1. NIH-NIDDK, No. DK114474 to JMS:

Project Summary: This proposal delineates a 5-year program to provide training toward the development of an independent academic research career in the study of integrated central and peripheral regulation of glucose homeostasis. The candidate has been prepared for this pathway by completing MD and PhD degrees and clinical training in Pediatrics and Gastroenterology. He has been scientifically productive at all levels of training through graduate and postdoctoral work, contributing to 15 manuscripts (7 of them first or co-first author), and successfully competing for fellowships from the American Heart Association and the NIH. The proposed research will be conducted in the laboratory of Dr. Michael Schwartz, an expert in the field of hypothalamic regulation of energy balance and glucose homeostasis. It will be overseen by an expert mentoring committee with two members of the Endocrinology Division (Dr. Gregory Morton and Dr. Joshua Thaler) as well as an external advisor (Dr. David Wasserman, Vanderbilt University). The comprehensive training plan involves continued education in the use of isotopic techniques and analytical methods to study regulation of glucose homeostasis and metabolism from the gene to the whole organism level. The proposal focuses on evidence that members of the fibroblast growth factor (FGF) family play a key role in the regulation of glucose homeostasis by targeting hypothalamic glucoregulatory neurocircuits. Using sophisticated metabolic phenotyping, the candidate demonstrated that a single central injection of FGF1 induces sustained remission of diabetic hyperglycemia in rodent models of diabetes. The anti-diabetic effect is not secondary to weight loss, and is not associated with an increase in insulin sensitivity. Furthermore, the ability of icv FGF1 to induce diabetes remission is lost in animals with severe insulin deficiency and additional preliminary data suggest that relapse of diabetes in animals previously responsive to icv FGF1 is associated with progressive pancreatic β-cell dysfunction. This research will characterize the mechanisms by which icv FGF1 induces remission of diabetic hyperglycemia through 2 specific aims. In Aim 1, we will characterize the specific receptors, intracellular signaling cascades, and synaptic changes that mediate sustained remission of diabetic hyperglycemia in response to icv FGF1. Aim 2 focuses on the requirement of an intact basal insulin signal for FGF1 to induce remission of diabetic hyperglycemia and the extent to which FGF1-induced diabetes remission is attributable to increased basal insulin secretion due to preservation of pancreatic β-cell function. The applicant's combination of expertise in neuroanatomy, molecular biology, histochemistry, pharmacology and physiology of the neural regulation of metabolism uniquely qualify him to conduct the studies in this proposal. Outcomes from these studies are expected to provide a compelling rationale for future studies investigating the mechanisms of FGF1-mediated diabetes remission, exploring the translational potential for centrally-targeted FGF1 and related peptides as anti-diabetic agents.

Link: https://reporter.nih.gov/project-details/10169426

1. NIH-NIDDK, No. DK128383 to JMS:

Project Summary: Over the past 3 decades, obesity and type 2 diabetes (T2D) have emerged as among the most common and costly chronic diseases confronting modern society. Treatment outcomes for patients affected with obesity or T2D have shown minimal improvement due to the absence of non-surgical medical treatments that have sustained efficacy. Therefore, an urgent need for new, more effective treatment options therefore exists, and strategies targeting the brain have important potential to meet this need. As one example of relevant preclinical work, our group has recently shown that signaling in the brain by exogenous administration of members of the fibroblast growth factor (FGF) family produces potent weight-loss and anti-diabetic effects. Our K08 proposal focused on the integrated central and peripheral mechanisms underlying the sustained anti-diabetic action of exogenous FGF1 in rodent models of obesity and T2D. In this application, we propose a parallel line of studies that will investigate the role of endogenous hypothalamic FGF1 signaling in the regulation of energy and glucose homeostasis. We have recently found that FGF1 is endogenously expressed by tanycytes and cells distributed in a number of key hypothalamic areas implicated in the control of body weight and glucose. Further, we have observed that endogenous hypothalamic FGF1 expression is regulated fasting and refeeding and in preliminary studies that deleting FGF1 from either hypothalamic neurons or tanycytes induces weight gain and glucose intolerance on chow diet. These data support the premise that endogenous hypothalamic FGF1 signaling plays a physiologic role in the regulation of energy and glucose homeostasis. We will investigate this hypothesis by determining the specific hypothalamic nuclei and cell types that express FGF1, identify which of these populations respond to acute and chronic changes in metabolic status and diet, and the extent to which disrupting endogenous hypothalamic FGF1 signaling is sufficient to promote the development of obesity and glucose intolerance. The data obtained from these investigations will form the basis of a new line of research centered on endogenous hypothalamic FGF1 signaling as a novel target to treat obesity and T2D.

