2014 NIDDK New PI Workshop

December 2-3, 2014

Natcher Conference Center

Bethesda, MD

2014 NIDDK New PI Workshop

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Agenda

Tuesday, December 2, 2014

7:30 – 8:00 a.m.	Meeting Registration and Check-In
8:00 – 8:10 a.m.	**Welcome to the Workshop** *Gregory Germino, M.D., Deputy Director, NIDDK*

Session I: Spotlight on the NIH Grant Application Process

8:10 – 8:30 a.m.	**Overview of NIDDK New PI Workshop** *Aaron Pawlyk, Ph.D., Program Director, Division of Diabetes, Endocrinology & Metabolic Diseases, NIDDK*
8:30 – 9:00 a.m.	**Submission, Receipt and Referral Assignments of NIH Grant Applications** *Cathleen Cooper, Ph.D., Director, Division of Receipt and Referral, Center for Scientific Review, NIH*
9:00 – 9:30 a.m.	**Roles of the Scientific Review Officer, Center for Scientific Review** *Robert Garofalo, Ph.D., Chief, Endocrinology, Metabolism, Nutrition and Reproductive Sciences (EMNR) Integrated Review Group, Center for Scientific Review, NIH*
9:30 – 9:45 a.m.	**Roles of the Scientific Review Officer, NIDDK** *John Connaughton, Ph.D., Chief, Training and Mentored Research Section, Review Branch, NIDDK*
9:45 – 10:00 a.m.	Panel Discussion (*Moderator: Aaron Pawlyk*)
10:00 – 10:15 a.m.	Break
10:15 – 10:45 a.m.	**Mock Study Session: Peering Into the Black Box of Peer Review** *John Connaughton, Ph.D., Chief, Training and Mentored Research Section, Review Branch, NIDDK*
10:45 – 11:15 a.m.	**How to Interpret Your Summary Statement** *Peter Perrin, Ph.D., Program Director, Division of Digestive Diseases and Nutrition, NIDDK*

11:15 – 11:30 a.m.	Discussion (*Moderators: John Connaughton and Peter Perrin*)
11:30 a.m. – 1:00 p.m.	Lunch with NIDDK Program Officers

Session II: Managing your R01: pathway to a successful renewal application

1:00 – 1:30 p.m.	Introductions: *Krystyna Rys-Sikora*, Ph.D., Program *Director, Division of Kidney, Urologic and Hematologic Diseases, NIDDK*
	Roles of the Program Officer *Tracy L. Rankin, Ph.D., Division of Kidney, Urologic and Hematologic Diseases, NIDDK*
1:30 – 1:45 p.m.	**Roles of the Grants Management Specialist** *Amanda Linehan, Grants Management Specialist, NIDDK*
1:45 – 2:00 p.m.	Discussion (*Moderator: Krystyna Rys-Sikora*)
2:00 – 2:45 p.m.	**New PI Perspectives**
	Diva De Leon, M.D., Department of Pediatrics, The Children's Hospital of Philadelphia
	Declan McCole, Ph.D., Department of Biomedical Sciences, University of California, Riverside
	Paula Fraenkel, M.D., Department of Medicine, Beth Israel Deaconess Medical Center
2:45 – 3:00 p.m.	Discussion (*Moderator: Krystyna Rys-Sikora*)
3:00 – 3:15 p.m.	Break
3:15 – 5:15 p.m.	Breakout Sessions/Small Groups *Program Staff, Review Staff, and Participants*
5:15 p.m.	Adjourn (dinner on your own)

Wednesday, December 3, 2014

Session III: NIDDK: Mission, Funding Opportunities, and Resources

8:00 – 9:15 a.m. Introductions: *Michael J. Grey, Ph.D., Program Director, Division of Digestive Diseases and Nutrition, NIDDK*

Introduction to the NIDDK, Its Budget and Mission
Gregory Germino, M.D., Deputy Director, NIDDK

NIDDK Funding Opportunities and Resources

Support for Trainees in your Research Program
Carol R. Haft, Ph.D., Program Director, Division of Diabetes, Endocrinology & Metabolic Diseases, NIDDK

Programs to Support Research for Therapeutic Discovery and Development
Michael J. Grey, Ph.D., Program Director, Division of Digestive Diseases and Nutrition, NIDDK

Collaborative Team Science Programs
Corinne M. Silva, Ph.D., Program Director, Division of Diabetes, Endocrinology & Metabolic Diseases, NIDDK

9:15 – 9:30 am Panel Discussion (*Moderator: Michael J. Grey, Ph.D.*)

9:30 – 9:45 am Break

Session IV: Building a Research Program: insights to a successful career in research

9:45 – 11:15 a.m. Introductions: *Carol R. Haft, Ph.D., Program Director, Division of Diabetes, Endocrinology & Metabolic Diseases, NIDDK*

Juanita Merchant, M.D., Ph.D., Professor, Departments of Internal Medicine and Integrative and Molecular Physiology, University of Michigan

Paul Palevsky, M.D., Professor, Department of Medicine, University of Pittsburgh

Rosalind Coleman, M.D., Professor, Departments of Nutrition and Pediatrics, University of North Carolina-Chapel Hill

11:15 a.m. – 12:00 p.m. Panel Discussion (*Moderator: Carol R. Haft*)

12:00 p.m. Workshop Wrap-Up and Adjournment

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

New PI Workshop

Natcher Conference Center, Building 45
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Bethesda, MD
December 2 – 3, 2014

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INTRODUCTION

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is one of 27 Institutes and Centers that make up the *National Institutes of Health* (NIH). Each Institute and Center offers opportunities for training scientists and students, both at the NIH campus in Bethesda, Maryland, and by providing financial support to individuals at universities and medical schools throughout the United States.

This brochure will provide you with the information you need to decide if you are eligible to apply for any of our research training and career development awards.

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Research Training and Career Development Funding

from the

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

NIH National Inst Diabetes and Digestive and Kidney Diseases

Typical" Research Career Pathway

Graduate/Medical School

T32 predoctoral slot (Ph.D. students only)
F30 (M.D./Ph.D. students only)
F31 and F31-D (Ph.D. students)
T35 slot (medical students only)
Medical Student Research Training (year-off program)

Postgraduate

T32 postdoctoral slot
F32 individual fellowship

Transition/Junior Faculty

K01, K08, K23, K25, K99/R00, R03

Tenured Faculty

R21, R01, P01, U01, K24

All NIH fellowships and most career development award mechanisms require U.S. citizenship or permanent resident status. Information about application forms is available via the NIH website. Completed applications must be submitted for specific deadlines to the NIH for review by a panel of scientists who will evaluate the applications. Once your application is reviewed, you will be notified that your numerical "score" and the reviewers' evaluations (i.e., summary statement) will be available on the NIH eRA Commons. The best applications are considered for funding.

Visit NIDDK Research Training & Career Development, under Research & Funding for Scientists on the NIDDK website **(www.niddk.nih.gov)**

National Research Service Awards (NRSAs)

NRSAs provide a stipend (which is meant to cover living expenses), as well as tuition/fees, travel funds for a scientific meeting, and training-related expenses. The latter includes the cost of health insurance for the student or trainee.

