

2010 Pilot & Feasibility Award Recipients

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Kate Ellacott

Kate L.J. Ellacott, Ph.D.

Assistant Professor of Molecular Physiology and Biophysics

"The Effect of Obesity on Cerebral Endothelial Cell Function"

Obesity is associated with chronic low-grade inflammation in the periphery, which in turn is linked to the development of metabolic syndrome and cardiovascular disease. Endothelial cells of the peripheral vasculature are negatively affected by inflammatory stimuli and this dysfunction contributes to the development of atherosclerosis in obese individuals. In addition to the peripheral vasculature, endothelial cells are also a critical component of the blood-brain barrier (BBB) and cerebral vasculature. Mounting evidence from clinical studies suggests that obesity is associated with increased vulnerability of the central nervous system (CNS); for example, obese individuals have a 6% higher incidence of stroke for every unit increase in body mass index greater than 30. Furthermore, obese individuals have an 11% increase in mortality following traumatic brain injury and a staggering 74% increased risk of dementia. Obesity and diabetes are known to affect transport across the BBB and alterations in function at this critical interface may contribute to the increased susceptibility of the CNS to damage. The molecular mechanisms underlying this phenomenon have not been examined. We hypothesize that obesity promotes alterations in cerebral endothelial cells, which lead to dysfunction, thus altering BBB and cerebral vascular physiology. This pilot grant proposal will address the following specific aims: 1) To identify specific molecular targets in cerebral endothelial cells regulated by chronic diet-induced obesity in mice; 2) To examine the regulation of expression of these targets over time with the development of obesity and metabolic syndrome. As a new independent investigator a DRTC P&F grant award would provide invaluable funding to allow my laboratory to generate preliminary data on this novel area of study for a National Institutes of Health (NIH) R01 application that we aim to submit in 2011.



Pandu R. Gangula, Ph.D.

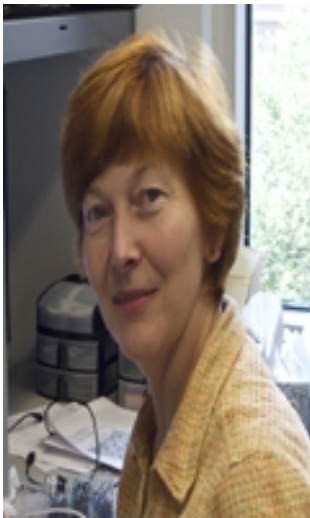
Associate Professor, Obstetrics and Gynecology, Meharry Medical College

"Oxidative Stress and Gastric Nitrergic Motility in Diabetics"

Gastroparesis is a debilitating disease affecting predominantly young women. The biological basis of this disorder and its associated gender bias remains poorly understood. Our recent data suggests that gastric motility is mainly regulated by nitrergic system and interstitial cells of Cajal (ICC) in healthy females and diabetes induction by STZ significantly impaired this system and leading to delayed gastric emptying associated with elevated reactive oxygen species (ROS). However, the underlying biochemical mechanisms by which ROS contributes to gastroparesis are not well understood. Nrf2 (NF-E2-related factor 2) is a transcriptional factor that regulates the expression of Phase II genes involved in regulating levels of reactive oxygen species. Heme Oxygenase I and glutathione (GSH) biosynthesis enzyme, Glutamate Cysteine Ligase subunits (Gclm and Gclc) are two examples of Phase II genes

regulated by Nrf2. GSH is a major soluble antioxidant in cells and is involved in many aspects of cellular metabolism, including detoxification of peroxides and xenobiotics. Nrf2 KO and Gclm KO mice have low GSH levels and are highly susceptible to oxidative stress. Our recent novel data demonstrated that gastric nitrergic relaxation is impaired in Nrf2 KO and in Gclm KO mice. These data suggest that chronic depletion of GSH may be one of the detrimental factors in the pathogenesis of diabetic gastroparesis due to increased oxidative stress. We have, therefore, designed this proposal to investigate the mechanisms responsible for the disturbances in the nitrergic control of gastric motility in Nrf2 KO and Gclm KO females with diabetic or non-diabetic gastroparesis. Based on our preliminary data, we hypothesize that reactive oxygen species is an important component in the pathogenesis of gastroparesis. To test this hypothesis we propose the following specific aim: Specific Aim: To determine the biochemical mechanism

responsible for impaired gastric nitrergic relaxation, gastric emptying and ICC in Nrf2 KO and Gclm-KO mouse models of diabetes. Preliminary data generated from DRTC funds will provide a basis to prepare a major grant application and to investigate in detail with regards to the protective role of GSH on gastric motility functions and mechanisms involved in this setting.



