

2016 Pilot & Feasibility Award Recipients

The Vanderbilt Diabetes Research and Training Center (DRTC) announces the awardees of Pilot and Feasibility Grants for 2016 in the areas below:

Diabetes Research & Training Center Grant

Covers Basic and/or Clinic Research related to Diabetes, Metabolism and/or Obesity

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Vanderbilt Diabetes Center Discovery Program Grant

Covers Diabetes and/or Obesity-related Pilot studies that utilize high-throughput Facility Bio VU and/or the Mass Spectrometry Research Centers

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Pilot & Feasibility Award Recipients

Nathan C. Bingham, M.D., Ph.D.

Department of Pediatrics, Division of Pediatric Endocrinology

Mitigation of hypothalamic inflammation via ablation of microglial IKKbeta

Rodents fed a high-fat diet (HFD), upregulate proinflammatory cytokines within the mediobasal hypothalamus (MBH), an important center of neuronal control of appetite and metabolism. This metabolically-induced inflammation, or 'metaflammation,' contributes to central leptin resistance, increased caloric intake, and obesity. These results run contrary to a large body of work that has identified hypothalamic inflammatory signaling as a mediator of the sickness-induced cachexia response triggered in response to classic inflammatory stimuli such as injury, infection, cancer, or autoimmunity.

As the innate immune cells of the CNS, microglia have been implicated as potential effector cells of both metabolic and classical inflammatory stimuli within the hypothalamus. Here, we propose strategies for defining the role of microglial NF-kB signalling, a key molecular of the microglial inflammatory response, in the development of hypothalamic inflammation. We have developed an inducible Cre-Lox mouse line to ablate NF-kB signaling specifically in microglia. Study of these mice will provide a better understanding of the mechanisms whereby microglia contribute to hypothalamic inflammation and could uncover novel targets for the treatment of diet-induced obesity and cachexia.

Justin M. Gregory, M.D.

Department of Pediatrics, Division of Pediatric Endocrinology

Peripheral Insulin Delivery's Contribution to Insulin Resistance in Type 1 Diabetes

The goal of this pilot and feasibility proposal is to determine the pathophysiologic mechanisms underpinning insulin resistance (IR) in type 1 diabetes (T1DM), a consistent but under-recognized problem in this condition and a major predisposing factor to macrovascular disease, the leading cause of death in these patients. My research will test the hypothesis that IR in T1DM is predominantly a consequence of iatrogenic hyperinsulinemia in the peripheral circulation (as opposed to an effect of chronic hyperglycemia, as is commonly thought). I will test this hypothesis using a novel cross-sectional study design evaluating IR in 3

groups: subjects with T1DM, glucokinase mutations, and non-diabetic controls. I will utilize the

hyperinsulinemic, euglycemic clamp to exploit key metabolic differences between these 3 groups and determine the etiology of T1DM IR at whole-body and tissue-specific levels. These studies will increase our understanding of IR in T1DM and how novel therapeutic approaches could alleviate this obstacle to optimal cardiovascular health for patients who live with this condition.

Carrie A. Grueter, Ph.D.

Department of Anesthesiology

DGAT1 as a central regulator of diet-induced obesity

Evidence indicates an essential role for the central nervous system (CNS), particularly lipid-sensing neurons in the hypothalamus, in the regulation of whole-body energy balance. It is suggested that different classes of lipids are used by lipid-sensing neurons, not as nutrients, but as cellular messengers which relay information regarding whole-body energy status. Even though the enzymes responsible for TG synthesis, acyl-CoA:diacylglycerol acyltransferase-1 and -2 (DGAT-1 and -2), are expressed in the brain and are known to regulate of whole-body EB, their function in the CNS has yet to be investigated. The long-term objective of my research program is to understand the physiological relevance(s) of intracellular TG and how it impacts CNS processes. The overall objectives for this proposal, which will establish the platform for achieving my long-term goal, are 1) to identify the neuroanatomical expression and distribution of Dgat1, 2) to elucidate the impact of central DGAT1 on the regulation of whole-body energy balance. I hypothesize that intracellular TG metabolism in the CNS, mediated by DGAT1, impacts lipid-sensing in the brain and thus regulates of whole-body energy balance. The rationale for this proposal is that identification of specific cell-types and lipid messengers mediated by DGAT1 in the CNS will provide mechanistic insight into how and where intracellular TG metabolism impacts the regulation of whole-body energy balance. These data will open the door for discovery of new therapeutic approaches for the prevention and treatment of obesity, type 2 diabetes and mechanistically related disorders such as depression and anxiety.

Discovery Program Grant Recipient

Raymond D. Blind, Ph.D.

Department of Medicine

Novel anti-diabetic therapeutics by nuclear receptor competitive displacement

The exogenous plant phospholipid DLPC was recently found to activate the nuclear receptor NR5A2 and have dramatic anti-diabetic effects in the mouse liver. DLPC is thought to activate NR5A2 the same way all nuclear receptors are thought to be activated - as an allosteric switch. However, we recently discovered that NR5A2 can act as scaffold for endogenous phospholipid ligands, and these phospholipids themselves mediate new interactions. This new paradigm suggests that past drug screening platforms that searched for allosteric modulators of NR5A2 were misguided, explaining why those efforts failed. Here, we propose a new type of nuclear receptor screen designed to detect endogenous phospholipid competitive displacement, not

allostery. This screen is ready for anti-diabetic therapeutic development as all the in vivo models, used to validate DLPC in vivo, are ready and await a new DLPC-like molecule. The NR5A2 target is exceptionally well validated, and the novel nature of our screen, based on new mechanistic information, suggests our new screen has an excellent chance to lead to novel & pharmacologically tractable DLPC-like anti-diabetes therapeutics.