Predoctoral M.D./Ph.D. NRSAs (F30) provide support for students not supported by an MSTP training grant who are enrolled in a combined M.D./Ph.D. program. Applicants should have identified a dissertation topic within the scope of the NIDDK's mission before applying.

Predoctoral NRSAs (F31) provide support for students enrolled in programs leading to a Ph.D. or equivalent research degree. The NIDDK supports F31s and F31-Ds, the latter to encourage a diverse workforce.

Postdoctoral NRSAs (F32) provide support for fellows who have received their M.D., Ph.D., or other doctoral level degree. Fellows need to identify a mentor and plan their research project before applying for 1 to 3 years of funding.

Institutional Short-Term Training Grants (T35) provide summer research experiences for medical students, usually between their 1st and 2nd year of medical school.

Institutional NRSAs, or Training Grants (T32), are in place at many major universities to provide pre- and postdoctoral support to fellows at those institutions. To be appointed to a training grant, contact the Director of the training program at your university. A listing of all NIDDK-supported training programs is available on the NIDDK Research Training & Career Development website.

Medical Student Research Training (MSRT) program provides support to medical students who wish to take a year off from their studies to pursue a research training experience with a mentor on an NIDDK-funded training grant. Instructions can be found on the NIDDK Research Training & Career Development website, under 'Graduate/Medical Student'.

Career Development Awards

"K-awards" provide a true salary, with fringe benefits, and an allowance for research supplies, travel, and technical support. Applicants for K-awards usually need a mentor and a well-developed research plan for 3, 4, or 5 years of support.

K01 (Mentored Research Scientist Development Awards)* are used by NIDDK to support Ph.D scientists who have at least 2, but not more than 5, years of postdoctoral training and who need to transition to independence.

K08 (Mentored Clinical Scientist Development Awards)* are aimed at physician-scientists to transition them to independence.

K23 (Mentored Patient-Oriented Research Career Development Awards)* are aimed at clinical investigators engaged in patient-based research.

K24 (Midcareer Patient-Oriented Research Career Development Awards) are available to established clinical investigators serving as mentors.

K25 (Mentored Quantitative Research Career Development Awards) are available to individuals with quantitative (e.g., engineering, mathematics, computer science) backgrounds who wish to pursue research in the area of biomedicine.

K99/R00 (Pathways to Independence Awards) are available to individuals with no more than 4 years of postgraduate research experience. A 1-2 year period of mentored support (K99) is followed by up to 3 years of independent (R00) support. U.S. citizenship is not required, but all 5 years of research must be performed in the United States.

**NIDDK-funded K01, K08, and K23 awardees may apply for a small grant (R03) to obtain additional funding during the last 2 years of their individual K-award.*

Comparisions of Collaborative Grants Supported by the NIDDK			
	Research Resource Project Grant (R24)	**Program Project Grant (P01)**	**Multiple-Principal Investigator Initiated Research Project (Multi-PI R01)**
Administrative Considerations			
Funding Opportunity Announcement	PAR-13-305	PAR-13-266	PA-13-302 (parent Announcement). Also solicited through varied FOAs. Check NIH Guide for Grants and Funding
Typical Budget (Direct Costs per Year)	Greater than $500K. Budgets vary and have no cap	$1 million. Capped at $6.25 million over five years	Up to $499,999. Higher budgets may be requested with NIDDK approval
Required Pre-Approval	Applicants requesting $500K or more in Direct Costs must contact NIDDK Program Staff at least 6 weeks prior to submission	Applicants requesting $500K or more in Direct Costs must contact NIDDK Program Staff at least 6 weeks prior to submission	Applicants requesting $500K or more in Direct Costs must contact NIDDK Program Staff at least 6 weeks prior to submission
Recommended Pre-Approval	Applicants are strongly encouraged to discuss proposed studies with NIDDK staff and generate the Pre-Approval letter at least 3 months, and preferably 6 months, before submission	Applicants are strongly encouraged to discuss proposed studies with NIDDK staff and generate the Pre-Approval letter at least 3 months, and preferably 6 months, before submission	Applicants are always encouraged to develop studies in consultation with the NIDDK. However, there is no formal recommended timeline for these discussions
Average Number of Investigators	3 to 4	4 to 5	2 to 3

Application Review	NIDDK Special Emphasis Panel	NIDDK Special Emphasis Panel	Center for Scientific Review
Organization	A highly collaborative, interdisciplinary team of investigators that collectively address a central question	Three or more Research Projects led by Project Leaders and relevant Scientific and Administrative Cores led by Core Directors all under the leadership of an overall P01 Leader	Two or more PIs working collaboratively to address two or more related Specific Aims
Scientific Considerations			
Scientific Scope	Single project using an interdisciplinary approach to address a central problem or to develop a unique resource/technology or to conduct a discovery-based study	Multiple Projects and Cores broadly and synergistically addressing central theme	Focused project to address an overall hypothesis
Preliminary Data	Preliminary data is not required, but evidence that study is feasible should be presented	Supporting preliminary data is essential	Supporting preliminary data is essential
Prior Collaboration Among PIs	Not Required, but potential for successful synergistic collaboration should be addressed	Not Required, but demonstrated prior successful collaboration would significantly strengthen study	Not Required, but demonstrated prior successful collaboration would significantly strengthen study
New Research versus Extension of Previous Research	Studies should not be next step extensions of current or previous research efforts, but should be new or significant departures from ongoing work that capitalize on interdisciplinary approaches to address gaps in knowledge	New studies or extensions of current or previous research efforts	New studies or extensions of current or previous research efforts

Project Number:	5R01DK095140-03	**Contact PI / Project Leader:**	ALONSO, LAURA C
Title:	FREE FATTY ACIDS, P16 AND PANCREATIC BETA CELL PROLIFERATION	**Awardee Organization:**	UNIV OF MASSACHUSETTS MED SCH WORCESTER

Abstract Text:

DESCRIPTION (provided by applicant): People with diabetes have reduced beta cell mass; developing therapies that increase beta cell mass, to increase insulin secretory capacity, is a primary goal in diabetes research. Beta cell proliferation rates are low in human autopsy studies, suggesting that factors either intrinsic or extrinsic to the beta cell restrain beta cell proliferation. Supporting this hypothesis is the observation that genome-wide association studies consistently link type 2 diabetes risks with the genetic locus encoding the cell cycle inhibitor p16, a strong beta cell anti- proliferative signal. Factors that restrain beta cell proliferation via p16 action remain unknown. One of the hallmarks of obesity and the metabolic syndrome is elevated circulating free fatty acids (FFAs). Using intravenous infusion of lipids into mice, we have discovered that FFAs block the compensatory beta cell proliferation induced by hyperglycemia. FFAs act directly on the beta cell, as FFA treatment of either primary islet cells or INS-1 cells also eliminates glucose-stimulated proliferation. Intriguingly, FFAs induce p16 expression in islets in vivo. Furthermore, p16 is also induced by FFAs in INS-1 cells, and knockdown of p16 eliminates the anti-proliferative effects of FFAs. We propose to dissect the mechanism and human relevance of these findings through the following specific aims: Aim 1: Establish whether p16 is required for FFA-inhibition of beta cell proliferation in mice, Aim 2: Explore the impact of aging-related p16 induction on glucose and FFA effects on beta cell proliferation, and Aim 3: Determine whether FFAs restrict human beta cell proliferation. To address these questions we will use a combination of novel and powerful techniques we have recently developed, including continuous intravenous infusion of glucose and/or lipids into genetically modified mice, into aging mice, and into mice engrafted with human islets. These studies have the potential to shed light on how the p16 locus contributes to diabetes risk, to explore a novel form of lipotoxicity (anti-proliferative), and to define a new arena of therapeutic targets: enhancing beta cell mass by blocking factors that restrict human beta cell proliferation.