Link: https://reporter.nih.gov/project-details/10368119

2. NIH-NIDDK, No. DK131695 to KLF

Project Summary Type 2 diabetes (T2D) and inflammatory bowel disease (IBD) are among the most challenging and costly medical disorders of modern society. Both disease processes also share a common pathophysiology characterized by a chronic inflammatory state, altered gut microbiome, and dysfunctional intestinal barrier. Hyperglycemia is the primary cause of the many complications of diabetes, and recent studies have shown that hyperglycemia is capable of directly impairing intestinal barrier function independent of diet and obesity. Population-based studies have shown that patients with IBD also have an increased risk of T2D, which has important clinical consequences as comorbid T2D in patients with IBD is a predictor of poor disease-

related outcomes, though the causative mechanisms remain unknown. In this proposal, we will investigate the novel hypothesis that diabetic hyperglycemia in the setting of diet-induced obesity (DIO) worsens IBD disease activity by increasing intestinal inflammation and associated barrier dysfunction. Specifically, we propose to characterize the effect of diabetic hyperglycemia on clinical and biochemical measures of intestinal inflammation and barrier function in murine models of IBD, and to determine the extent to which control of glycemia decreases intestinal inflammation and improves clinical outcomes in diabetic murine models of IBD. Diabetic-range hyperglycemia will be induced by administration of low-dose streptozotocin (STZ) in two independent models of IBD: 1) C57BL/6J wild-type (WT) mice treated with dextran sodium sulfate (DSS) and 2) Mdr1 knockout mice that spontaneously develop colitis, made obese by consumption of an obesogenic high-fat diet (HFD) or fed standard chow. The impact of hyperglycemia on intestinal barrier function and IBD pathology in the setting of DIO will be assessed using immunohistochemical staining, dextran-FITC permeability assays, and characterization of the components of the intestinal extracellular matrix. We will then investigate the translational potential of treating diabetic hyperglycemia to decrease IBD progression by administering a sodium-glucose cotransportor-2 (SGLT2) inhibitor to normalize glycemia in diabetic murine models of IBD. Lastly, SGLT2 inhibitors will be administered in combination with topical 5-aminosalysilic acids, which are standard first line therapy for mild-to-moderate ulcerative colitis but often fail to control more significant disease, to determine whether treating diabetic hyperglycemia improves the efficacy of introductory IBD therapies. The proposed project unites the clinical gastroenterology, hepatology and nutrition interests and research skills of the applicant as well as the considerable multi-disciplinary resources of the University of Washington Diabetes Institute to advance understanding of the mechanisms by which diabetic hyperglycemia influences intestinal inflammation, with the ultimate goal of understanding shared pathogenic mechanisms and identifying more effective treatments for both conditions.

Link: https://reporter.nih.gov/project-details/10597035

3. NIH-NIDDK, No. DK101997 to MWS:

Project Summary: Following a glucose challenge, both insulin-dependent and -independent mechanisms contribute to the return to baseline blood glucose concentrations. Referred to as glucose effectiveness (GE), the insulin- independent component contributes as much to overall glucose homeostasis as insulin, but it has been viewed as a fixed and largely unregulated process and hence has not been a research focus for investigators. Several recent observations, however, offer evidence of the brain's capacity to potently induce glucose lowering via insulin-independent mechanisms. Adding to this work is our preliminary data showing that in leptin-deficient ob/ob mice, intracerebroventricular (icv) injection of the ani-diabetic hormone fibroblast growth factor-19 (FGF19) rapidly normalizes glucose tolerance despite having