Irina Kaverina, Ph.D.

Assistant Professor, Cell and Developmental Biology

"Role of Distinct Microtubule Populations in Beta Cell Insulin Secretion"

Impairment of insulin secretion contributes to the development of type 2 diabetes. During the extended second phase of glucose-stimulated secretion insulin granules residing in the cell interior are transported toward the plasma membrane by microtubule-dependent transport. Organization of microtubule tracks is an important factor in efficiency of secretion but its regulation is poorly understood. The goal of this pilot project is to determine major pathways that define configuration of microtubule network in pancreatic beta cells through regulation of nucleation and stabilization of microtubules. While microtubules in vertebrate cells are known to nucleate at the centrosomes, most microtubules detected in beta cells are associated with membrane structures such as the Golgi rather than the centrosome. We have recently identified the Golgi complex as an alternative microtubule-organizing center and now propose to test whether Golgi-derived microtubules serve as major tracks for insulin traffic (Aim 1).

Microtubules are also needed to support Golgi integrity. We propose to test whether Golgi-derived microtubules support Golgi reorganization triggered by glucose to facilitate fast insulin processing (Aim 2). Glucose stimulation not only induces insulin secretion but also increases amounts of tubulin polymer, suggesting that this stimulus may increase number of stable microtubules, which are preferred tracks for granule delivering motor kinesin-1. Based on our preliminary data, we propose to test whether microtubules that serve as tracks for insulin granules are specifically stabilized by Rab6A-dependent mechanism (Aim 3). Research strategy includes cutting-edge microscopy and cell manipulation approaches, as well all molecular and biochemical tools. The results of this pilot project will potentially lead to an extensive mechanistic study that could, in turn, contribute to diabetes treatment strategies by revealing new molecular therapeutic targets regulating efficiency of insulin secretion.



Chandra Y. Osborn, Ph.D., M.P.H.

Assistant Professor, Center for Health Services Research

"Leveraging Patient Portals to Provide Medication Adherence Support in Diabetes"

Antihyperglycemic, antihypertensive, and lipid lowering medications have enormous promise for reducing morbidity and mortality in patients with T2DM, but adherence is often suboptimal. Readily available health information technologies (HIT) can provide real-time information and feedback to patients and providers to support medication safety, identify adverse drug events, and improve patient adherence. This proposal describes a research plan that will result in pilot data for the candidate's K award resubmission to NIDDK, in which a patient portal delivered medication adherence will be evaluated among patients with diabetes. As a social/health psychologist who has already received a fair amount of training in behavioral health research, this DRTC Pilot & Feasibility mechanism is crucial to

providing Dr. Osborn with experience using HIT delivery systems, pilot data on the feasibility of her proposed intervention, and a jump start on her career as an independent investigator in the Prevention & Control Core of the Vanderbilt DRTC. Dr. Osborn's immediate goal is to develop and test the usability of a medication adherence intervention for patients with T2DM and co-morbid hypertension and/or dyslipidemia that will be delivered through the My Health at Vanderbilt patient portal. This will be achieved by conducting focus groups to inform intervention content and collecting usability data from diabetes patients once the intervention is developed. The pilot study aims are twofold to 1) identify the optimal structure and content of a patient portal delivered medication adherence intervention for diabetes patients and 2) design, test for usability and refine this intervention for future testing in a three-arm randomized trial (i.e., NIDDK K Award proposal). Leveraging technology in the proposed research will augment the candidate's existing training in the design and evaluation of behavior change interventions. Most importantly, it will accelerate her career as a successful independent investigator well equipped for significant contributions to designing cutting-edge, evidence-based interventions that have broad application and are effective at improving the care of patients with diabetes.