Project Number:	5R01DK098414-02	**Contact PI / Project Leader:**	APTE, UDAYAN
Title:	MECHANISMS OF LIVER REGENERATION AFTER ACETAMINOPHEN-INDUCED ACUTE LIVER FAILURE	**Awardee Organization:**	UNIVERSITY OF KANSAS MEDICAL CENTER

Abstract Text:

DESCRIPTION (provided by applicant): Overdose of acetaminophen (APAP), the popular analgesic and antipyretic agent, is the most common cause of acute liver failure (ALF) in the developing countries. Treatment options for APAP-induced ALF are extremely limited. Most ALF patients are treated with N-acetyl cystein, a precursor of glutathione, which works only if delivered within hours after APAP overdose. The only other therapy is liver transplantation, which is complicated by scarcity of donor organs, lifelong immunosuppressant use and exorbitant cost. There is a critical need to develop novel therapies for APAP-induced ALF. Recent studies in animal models and patients have demonstrated that timely stimulation of innate liver regeneration is associated with better outcomes including transplant free survival in APAP-induced ALF. These studies indicate that without proper liver regeneration APAP-induced acute liver injury can develop into ALF and result in death. Whereas these reports have underscored the therapeutic potential of liver regeneration following APAP-induced ALF, the mechanisms of liver regeneration after APAP overdose are not completely known. Our preliminary studies indicate that canonical Wnt signaling culminating in β-catenin activation plays a critical role in liver regeneration after APAP- induced ALF and could be used for therapeutic targeting. The studies in the first specific aim will determine the role of each component of canonical Wnt pathway including β-catenin, GSK3β, disheveled, Lrp5 and Wnt4 in liver regeneration after ALF. Another significant problem in developing regenerative therapies for ALF is the lack of reliable and easy to use biomarkers of liver regeneration. Currently, there are no reliable biomarkers that can be easily measured in serum of ALF patients, which can reveal the status of innate liver regeneration in ALF patients. Predictive models that factor in biomarkers of regeneration will allow clinicians to track status of patient's innate liver regeneration and aid in decisions on listing for transplantation. Our preliminary data indicate that serum levels of leukocyte derived chemotaxin-2 (Lect2) could be used as a reliable biomarker of liver regeneration following acute liver failure. These studies will not only determine the role of Lect2 as a biomarker of regeneration in ALF but also determine role of Lect2 in stimulation of hepatocyte proliferation providing an additional therapeutic target. Overall, the studies in this grant proposal will determine the mechanisms of liver regeneration and identify novel biomarkers of liver regeneration specific to APAP-induced ALF. Successful completion of these studies will have substantial impact on clinical management of APAP-induced ALF patients.

Project Number:	5R01DK090326-03	**Contact PI / Project Leader:**	ATTANASIO, MASSIMO
Title:	ROLE OF GLIS2 IN THE DEVELOPMENT OF CYSTIC KIDNEY DISEASE	**Awardee Organization:**	UT SOUTHWESTERN MEDICAL CENTER

Abstract Text:

DESCRIPTION (provided by applicant): Nephronophthisis (NPHP), one of the most frequent genetic causes of chronic renal failure in the first three decades of life, is a group of autosomal recessive diseases characterized by progressive kidney cystic degeneration and fibrosis. Mutations in the gene GLIS2/NPHP7 are the cause of nephronophthisis type 7 both in humans and mice. GLIS2 is a transcription factor with high sequence homology to GLI1, GLI2 and GLI3, the vertebrate orthologs of Drosophila Ci (cubitus interruptus). Like Drosophila Ci, GLI proteins are key molecules in the vertebrate Hedgehog (Hh) signaling, a pathway highly conserved in the evolution and central in the regulation of proliferation, differentiation and repair during embryonic and postnatal life. We have recently tested and confirmed the hypothesis that Glis2 is a repressor of Hh signaling in the postnatal kidney and demonstrated that malfunctioning of this pathway results in kidney cysts and fibrosis, increased inflammatory infiltration and apoptosis, but the molecular events leading to this kidney phenotype are still unexplained. Preliminary studies performed in my laboratory have unexpectedly revealed that loss of Glis2 results in over expression of Toll like receptor 2 (Tlr2) and other components of the pro-inflammatory TLR/NF-κB pathway in kidney epithelial cells and in the Tlr2-dependent activation of this pathway. We have also found that expression of several miRNAs in kidney epithelial cells is controlled by Glis2, suggesting that microRNAs are effectors of Glis2/Hh signaling in mouse kidneys. We propose to test in vivo the effect of the inhibition of TLR-2/NF-κB signaling on the inflammatory infiltration and fibrosis in Glis2mut/mut mice kidneys by generating Tlr2-/-;Glis2mut/mut and Myd88flox/flox;Glis2mut/mut;KspCre double mutants and establishing Tlr2-/-;Glis2mut/mut bone marrow chimeras. In addition, we propose to systematically identify at genome wide level the canonical and non-canonical Glis2 target genes by chromatin immunoprecipitation-highly parallel sequencing (ChIP-Seq) and high-throughput microRNA sequencing (miRNA-Seq). In light of our most recent results, identifying downstream effectors that are deregulated in Glis2 knockout kidneys has gained even more importance, and is likely to produce further insights in the complex regulatory network that is altered in our model of cystic kidney diseases and fibrosis.

Project Number:	5R01DK094930-03	**Contact PI / Project Leader:**	AWAD, ALAA S
Title:	ROLE OF ARGINASE IN DIABETIC NEPHROPATHY	**Awardee Organization:**	PENNSYLVANIA STATE UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Diabetes mellitus (DM) is a global health problem. The prevalence of diagnosed and undiagnosed diabetes in the US is progressively increasing from 7.8% in 2007, 14.5% in 2010 and expected to rise between 24.7% to 32.8% in 2050. Diabetes is the most common cause of end stage renal disease, responsible for more than 40% of all cases in the US, and this number are likely to continue to increase unabated. Endothelial cell dysfunction is a central pathophysiological mechanism that contributes to diabetes and diabetic nephropathy (DN). Dramatic alterations in arginine metabolism occur in endothelial injury due to changes in the activity and/or expression of nitric oxide synthases (NOS) and arginases. Arginase-2 is constitutively expressed and also inducible in endothelial cells as well as in kidney cells and, when elevated, can inhibit NOS activity/expression and induce endothelial NOS uncoupling, thus reducing NO bioavailability and inhibiting the NO/cGMP pathway. We hypothesize that arginases promote the development and progression of diabetic kidney damage. Aim 1: Test the hypothesis that arginase inhibition will be effective in the primary and secondary prevention of DN. Aim 2: Test the hypothesis that reduction in plasma arginine bioavailability contributes to the development and progression of DN. Aim 3: Test the hypothesis that elevated arginase-2 in endothelial cells contributes to tissue damage in DN. Our experimental approach will use both whole animals (Ins2Akita mice and their wild type (WT) littermates, Zucker diabetic fatty rats), genetically altered mice (mice with complete absence of arginase-2 expression (Arg2-/-), and transgenic mice that overexpress arginase-2 specifically in endothelial cells (Tie2Arg2) and cultured cells (glomerular microvascular endothelial cells (GMVEC) and endothelial cells that overexpress arginase-2) to fully define the role of arginases in DN. An understanding of the interaction between diabetes and arginases may help to elucidate mechanisms involved in diabetic renal disease and lead to the development of new therapeutic strategies to manage the disease process.