no effect on either insulin secretion or insulin sensitivity. Instead, this effect i mediated entirely by a selective, 3-fold increase of GE. Although the peripheral mechanism underlying this effect is unknown, our data strongly implicate a process whereby glucose is taken up into peripheral tissues via an insulin-independent mechanism, followed by its metabolism to lactate that is subsequently released back into circulation. With this background, we propose Specific Aim 1: To determine how FGF19 increases insulin-independent glucose disposal. Studies in this aim will 1) quantify this brain-mediated increase of glucose uptake and metabolism to lactate in response to FGF19, 2) determine the extent to which it explains the associated increase of GE, and 3) identify the tissues in which it occurs. These goals will be accomplished in mice using a combination of methods ranging from hyperglycemic clamp to metabolomics and biochemical analyses. Could a similar process contribute to the anti-diabetic effects of bariatric surgery? Rodent data implicate the brain in the glucose-lowering effects of bariatric procedures, and in some cases, glucose lowering involves insulin-independent as well as insulin-dependent mechanisms. Moreover, bariatric procedures increase FGF19 secretion from the GI tract. Based on these considerations, we propose Specific Aim 2: To determine if increased GE contributes to the anti-diabetic effect of bariatric surgery. Studies in this aim will determine if bariatric surgery activates CNS mechanisms analogous to those engaged by FGF19, including stimulation of insulin-independent glucose uptake, followed by conversion to lactate, which is then released into circulation. Our finding that FGF19 action in the brain rapidly, potently and selectively increases insulin-independent glucose disposal identifies a novel, CNS-driven mechanism with translational implications for both the pathogenesis and treatment of human diabetes. Studies in this proposal seek to clarify how this occurs and the extent to which it explains the anti-diabetic effect of bariatric surgical procedures.

Link: https://reporter.nih.gov/project-details/9441007

4. NIH-NIDDK, No. DK083042 to MWS:

Project Summary: Both behavioral and metabolic consequences of uncontrolled, insulin-deficient diabetes mellitus (uDM) arise in part from the response of key brain areas such as the hypothalamic arcuate nucleus (ARC) and ventromedial hypothalamic nucleus (VMN) to changes in the humoral milieu, including marked decreases in the circulating levels of both insulin and leptin, and elevated levels of ghrelin. Rodent models of uDM therefore constitute a unique and valuable tool with which to study these neuroendocrine control systems. Among ARC neuronal subsets activated in uDM are those that express orexigenic (or 'food intake-stimulatory') peptides such as neuropeptide Y (NPY) and agouti-related peptide (AgRP), whereas adjacent anorexigenic, melanocortin-producing (or 'POMC') neurons are inhibited, a combination of responses implicated in the pronounced increase of food intake characteristic of uDM (termed "diabetic hyperphagia"). At the cellular level, signaling

