocrine demands throughout life. Increases in ÃŸ cell mass can occur via self-duplication of existing ÃŸ cells, but is also proposed to occur via ÃŸ cell neogenesis from adult stem/progenitor cells. Notch signaling is a critical molecular component for lineage commitment decisions of pancreatic progenitors during embryonic development, regulating multiple steps of cell maturation relative to neighboring cells. While this embryonic role has been described, it is unknown if Notch signaling plays a role during activation of adult multipotent progenitors in response to injury, regulating new islet formation. We hypothesize that Notch signaling is crucial for lineage commitment and/or cell fate decisions of the facultative progenitor cells within the adult pancreatic ductal epithelium following partial duct ligation. The aims within this proposal will take advantage of pre-existing mouse models that enable lineage tracing and inducible lineage-specific ablation of Notch signaling within the keratin 19-positive ductal epithelium.

Patricia A. Labosky, Ph.D.
Associate Professor
Department of Cell and Developmental Biology

"Control of Beta Cell Proliferation during Pregnancy"

Diabetes affects an estimated 150 million people worldwide and the disease carries with it a myriad of associated health problems. Unfortunately, most treatments for diabetic patients are inadequate because they do not regulate blood glucose levels precisely enough to eliminate complications. The insulin producing cells of the pancreas, beta cells, do not normally proliferate extensively in adults. However, under certain conditions of metabolic challenge (pregnancy and obesity), beta cells undergo proliferation and beta cell mass expands up to two-fold. One hope for developing promising diabetes treatments is based on manipulating beta cell proliferation. A critical piece of information needed for this strategy is an understanding of the molecular mechanisms controlling beta cell proliferation. Our goal is to understand how normal beta cell proliferation in response to metabolic demands is regulated with the long-term expectation that this information could then be used to increase beta cell mass in diabetic patients. The transcription factor Foxd3 is required for the survival, selfrenewal and multipotent nature of several disparate progenitor cell types, embryonic stem (ES) cells, trophoblast and neural crest progenitor cells. Foxd3 is also expressed in the pancreatic primordium beginning at 10.5 dpc and becomes localized predominantly to beta cells after birth. Mice carrying a tissue specific deletion of Foxd3 in the pancreatic epithelium have normal glucose homeostasis. However, pregnant mutant mice exhibit gestational diabetes. Here we propose a series of experiments to test the hypothesis that Foxd3 is required for altered beta cell function and/or proliferation during pregnancy with the expectation that a better understanding of the molecules controlling these compensatory beta cell changes will augment the development of improved therapies for diabetes.

John M. Stafford, M.D., Ph.D.
Assistant Professor
Department of Medicine

"Portal Glucose as a Driver of Diabetic Dyslipidemia"

In recent decades, death from coronary heart disease
(CHD) has declined by 40% in the US population. By stark contrast, for patients with diabetes, risk of death from CHD continues to rise. This difference in CHD risk between diabetic patients and the general population may result from additional CHD risk factors associated with elevations in serum triglyceride (TG). Hyperglycemia is a major driver of TG production in diabetes. Several key control points in hepatic TG production are independently controlled by both glucose and insulin - In normal physiology, glucose and insulin signals are coordinated to control the production and utilization of TG, the bodyâ€™s main energy source. Much of this coordination may be due to the functional organization of the liver and portal venous system. Remarkably, after a mixed-meal gut enterocytes shuttle meal-lipid into gut lymphatics, which drain to the systemic circulation, avoiding the liver. By contrast, mealrelated glucose is directed into the portal venous system, which drains directly to the liver. This anatomic organization is mirrored in the structure of liver acini, which compartmentalize glucose production from lipid production. Portal delivery of glucose also activates a â€œportal signalâ€ mediated by the autonomic nervous system to promote hepatic glucose uptake, and may limit lipid production. Diabetic patients have abnormalities in both postprandial glucose and lipid metabolism. We propose that with diabetes, the anatomic organization of the portal system contributes to augmented glucose-mediated lipid production. Our pilot data using clamp and tracer techniques combined with molecular dissection of the insulin-signaling pathway demonstrate that peripheral delivery of glucose promotes VLDL production only with impaired insulin action. In this proposal, we test the hypothesis that portal glucose delivery will further augment hepatic VLDL production (AIM1) and that portal glucose more potently promotes VLDL secretion when insulin action is disrupted (AIM2). This situation is analogous to the physiology of diabetes where either insulin deficiency (DM1) or insulin resistance (DM2) contribute to postprandial glucose and lipid abnormalities. These studies are highly collaborative with Dr. Masa Shiota, director of the Rat Metabolic Physiology Core. Collectively these studies will provide detailed information about the contribution of hyperglycemia to altered VLDL in diabetes, a major contributor to CHD in diabetic patients. The molecular mechanisms of how this metabolic control is coordinated will be the subject of future experiments, and will undoubtedly serve as the roots of many years of future studies for the lab. Support of the DRTC Pilot and Feasibility Program will be an important contributor to my prolonged success in diabetes research.