Project Number:	5R01DK097361-02	**Contact PI / Project Leader:**	AYALA, JULIO E
Title:	REGULATION OF FOOD INTAKE VIA THE GLUCAGON-LIKE PEPTIDE-1 RECEPTOR	**Awardee Organization:**	SANFORD-BURNHAM MEDICAL RESEARCH INSTIT

Abstract Text:

DESCRIPTION (provided by applicant): Satiety hormones such as glucagon-like peptide-1 (Glp1) are secreted in response to feeding and activate neural processes that subsequently suppress food intake. While the satiety effects of Glp1 have been known for over 15 years, the mechanism mediating this effect is not clearly defined. This is significant since some Glp1-based therapies for type 2 diabetes display modest weight loss effects. Understanding how Glp1 regulates food intake may, therefore, lead to the design of therapeutic interventions with improved efficacy for weight loss. Based on our preliminary data, we hypothesize that the anorectic effect mediated via the central Glp1 receptor (Glp1r) is integrated with hypothalamic signaling proteins that respond to changes in circulating glucose. Activation of the hypothalamic Glp1 receptor (Glp1r) inhibits the cellular energy sensor AMP-activated protein kinase (AMPK). Considering that the anorectic effects of leptin, insulin and glucose are mediated in part by inhibition of hypothalamic AMPK, we hypothesize that this is also a mechanism by which Glp1 suppresses food intake. We also show that inhibition of AMPK by the Glp1r agonist Exendin-4 (Ex4) in hypothalamic cell lines occurs only with increasing glucose concentration. Ex4 also stimulates glucose uptake and metabolism in a glucose concentration-dependent manner. Since increased glucose metabolism inhibits AMPK, we hypothesize that central Glp1r activation inhibits AMPK and subsequently reduces food intake by stimulating central glucose metabolism. Supporting this hypothesis, we show that inhibition of glycolysis in the brain blocks the anorectic effect of Ex4. Contrasting the effects of glucose, central administration of fructose attenuates the anorectic effect of Ex4. Fructose activates hypothalamic AMPK. This suggests that by activating hypothalamic AMPK fructose can "short-circuit" the Glp1r signaling pathway and promote central Glp1 resistance. This could partially explain our observation that mice fed a sucrose diet, which provides fructose and glucose, eat more compared to mice fed an isocaloric starch diet that only provides glucose. This also has clinical implications based on the association between increased fructose consumption and the obesity epidemic, particularly in children. Since the Glp1r is expressed in multiple hypothalamic nuclei, the first aim is to identiy hypothalamic regions mediating the anorectic effect of Glp1r agonists. The second aim will combine hypothalamic nuclei- specific modulation of the Glp1r with pharmacological agents that target processes we hypothesize are downstream of the Glp1r - glucose metabolism and AMPK activity. The final aim will assess whether dietary fructose is an inhibitor of the satiety effects mediated by central Glp1r activation. The long-term goal of this application is to elucidate the mechanisms that regulate multiple aspects of feeding behavior. Defining the mechanisms by which the central Glp1r regulates food intake will identify key control points that could be sites for disruption by obesogenic factors and targets for therapeutic intervention.

Project Number:	5R01DK092590-04	**Contact PI / Project Leader:**	BERDEAUX, REBECCA L
Title:	DYNAMIC REGULATION OF HEPATIC SIK1 DURING FASTING AND FEEDING	**Awardee Organization:**	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON

Abstract Text:

DESCRIPTION (provided by applicant): Elevated hepatic glucose output during fasting is a major contributor to type 2 diabetes, which affects 10-25% of Americans. The cAMP response element binding protein CREB and its co-activator CRTC2 regulate hepatic glucose output by transcriptional induction of rate-limiting gluconeogenic enzymes during fasting. Given that CREB activity becomes aberrantly activated in diabetic rodents, we aim to identify molecular mechanisms by which this pathway can be inhibited. Recent studies in mouse models and cultured hepatocytes implicated a family of AMPK-related kinases called Salt-Inducible Kinases (SIK1-3), in the control of CRTC co-activator function during fasting and re-feeding. Among these, SIK1 is unique in that fasting stimuli induce hepatic SIK1 mRNA transcription. SIK1 protein then feeds back to inhibit CREB/CRTC2 and glucose output after a meal. This cycle is reset during the postprandial period, during which SIK1 protein levels decline, thus allowing re- activation of CREB at the onset of the next fast. Based on the temporal nature of SIK1 expression and its potent inhibitory effects on hepatic glucose output, we hypothesize that the timing of SIK1 activity is limited by regulated degradation during the fasting to feeding transition. We propose to test this hypothesis using a variety of molecular and genetic techniques. We will investigate the dynamics of SIK1 activity in hepatocytes and liver tissue and explore the structural determinants of SIK1 that regulate its degradation. We will also test the role of a candidate E3 ubiquitin ligase in limiting SIK1 activity during the postprandial period. Finally, we will characterize metabolic phenotypes resulting from liver-specific deletion of the Sik1 gene in mice. We have generated several transgenic animal strains for these studies, including transgenic luciferase reporter mice to visualize CREB-dependent transcription in vivo. The goal of this work is to determine how dynamic regulation of SIK1 contributes to maintenance of glucose homeostasis and identify new molecular mechanisms by which SIK1 activity is regulated. Molecular insight into this pathway will reveal new therapeutic strategies for inhibition of hepatic glucose output in diabetic patients.