via the insulin receptor substrate-phosphotidylinositol-3 kinase (IRS-PI3K) pathway plays a critical role in insulin action in peripheral tissues and while this pathway is also critical for both leptin and insulin action in the CNS, the specific neuronal subsets involved remain to be determined. Signaling molecules downstream of PI3K include protein kinase B (PKB) and mammalian target of rapamycin (mTOR), both of which are also implicated in hypothalamic control of food intake. Growing evidence also suggests that hypothalamic neurocircuits that sense input from insulin, leptin and ghrelin participate in the control of insulin sensitivity in peripheral tissues, and our recent work implicates dysfunction of these neurocircuits, triggered by reduced PI3K signaling, in the progressive insulin resistance seen in rats with uDM induced by the b-cell toxin, streptozotocin (STZ). Based on these observations, we propose in Specific Aim 1 to employ mouse models of STZ-induced uDM that enable us to identify the specific brain areas and neuronal subsets in which signal transduction via the IRS-PI3K-PKB pathway regulates food intake and glucose metabolism. Specifically, we will use a combination of Cre-loxP genetic and adenoviral gene therapy techniques to increase PKB specifically in NPY/Agrp neurons, POMC neurons, neurons that express leptin receptors, or VMN neurons (that express the transcription factor SF- 1) in mice with STZ-induced uDM. In this way, we will identify neuronal subsets in the ARC and VMN in which reduced PKB signaling contributes to feeding and metabolic consequences of uDM. Similarly, Aim 2 seeks to delineate the role of reduced hypothalamic mTOR signaling in behavioral and metabolic responses to uDM in rats. In Aim 3, we investigate mechanisms underlying increased plasma ghrelin levels in uDM and determine the contribution made by this increase to hyperphagia and insulin resistance in this setting. Together, this information will shed new light on neuroendocrine mechanisms controlling food intake and insulin sensitivity and help to clarify how dysfunction within these systems contributes to the pathogenesis of disordered feeding behavior and glucose metabolism in obesity and diabetes. PUBLIC HEALTH RELEVANCE Obesity and diabetes mellitus are closely related metabolic disorders that take an increasing toll on human health. Recent findings suggest that dysfunction of key hypothalamic neurons that regulate food intake, autonomic function and glucose metabolism contributes to the link between these metabolic disorders. The identification of neuronal circuits upon which hormones such as insulin, leptin and ghrelin act to control both food intake and glucose metabolism is therefore an important scientific priority. Towards this end, this proposal employs rat and mouse models of uncontrolled diabetes mellitus to further define neuroendocrine mechanisms controlling food intake, body fat storage and insulin sensitivity in peripheral tissues. By improving our understanding of how mechanisms driving obesity and diabetes are linked to one another within the brain, our ultimate goal is to find new strategies for their prevention and treatment.

Link: https://reporter.nih.gov/project-details/8119562

5. NIH-NIDDK, No. DK089056 to GJM:

Project Summary: While the systems that regulate circadian rhythms and energy homeostasis are tightly coupled together, the pathways which connect them together are not well understood. Our recent findings have identified a novel, physiological role for a subset of neurons in the dorsomedial hypothalamus (DMH) that express the leptin receptor in the circadian control of feeding, locomotor activity and associated metabolic rhythms. The overarching goal of this proposal is to identify the neurocircuitry linking circadian rhythms to control of DMH leptin receptor (LepR) neurons and associated feeding and metabolic responses. Proposed aims seek to 1) characterize the rhythmicity of DMH LepR neuronal activity; 2) identify the contribution made by specific subsets of these neurons in the circadian control of feeding behavior, metabolism and locomotion, and 3) to identify upstream regulators of DMH LepR neurons that regulate circadian control of feeding and metabolism. To accomplish this, we will integrate advanced neuroscience techniques including in vivo fiber photometry, viral track tracing and chemogenetic techniques, along with an intersectional genetics approach and comprehensive rodent metabolic phenotyping. Together, this work will fundamentally advance our knowledge of the neural circuits underlying endogenous rhythms of behavior, feeding, and metabolism and can be expected to facilitate the development of new strategies for the treatment and prevention of obesity and related disorders in humans.

Link: https://reporter.nih.gov/project-details/10617310

6. NIH-NIDDK, No. DK124238 to GJM:

Project Summary The thermoregulatory and energy homeostasis systems are tightly coupled to ensure the stability of both core temperature and body fat stores across a wide range of environmental temperatures. This interaction is highlighted by the adaptive metabolic response to cold exposure, as the increase of heat production needed to maintain core temperature is accompanied by a proportionate increase in energy intake to maintain body fat stress. These adaptive responses are rapid and robust and our recent findings implicate a role for agouti- related peptide (Agrp) neurons in the adaptive feeding response since Agrp neurons are activated during cold-exposure, and this activation is required for cold-induced hyperphagia, but not cold-induced thermogenic responses. The overarching goal of the proposal is to identify the neurocircuitry linking thermoregulation to control of Agrp neuronal activity and associated feeding responses. Proposed studies seek 1) to examine the temporal relationship between changes in ambient temperature, Agrp neuron activity and associated feeding responses and 2) to identify and characterize neurocircuits that link thermoregulation to cold-induced hyperphagia. To accomplish this, state-of-the-art neuroscience techniques including chemogenetics, optogenetics and fiber photometry systems approaches are utilized, in combination with immunohistochemical and advanced metabolic phenotyping. Together, this work will advance the understanding

of the neurocircuitry linking thermoregulation to Agrp neurons and feeding and may identify novel strategies for the treatment of obesity by blunting the associated hyperphagic response.

