2013 Pilot & Feasibility Award Recipients

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Jerod Denton, Ph.D.

Jerod S. Denton, Ph.D. »
Assistant Professor, Division of Anesthesiology, Department of Medicine

"Development of small-molecule Kir4.2 modulators for treatment of type 2 diabetes"

Type 2 Diabetes Mellitus (T2DM) imposes a substantial burden on society through increased healthcare costs, loss of productivity, and reduced quality of life. The number of diagnosed T2DM patients is projected to increase dramatically in the coming decades. Therefore, developing improved treatment strategies will be essential to lessen the economic and societal impact of T2DM. KCNJ15, which encodes the inward rectifier potassium (Kir) channel Kir4.2, was recently identified as a T2DM susceptibility gene. Kir4.2 is expressed in glucose-responsive, insulin-secreting beta-cells of the pancreas, where recent studies suggest that its up-regulation in T2DM leads to diminished glucose-induced insulin secretion. Importantly, siRNA-mediated knock-down of Kir4.2 expression in vivo increases insulin secretion and lowers blood glucose in diabetic mice. Taken together, these studies raise important questions regarding the physiology of Kir4.2 in beta cells and suggest the intriguing possibility that Kir4.2 represents a novel drug target for T2DM. There are currently no specific pharmacological modulators of Kir4.2. Therefore, the goal of this proposal is to develop, validate, and implement a high-throughput screening (HTS) assay to enable the discovery of the first small-molecule probes of Kir4.2 function. In Aim 1, the investigators will develop a thallium flux-based fluorescence assay to monitor Kir4.2 activity in a 384-well plate format. The robustness of the assay will be determined by meeting a series of performance benchmarks and running a pilot screen of 3,655 compounds in the Vanderbilt HTS center. In Aim 2, the investigators will perform a 30,000 compound screen (15,000 compounds each in funding years 1 and 2) of the Vanderbilt Institute of Chemical Biology Library. The potency and selectivity of Kir4.2 modulators will be characterized in Aim 3 using a panel of established high-throughput thallium flux assays for 9 different Kir channels. These assays dramatically shorten the time from hit discovery in a primary screen to lead compound identification and optimization. The successful outcome of the proposed work will be the development of pre-clinical tool compounds for exploring the physiology of Kir4.2 in beta cells and its therapeutic potential in T2DM.

Kasey C. Vickers, Ph.D. »

Kasey C. Vickers, Ph.D. »
Assistant Professor, Medicine and Molecular Physiology & Biophysics

"Mechanisms and consequences of HDL microRNA communication in diabetes"

We have previously reported that HDL transports and delivers beta-cell specific miRNAs to recipient hepatocytes. Therefore, we aim to determine if beta cells export specific miRNAs to HDL to be delivered to theliver as part of a novel endocrine-like communication network. Furthermore, we aim to determine if this cell-tocellcommunication is altered in hyperglycemia and corrected by Colesevelam treatment, a diabetes drug thathas been found to improve beat cell function and insulin secretion. Results from this pilot and feasibility studywill provide a foundation of basic understanding into a new paradigm of cell communication that likely

contributes to systemic glucose homeostasis.Extracellular RNA and HDL-mediated intercellular communication has tremendous applicability to manydiseases. As new investigator to Vanderbilt, I have a strong interest in expanding my research program toinclude diabetes, and have a significant interest in a research career in diabetes. Nevertheless, myinvestigation into diabetes is just beginning; therefore, this award will provide the necessary funds to obtainsufficient data for individual grant support in the field of diabetes.

Danny Winder, Ph.D.

Danny G. Winder, Ph.D. »
Professor, Molecular Physiology & Biophysics

“BNST CRF and maintenance of weight loss”

Maintenance of diet-induced weight loss is a major problem in the treatment of type II diabetes. Animal model studies have suggested an important role for corticotropin releasing factor (CRF) neurons in the bed nucleus of the stria terminalis (BNST) in stress-reward interactions, and more recently in feeding behavior. In particular, CRF signaling within the BNST produces anorexia. Recent studies demonstrate that caloric restriction in mice produces a profound decrease in CRF levels in the BNST that persists even after a return to ad libitum feeding.

This may represent the removal of an important brake on stress-induced feeding behavior that contributes to diet relapse. Currently, however, very little is understood regarding the CRF system in the BNST. We have recently successfully utilized a genetic reporter strategy to isolate CRF neurons within the BNST for morphological and electrophysiological analysis. Here, we propose to use optogenetic and fluorescent-reporterbased animal models to determine inputs and outputs of CRF neurons in the BNST, to determine the specific inputs to the BNST that are opposingly regulated by CRF and orexin, and to examine the long-term impact of

caloric restriction on the excitability of BNST CRF neurons and neuropeptide function in the region. The successful completion of these studies will delineate a microcircuit potentially involved in diet relapse and set the stage for 1) further ex vivo studies testing for means of controlling this circuit and 2) in vivo analysis of the impact of activation and inhibition of this circuit on feeding behavior.