Project Number:	5R01DK091565-04	**Contact PI / Project Leader:**	BHALLA, VIVEK
Title:	ENAC TRANSPORT IN INSULIN RESISTANCE: ROLE OF INSULIN & IGF-1 RECEPTORS	**Awardee Organization:**	STANFORD UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Hypertension affects 60 million adults in the United States, and the insulin resistance syndrome induces a salt- sensitive form of hypertension in approximately half of these individuals. In the insulin resistance syndrome compensatory hyperinsulinemia provoked by peripheral resistance increases sodium retention and hence, blood pressure via direct effects on the renal tubule. The epithelial sodium channel (ENaC) expressed in principal cells of the collecting duct is fundamental to this process. However, the receptors in principal cells which propagate insulin-induced ENaC stimulation in the insulin resistance syndrome are not established. Experimental studies have yielded conflicting results on the role of the insulin receptor in mediating renal sodium reabsorption. On the other hand, several studies have suggested that activation of the insulin-like growth factor-1 (IGF-1) receptor can enhance sodium reabsorption via ENaC. The objective in this proposal is to determine the mechanisms that specifically regulate ENaC activity in models of insulin resistance. The R01 Grant will provide the necessary resources for the principal investigator (PI) to test the hypothesis that hyperinsulinemia provoked by peripheral insulin resistance induces salt-sensitive hypertension via activation of the insulin and/or the IGF-1 receptor, initiation of downstream signaling cascades, and enhancement of ENaC- mediated sodium transport. To test this hypothesis, two specific aims are proposed. Aim 1 is to define the contribution of the insulin and/or IGF-1 receptor to blood pressure, sodium reabsorption, and ENaC-mediated sodium transport in mouse models of insulin resistance. Using wild-type and principal cell-specific insulin or IGF-1 receptor knockout mice, the PI will induce insulin resistance in these mice and then measure systemic blood pressure, urine sodium excretion in the presence and absence of an ENaC-specific inhibitor, and sodium transport across in vitro microperfused collecting duct. Aim 2 is to determine the cellular mechanisms by which insulin-mediated activation of the insulin and/or IGF-1 receptor stimulates ENaC-mediated sodium transport in principal cells. The PI will measure receptor activation in control vs. insulin-resistant wild-type mice; measure ENaC expression in insulin-resistant wild-type vs. knockout mice; and compare ENaC-mediated currents and receptor signaling pathways using a novel technique to isolate principal cells from wild-type and knockout mice. The expected outcomes of the proposed aims are to identify the receptors and post-receptor signaling pathways required for stimulation of ENaC and hence, salt-sensitive hypertension in the insulin resistance syndrome. We anticipate that these results will significantly advance the field by identifying appropriate targets for the prevention and treatment of hypertension in diseases associated with insulin resistance, such as obesity and Type 2 diabetes mellitus. The proposed research is innovative in that we will directly compare the insulin and IGF-1 receptor and employ novel techniques to challenge the unilateral paradigm of hyperinsulinemia simply activating the insulin receptor in ENaC-expressing principal cells of the collecting duct.

Project Number:	5R01DK094162-03	**Contact PI / Project Leader:**	BIDDINGER, SUDHA B
Title:	CONTROL OF LIPID METABOLISM IN INSULIN RESISTANT STATES	**Awardee Organization:**	CHILDREN'S HOSPITAL CORPORATION

Abstract Text:

DESCRIPTION (provided by applicant): The metabolic syndrome is a state of insulin resistance characterized by multiple derangements in lipid homeostasis, leading to dyslipidemia, atherosclerosis, hepatic steatosis, and cholesterol gallstones. The factors that drive these derangements are unknown but must be determined in order to effectively treat the metabolic syndrome. The transcription factors FoxO1 and Sterol Regulatory Element Binding Protein (SREBP)-1c are key regulators of insulin action. FoxO1 promotes transcription of the gluconeogenic enzymes, but also the enzymes necessary for VLDL secretion and biliary cholesterol secretion. SREBP-1c, on the other hand, induces the lipogenic enzymes. In normal livers, insulin suppresses FoxO1 and activates SREBP-1c. In the metabolic syndrome, insulin fails to suppress FoxO1 but SREBP-1c is paradoxically increased. This raises the question, what drives SREBP-1c in the presence of insulin resistance? Our preliminary data show that the livers of Liver Insulin Receptor Knockout (LIRKO) mice, which are unresponsive to insulin, show a rapamycin- sensitive increase in SREBP-1c in response to dietary carbohydrates. These data indicate the existence of an insulin-independent signaling pathway that could potentially allow the excessive consumption of carbohydrates to activate SREBP-1c and lipogenesis, even in the presence of insulin resistance. The overarching goal of this proposal is to identify the key driver of lipid metabolism in the insulin resistant state. We hypothesize that FoxO1, which fails to be suppressed by insulin, drives dyslipidemia, atherosclerosis and gallstones; but that SREBP-1c, induced by nutrients, drives lipogenesis and steatosis. Our aims are to (1) determine the extent to which FoxO1 and SREBP-1c promote atherosclerosis, steatosis, and cholesterol gallstones by knocking down FoxO1 or reconstituting SREBP-1c expression in the livers of LIRKO mice; and (2) to define the insulin-independent signaling pathways by which nutrients can activate SREBP-1c and lipogenesis. We expect to find that FoxO1 and SREBP-1c define two distinct metabolic signaling pathways that are both necessary for the full complement of derangements present in the metabolic syndrome.

Project Number:	5R01DK095058-03	**Contact PI / Project Leader:**	BONEGIO, RAMON G.B.
Title:	ENDOGENOUS RNA LIGANDS FOR TOLL-LIKE RECEPTORS IN IMMUNE-COMPLEX NEPHRITIS	**Awardee Organization:**	BOSTON MEDICAL CENTER

Abstract Text:

DESCRIPTION (provided by applicant): A number of common kidney diseases are cause when antibodies in the form of immune complexes deposit in the kidney. The resulting kidney inflammation or glomerulonephritis is often destructive and progresses over time to end-stage kidney failure that requires dialysis or transplantation. Current therapies are non-specific, toxic and not always effective. There is a fundamental gap in the understanding of how antibody deposition in the kidney induces subsequent chronic inflammation. Toll-like receptors are cell surface receptors that usually function to induce immune responses to pathogens and are well conserved in all mammals. We hypothesize that endogenous ligands for Toll-like receptors are released following antibody deposition in the glomerulus and that such ligands serve as a "danger signal" that initiates injurious inflammatory responses in the glomerulus. In order to better understand the role of endogenous Toll-like receptor ligands during the pathogenesis of immune complex glomerulonephritis, we have developed a unique mouse model that mimics many of the characteristic features of immune complex glomerulonephritis in humans. In preliminary studies using this model, we discovered an important role of Toll-like receptor 7 (TLR7), a receptor activated by single stranded RNA, in the pathogenesis of immune complex glomerulonephritis. In aim 1, we will define the source(s) of immunostimulatory RNA in the injured glomerulus and determine if Toll-like receptor 3, another RNA-sensing receptor, also plays a role in disease development. In aim 2, we will identify the immune or kidney cells responsible for sensing endogenous RNA. As TLR7 engagement may activate several distinct signaling cascades, in aim 3 we will determine to what extent the different TLR7-induced cascades regulate disease phenotype and the rate of disease progression. Our long term goal is to use the detailed knowledge that we will gain about pathogenic Toll-like receptor signaling pathways in mice to identify rational targets to treat immune complex disease in humans.