Link: https://reporter.nih.gov/project-details/10620136

7. Abstract for DOD W81XWH2110635: I don't have access to this non NIH abstract material. I am asking someone else at UW for this

8. Abstract for A139339: I don't have access to this non NIH abstract material. I am asking someone else at UW for this.

9. Abstract for 1-19-IBS-192: I don't have access to this non NIH abstract material. I am asking someone else at UW for this.

10. NIH-NIDDK T32 Training Grant, No. DK007742 to KLF:

Project Summary: The University of Washington School of Medicine serves as the sole medical educational resource for 5 states in the US Northwest: Washington, Wyoming, Alaska, Montana, and Idaho. It is also recognized as a major institution in biomedical research; since 1974, UW ranks first amongst American public universities for federal research funding and in the top three amongst all universities (public and private) since 1991 for competing federal science and engineering grants. Within the UW, the Division of Gastroenterology of the Department of Medicine, composed of a core of 45 full-time faculty members, operates from five medical centers: the University of Washington Health Sciences Center, the Veterans Affairs Puget Sound Health Care System, the Harborview Medical Center, Northwest Hospital and the Seattle Cancer Care Alliance/Fred Hutchinson Cancer Research Center. In this renewal application for the UW GI Training Grant, we have developed a formal collaboration with Seattle Children's Hospital to increase the pool of talented candidates, enhance the resources available to trainees, and to expand discovery across the lifetime of patients with gastrointestinal and liver disease. Our diversity allows the research and clinical programs of the GI Division to benefit from complementary strengths, ranging from pediatric to adult patients, from tertiary referral centers to primary care centers in urban or rural settings, and from highly specialized centers to broadly diversified county medical centers. Benefiting from these strengths, the UW GI Division has had a long tradition of training academic fellows, dating to the 1950's, and the UW GI Training Grant has funded 40 fellows over the past two decades, of whom 30 have successfully achieved and currently thrive in research-focused careers. This application requests two trainees per year who will undergo rigorous research training for two years (4 positions total).

Link: https://reporter.nih.gov/project-details/10437955

11. NIH-NHLBI T32 Training Grant, No. HL007028 to KMA:

The Nutrition, Obesity and Atherosclerosis Training Program at the University of Washington is a successful Training Program, now in its 45th year of funding. The overall goal of the program continues to be to provide a highly qualified group of postdoctoral MD physician-scientists and PhD scientists with the research skills they need to become fully independent investigators in the areas of nutrition, obesity and atherosclerosis. The Training Program utilizes 32 investigators at the University of Washington who are performing basic, population science and clinical research in these areas as preceptors. Use is also made of a number of basic and clinical scientists with whom the core faculty collaborates, additional training opportunities provided by our External Advisors, and institutional support to broaden research training and resources available to trainees in the Program. Trainees entering the Program previously have obtained either an MD or PhD degree (or both) and most MD candidates have completed residency training. Some have had some prior research experience. PhD candidates have demonstrated ability in a basic science or population science discipline and have demonstrated capability for research related to the focus of this https://reporter.nih.gov/search/75j-Oq7S1UaNm_IPBim8yg/project-details/10553804Program. Selection of the 4 candidates supported by this training grant is made from a large pool of qualified applicants who continue to apply for research training in nutrition, obesity and atherosclerosis at the University of Washington. This Program provides trainees with research experience in basic- population- and clinical science necessary in preparation for independent research careers. Appointments to the Training Program are for at least 2 years, with an optional 3rd year available. The program also includes opportunities for trainees to obtain Master of Public Health or Master of Science degree in the areas of nutritional sciences, epidemiology, global health, and health systems and population health, to interact through program-specific meetings, and to present their research to peers, preceptors, invited scientists from other academic institutions, and at national scientific meetings. A series of didactic lectures, seminars, and journal clubs related to the topics of lipids, obesity, nutrition and atherosclerosis, as well as in scientific methods and biomedical ethics, complement the research training. Rigorous evaluation of trainees and preceptors is performed bi-annually and is overseen by the Internal Advisory Committee and an External Advisory Committee. The Nutrition, Obesity and Atherosclerosis Training Program has been highly successful in training productive scientists, including scientists from underrepresented groups, in these areas during the current funding period, and will provide an even stronger training environment due to several changes to increase diversity, coherence, and training opportunities during the next funding period.

Link: https://reporter.nih.gov/project-details/10553804

12. NIH-NIDDK-funded University of Washington Diabetes Research Center, No. P30DK017047:

The Diabetes Research Center at the University of Washington is part of the national program supported by NIDDK and acts as the focal point and umbrella for diabetes research in the Greater Seattle area. Its mission is to enhance research, education and training in diabetes, obesity, and related disorders and to promote an environment of collaborative research in these conditions by (1) Providing support to affiliate investigators through its four biomedical research cores; (2) Conducting a pilot and feasibility program that provides grant support for new investigators in diabetes research and to established investigators in other disciplines; (3) Sponsoring an interactive enrichment program comprising symposia, named lectures, retreats and workshops to inform the community of the latest developments in the area; (4) Ensuring the development of young investigators by providing postdoctoral and graduate student fellowships for salary support and training in its biomedical research cores; and (5) Developing new research methods and technologies based on the evolving needs of its investigators. To accomplish this goal, the Center is organized around four biomedical research cores (Cellular and Molecular Imaging Core, CRISPR, Vector and Transgenic Mouse Core, Metabolic and Cellular Phenotyping Core, and Proteomics and Bioinformatics Core) and an Administrative Core that also manages the Pilot and Feasibility (P&F) and Enrichment Programs. Along with the commitment of the University of Washington and other Seattle institutions of research space and additional financial support, the Diabetes Research Center is a dynamic and constantly evolving center that supports 116 Seattle-based affiliate investigators who receive annual funding in excess of $135.9 million in overall direct costs (more than $116.2 million of which is from NIH and $24.5 million from NIDDK). These investigators are making important scientific contributions in the areas of (1) Pathophysiology, prevention and treatment of type 2 diabetes; (2) Central regulation of body weight and glucose metabolism; (3) Complications of diabetes; (4) Etiology, pathogenesis and treatment of type 1 diabetes; and (5) Clinical trials and large-scale epidemiologic studies.

Link: https://reporter.nih.gov/project-details/10588068

13. NIH-NIDDK-funded University of Washington Nutrition Obesity Research Center, No. P30DK035816

The NORC Pilot and Feasibility (P/F) program has been an integral part of the NORC mission since its inception in 1985, because it provides critical support for i) talented and promising junior faculty members, and ii) established investigators in other fields wishing to move into nutrition, obesity or metabolic research. The overarching goal of this program is to provide sufficient pilot funding to enable the recipient to generate the data needed compete for R01-level funding and thereby establish their career in our field, and we continue to have outstanding success in this effort. Each cycle is met with

a large number of qualified applicants from diverse divisions, departments and schools within the University of Washington (UW) in research areas ranging from basic to translational to clinical, epidemiological and public health. The success of this P/F program is highlighted by the large number of previous P/F recipients that have gone onto successful academic careers in nutrition- and obesity-related research, supported by independent peer-reviewed grants, some of whom are now assuming leadership roles both at the UW and at other institutions. The Specific Aims are: Specific Aim 1: To provide junior investigators of high promise the opportunity to obtain crucial pilot data needed to launch their career and to compete successfully for independent peer-reviewed funding. Specific Aim 2: To provide a mechanism for encouraging talented junior investigators to embark on academic careers in nutrition/obesity research.

Link: https://reporter.nih.gov/project-details/10645180