Project Number:	5R01DK098222-02	**Contact PI / Project Leader:**	BONILHA, HEATHER SHAW
Title:	IMPACT OF PULSE RATE ON SWALLOWING IMPAIRMENT ASSESSMENT AND RADIATION EXPOSURE	**Awardee Organization:**	MEDICAL UNIVERSITY OF SOUTH CAROLINA

Abstract Text:

DESCRIPTION (provided by applicant): Modified Barium Swallow Studies (MBSSs) are the key diagnostic test to identify abnormalities in the structures and functions of swallowing. MBSSs are also used to test diet modifications, compensatory strategies and exercises to support clinicians' treatment decisions for patients with dysphagia. However, MBSSs are a type of fluoroscopic study that uses ionizing radiation. Radiation exposure from medical tests are mandated to be as low as reasonable achievable. Pulse rate is a MBSS setting that is a main target for reducing radiation exposure. Unfortunately, decreasing pulse rate also decreases the information available from which to judge swallowing impairment. Since the oropharyngeal swallow only lasts approximately 1 second, when pulse rate is decreased from 30 to 15, the number of unique images available to judge swallowing impairment also decreases from 30 to 15. The effect of this reduction of information could threaten the accuracy of our judgments of swallowing impairment and lead to the use of incorrect rehabilitation strategies. The consequences of incorrectly assessing swallowing impairment are serious. If swallowing impairment exists and is un- or under- detected, airway protection and nutrition may be at risk. Inaccurate judgments may also err on the side of overly conservative recommendations of oral intake restriction such as modifications in diet or tube feeding placement and which would unnecessarily decrease a dysphagic patient's health status and quality of life. Furthermore, it is not even clear that decreasing pulse rate is a meaningful decision with respect to reducing cancer risk as we do not know the levels of radiation exposure and cancer risks associated with MBSSs. Knowledge of the effect of reducing pulse rate on judgments of swallowing impairment and radiation exposure is important to the ability to weigh the risk of erroneous judgments of swallowing impairment against the benefit of the radiation reduction and make informed decisions about pulse rate setting. Thus, the goal of this study is to quantify the effect of reducing pulse rate on judgments of swallowing impairment and radiation exposure. Toward this goal, the specific aims of this proposal are: Aim 1. Quantify the impact of pulse rate on swallowing impairment severity assessment and treatment recommendations. Aim 2. Quantify radiation dose during MBSSs. Aim 3. Quantify the cancer risk based on radiation dose. The results of this study will provide the information needed to weight the risks and benefits of the different pulse rates used in MBSSs. This evidence will serve as a guide for speech-language pathologists, radiologists and hospital safety boards when evaluating MBSSs procedures and inform patient management decisions.

Project Number:	5R01DK098646-02	**Contact PI / Project Leader:**	BOUDINA, SIHEM
Title:	NOVEL PATHWAYS FOR FAT BURNING THAT PROTECTS FROM HIGH FAT DIET-INDUCED METABOLIC	**Awardee Organization:**	UNIVERSITY OF UTAH

Abstract Text:

DESCRIPTION (provided by applicant): Obesity rates are increasing in the United States, with recent statistics estimating more than 35.7% of adults and 16.9% of children and adolescents are considered obese. Obesity is a risk factor for insulin resistance, the metabolic syndrome and cardiovascular disease. Despite its public health importance, the pathogenesis of obesity is not well understood. Increased oxidative stress in adipose tissue of obese humans and animals in response to excess nutrient intake has been documented. However, the role of adipose oxidative stress in the pathogenesis of obesity and its associated metabolic alterations in not understood. To address this, we generated mice with increased superoxide production in adipocytes through deletion of manganese superoxide dismutase (MnSOD), the sole enzyme responsible for detoxifying superoxide to hydrogen peroxide in the mitochondrial matrix. The adipocyte- specific MnSOD KO (AdSod2KO) mice are lean, have increased whole body fat oxidation and resist diet-induced glucose intolerance, insulin resistance and hepatic steatosis. The overarching goal of this proposal is to elucidate the mechanisms underlying enhanced fat oxidation and improved metabolic homeostasis in response to HFD in AdSod2KO mice. This proposal has two specific aims: Specific Aim 1 will identify the underlying mechanisms by which adipocyte MnSOD deletion and/or oxidative stress enhanced whole body fat oxidation. Under this aim, we will first determine the contribution of white and brown adipose tissue, liver and skeletal muscle in enhancing whole body fat oxidation, then investigate whether the increase in whole body fat oxidation results from coupled or uncoupled mitochondrial oxidation of fatty acid and finally identify redox-dependent mechanisms that can increase fatty acid oxidation in white adipose tissue. Specific Aim 2 will determine tissue-specific mechanisms by which MnSOD deletion and/or enhanced oxidative stress in mature adipocytes protects against HFD-induced glucose intolerance, insulin resistance and hepatic steatosis in mice. Under this aim, we will examine whether adipocyte MnSOD deletion affects lipolysis, determine if adipocyte MnSOD deletion and/or oxidative stress enhance whole body insulin sensitivity during HFD and β-cell function and identify known and unknown adipose-secreted factors that could mediate the beneficial systemic effect on metabolism during HF feeding in AdSod2KO mice. These studies have high impact on obesity research as it provides a new paradigm for adipose tissue oxidative stress and its impact on whole body energy metabolism and insulin sensitivity. We believe that this research will provide new insights on the redox-regulation of metabolism and could identify new targets that could be modulated to enhance whole body fat oxidation and protects from the development of insulin resistance and diabetes during obesity.

Project Number:	5R01DK093668-03	**Contact PI / Project Leader:**	CADWELL, KEN HASHIGIWA
Title:	DEFINING THE ROLE OF NOD2 AND BACTERIA IN ATG16L1-DEPENDENT INTESTINAL DISEASE.	**Awardee Organization:**	NEW YORK UNIVERSITY SCHOOL OF MEDICINE

Abstract Text:

DESCRIPTION (provided by applicant): Our long-term goal is to understand how genetic susceptibility and environmental factors combine to mediate inflammatory bowel disease. Atg16L1 and Nod2 are two Crohn's disease susceptibility genes that have received much attention because of their critical function in innate immune defense against bacteria. While an essential role for Atg16L1 in autophagy and Nod2 in bacterial recognition have been demonstrated, it is now clear that mutating these molecules have complex and unanticipated consequences at both the cellular and whole organism level. Therefore, it is critical that we examine these susceptibility genes in the context of intestinal disease to interpret the recent studies that are revealing new downstream functions and pathways. We previously demonstrated that Atg16L1 mutant mice (Atg16L1HM) develop intestinal abnormalities when infected with the mouse norovirus MNV. These abnormalities include the generation of Crohn's-like pathologies when MNV-infected Atg16L1HM mice are injured with the chemical DSS. Remarkably, we have now found that development of these pathologies depends on both commensal bacteria and Nod2. When Atg16L1HM mice are treated with antibiotics or crosed to Nod2 knockout mice, they are protected from intestinal disease induced by MNV and DSS treatment. Given the current challenge in the field in defining Nod2 function and the great interest in understanding commensal bacteria, we will take advantage of these observations to gain insight into mucosal immunity and Crohn's disease pathogenesis. In this proposal, we will test a model in which Nod2 senses specific intestinal bacteria to mediate inflammation in Atg16L1HM mice. We will also determine if the Nod2 frameshift mutation (Nod2fs) associated with Crohn's disease is similar or distinct to Nod2 deletion in the presence of Atg16L1 mutation since this information will have important implications for gene-gene interactions in inflammatory diseases. We will address these issues with the following specific aims: (1) Identify the Nod2 signaling pathway that is responsible for Crohn's-like pathologies in Atg16L1HM mice, (2) Define the specific bacterial population required for disease in Atg16L1HM mice, and (3) Compare the effect of Nod2 deletion and Nod2fs expression in intestinal inflammation. We have a unique opportunity to characterize two susceptibility genes of great interest and the commensal bacterial flora in a multi-hit disease model that recreates pathologies similar to those observed in patients.

Project Number:	5R01DK091338-02	**Contact PI / Project Leader:**	CAI, LU
Title:	LOW-DOSE IRRADIATION AS A NOVEL INTERVENTION FOR DIABETIC NEPHROPATHY	**Awardee Organization:**	UNIVERSITY OF LOUISVILLE

Abstract Text:

DESCRIPTION (provided by applicant): The goal of this study is to develop low-dose radiation (LDR) as a new tool to prevent and treat diabetic nephropathy. Currently no effective preventive or therapeutic approaches are available to treat diabetic nephropathy, which is the most common cause of renal failure. We have been investigating the biological effects of LDR, including its hormesis and adaptive response, in vitro and in vivo. A major advantage of LDR is that it activates many genes in antioxidant and anti-inflammatory pathways, rather than just single protective gene, potentially making LDR a very potent and novel therapeutic approach. This was borne out by our preliminary studies that show that LDR at 25 mGy decreases diabetic nephropathy, by significantly reducing diabetes-induced renal oxidative damage and inflammation. Our latest preliminary data show up-regulation of nuclear factor erythroid 2-related factor 2 (Nrf2) expression and protein kinase B (also called Akt) phosphorylation in the kidney of diabetic mice, also exposed to LDR at 25 mGy. NRF2 is a transcription factor involved in expression of a broad range of protective genes. Therefore our central hypothesis is that exposure of diabetic animals to LDR can prevent and treat diabetic nephropathy by activation of many protective genes through stimulation of the Nrf2 pathway. This hypothesis will be tested through three specific Aims: (1) LDR at the optimal condition not only prevents, but also delay diabetic nephropathy; (2) the optimal LDR is safe for diabetic subjects; (3) the renal protection by the optimal LDR is predominantly mediated by up- regulating Nrf2-mediated multiple antioxidant components. The great advantage of LDR is that it offers a highly controllable, non-invasive method for eliciting endogenous, synergistic tissue protection and repair mechanisms. This innovative approach will be particularly valuable for the diabetic patient who already has significantly decreased renal function that increases the toxicity of invasive drugs. Therefore, this project will open a new avenue for the prevention and treatment of diabetic complications.

Project Number:	5R01DK093507-03	**Contact PI / Project Leader:**	CHANG, JOHN T
Title:	ROLE OF ATYPICAL PROTEIN KINASE C IN INFLAMMATORY BOWEL DISEASE	**Awardee Organization:**	UNIVERSITY OF CALIFORNIA SAN DIEGO

Abstract Text:

DESCRIPTION (provided by applicant): Inflammatory bowel disease is believed to result from an inappropriate immune response to commensal intestinal microbes in a genetically susceptible host. Aberrant sensing of microbes by the innate immune system triggers the development of pathogenic T lymphocytes that initiate and propagate intestinal inflammation. Recent evidence has suggested a novel role for an evolutionarily conserved mechanism called asymmetric cell division in regulating adaptive immune responses to microbes. During asymmetric division, segregation of cell fate determinants to one side of the plane of division enables their unequal inheritance and the divergence of daughter cell fates. We have previously shown that a T lymphocyte appears to undergo asymmetric division to give rise to two differentially fated daughter cells (J.T. Chang et al., Science 2007). We observed, moreover, that the conserved atypical PKC (aPKC)-Par3-Par6 and Scrib-Dlg-Lgl polarity complexes, which regulate polarity and asymmetric division in other model organisms, establish complementary domains within dividing T cells recruited into an immune response against a microbial pathogen. Preliminary evidence from our laboratory using an adoptive transfer model of colitis suggests that CD4+ T cells may undergo asymmetric division during a dysregulated immune response to commensal intestinal microbes. We hypothesize that the polarity network regulates asymmetric division in activated CD4+ T cells, influencing their differentiation into pathogenic, colitis-inducing cells. In this proposal, we will test the hypothesis that the aPKC and Scrib polarity complexes regulate the ability of CD4+ T lymphocytes to undergo asymmetric division, differentiate into pathogenic Th1 and Th17 effector cells, and mediate intestinal inflammation. Accomplishment of these aims is likely to yield important insights about fundamental mechanisms underlying the pathogenesis of IBD, and could identify new targets against which future therapies might be directed.

Project Number:	5R01DK096028-02	**Contact PI / Project Leader:**	CHASENS, EILEEN R
Title:	THE EFFECT OF TREATMENT OF OSA ON DIABETES SELF MANAGEMENT AND GLYCEMIC CONTROL	**Awardee Organization:**	UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Abstract Text:

DESCRIPTION (provided by applicant): While diabetes self-management has been improved and refined over the last 30 years, many persons with T2DM continue to have difficulty in achieving glycemic goals. Obstructive sleep apnea (OSA) has a high prevalence among adults with type 2 diabetes (T2DM) and is associated with excessive daytime sleepiness, impaired mood, decreased vigilance, and reduced functional outcomes. The degree that OSA affects diabetes self-management, a known determinant of glycemic control, remains unstudied. The most effective treatment for OSA, continuous positive airway pressure (CPAP), results in improved self-reported daytime functioning. However, the effect of CPAP treatment on reception of diabetes education remains unknown. The underlying premise of the proposed study from this new investigator is that OSA hinders diabetes self-management in adults with T2DM. This study expands on our pilot/feasibility study that suggested that CPAP treatment is associated with decreased fatigue, increased physical activity, and improved glucose control. Our goal is to improve understanding of the effect of OSA on diabetes self-management and to determine the efficacy of CPAP treatment in improving diabetes outcomes in adults treated with CPAP compared to those on sham- CPAP. We propose to enroll 210 adults (50 percent female; 40 percent minority) with T2DM and moderate-to-severe OSA (apnea + hypopnea index > 15) who have suboptimal glycemic control (A1C e 7.0 percent) for a double blind, randomized, placebo-controlled trial to determine if diabetes self-management outcomes and glycemic control are better in subjects with OSA who are treated with CPAP and receive diabetes education and counseling compared to control subjects who are on sham-CPAP and receive diabetes education. We will compare the effectiveness of the intervention after 6 weeks and 12 weeks on measures of glycemic control, retention of information taught during the diabetes education sessions, lifestyle behaviors required for optimal diabetes control, reported monitoring of self-management activities, physical activity, and diabetes-related distress. We will explore whether the average nighttime use (adherence) of CPAP, sleep quality, daytime sleepiness, mood, and vigilance mediate the effect of CPAP treatment on glycemic control and diabetes self-management outcomes. We will also explore if adherence to CPAP is associated with outcome measures of glycemic control and lifestyle behaviors in the entire sample after 24 weeks of therapeutic CPAP. This study uses objective measures to measure CPAP adherence, physical activity, vigilance, and glycemic control. After 12-weeks, subjects who were originally on sham-CPAP will be crossed over to active treatment. The overall impact of this study will be increased knowledge about the effect of sleep apnea on diabetes self-management. Expanding our understanding of the effect of sleep disturbances on diabetes self-management may lead to improved guidelines for screening and treatment of OSA in the increasingly large portion of the population with diabetes.

Project Number:	5R01DK095137-03	**Contact PI / Project Leader:**	CHUN, TAE-HWA
Title:	MMP14-DEPENDENT REGULATION OF ADIPOSE TISSUE REMODELING AND FUNCTION (R01)	**Awardee Organization:**	UNIVERSITY OF MICHIGAN

Abstract Text:

DESCRIPTION (provided by applicant): Excess accumulation of collagen fibers next to fat cells (peri-adipocyte fibrosis) is observed in insulin-resistant individuals with inappropriate fat mass (obesity and lipodystrophy). The molecular mechanism underlying the formation of peri-adipocyte fibrosis, however, is poorly understood. MMP14 encodes a pericellular collagenase that plays a critical role in type I collagen turnover. Moreover, MMP14 has been shown to maintain pro- transcriptional histone acetylation (H3K9ac) by cleaving juxtaposed type I collagen fibers. The central hypothesis of this research is that MMP14-dependent peri-adipocyte collagen turnover promotes healthy adipocyte function via epigenetic gene regulation. My central hypothesis here is that MMP14 expressed by adipocytes directs peri-adipocyte collagen turnover and maintains healthy adipocyte function. I aim to pursue the following three aims to test my hypothesis. Aim 1. Characterize the role of adipocyte MMP14 in preventing peri-adipocyte fibrosis and adipocyte dysfunction in vivo: I hypothesize that MMP14 tethered to adipocytes maintains the anti-fibrotic and anti- inflammatory state of adipose tissues. Using a peri-adipocyte fibrosis model, i.e., tamoxifen-inducible adipocyte-selective MMP14 gene deletion, I will characterize the link between peri-adipocyte fibrosis, inflammatory tissue damage, and the induction of insulin resistance. Aim 2. Define type I collagen-dependent and -independent regulation of adipocyte function in vitro and in vivo: I hypothesize that MMP14-dependent type I collagen cleavage is the primary event that leads to epigenetic histone modification necessary for adipocyte gene regulation. By using MMP-resistant mutant type I collagen mice and non-collagenous 3-D nanomaterial, I will determine the type I collagen-dependent and - independent mechanisms underlying adipocyte gene regulation. Aim 3. Define the epigenetic histone modification regulated by MMP14 in vitro and in vivo: I propose that MMP14-dependent peri-adipocyte collagenolysis regulates pro-transcriptional histone modification (H3K9ac) that intersects with PPARγ-dependent adipocyte gene regulation. By using peri-adipocyte fibrosis model, I will define the role of MMP14 in regulating the interaction between H3K9ac and PPARγ in regulating adipocyte gene expression. This study is expected to demonstrate that MMP14-dependent peri-adipocyte collagen turnover enhances PPARγ-dependent gene regulation via histone acetylation. Together, expected outcomes will define the role of MMP14 in preventing peri-adipocyte fibrosis and adipocyte dysfunction. The knowledge will help us understand the pathogenesis of insulin resistance and obesity-related metabolic diseases from the perspective of peri-adipocyte collagen turnover.

Project Number:	5R01DK083414-04	**Contact PI / Project Leader:**	DASARATHY, SRINIVASAN
Title:	MECHANISMS OF MALNUTRITION IN CIRRHOSIS WITH PORTOSYSTEMIC SHUNTING	**Awardee Organization:**	CLEVELAND CLINIC LERNER COM-CWRU

Abstract Text:

DESCRIPTION (provided by applicant): Abstract End stage cirrhosis and its complications result in 27,000 deaths and 6,500 liver transplants annually in the United States. Reduced skeletal muscle mass or sarcopenia is one of the major complications of portosystemic shunting (PSS) that accompanies cirrhosis. Sarcopenia contributes significantly to the morbidity and mortality of these patients. There are no effective treatment options since the underlying mechanisms are currently unknown and most studies to date have been descriptive. Patients with cirrhosis and PSS as well as animal models have reduced muscle protein synthesis but the molecular mechanisms regulating this process are currently not known. Hyperammonemia is a consistent abnormality in cirrhosis and PSS due to impaired hepatic detoxification of ammonia. Our preliminary data in animal models of hyperammonemia and in muscle cell cultures exposed to ammonia showed an increased expression of myostatin. Myostatin inhibits skeletal muscle protein synthesis and results in lower muscle mass. The mechanism of increased myostatin induced by ammonia is not known. Our preliminary studies have demonstrated NFκB binding sites on the myostatin promoter and NFκB may be an upstream regulator of myostatin during hyperammonemia. In our preliminary studies in myoblast cells, NFκB was increased in response to ammonia and preceded the elevated expression of myostatin. Finally, in both our in vivo studies in PCA rat as well as cell cultures, we observed greater activation of a cellular energy sensor, AMP kinase when myostatin expression was elevated and these alterations were reversed by blocking myostatin in vivo. We therefore hypothesized that hyperammonemia induced increased expression of myostatin inhibits muscle protein synthesis and muscle mass constituting a liver muscle axis. To identify the underlying molecular mechanisms responsible for the reduced muscle protein synthesis with PSS we propose the following aims: 1) Establish that ammonia induced myostatin expression constitutes a liver-muscle axis in vivo, 2) Demonstrate that the mechanism of hyperammonemia mediated upregulation of myostatin expression is NFκB dependent and 3) Establish that the regulation of mTOR by myostatin is independent of Akt and is mediated by AMP kinase in hyperammonemia. Pharmacological, chemical and genetic approaches in animal models and cell culture systems will be used in these studies. The proposed studies are innovative because they will demonstrate the mechanism by which hyperammonemia inhibits muscle protein synthesis and identify a novel regulatory crosstalk between myostatin and mTOR, a critical signaling molecule that regulates protein synthesis. These studies are very significant because they will lay the foundation for understanding the mechanisms of sarcopenia in portosystemic shunting and identify potential therapeutic targets. Furthermore, the results from these studies have the potential to be rapidly translated to clinical application by using pharmacological methods to lower ammonia mediated increased myostatin expression.

Project Number:	5R01DK098517-02	**Contact PI / Project Leader:**	DE LEON, DIVA DEL CARMEN Li, CHANGHONG
Title:	FUEL METABOLISM AND INSULIN SECRETION IN KATP-HYPERINSULINISM HUMAN ISLETS	**Awardee Organization:**	CHILDREN'S HOSP OF PHILADELPHIA

Abstract Text:

DESCRIPTION (provided by applicant): Inactivating mutations in KATP channels cause the most common and severe form of congenital hyperinsulinism (KATPHI). Children with KATPHI are usually unresponsive to medical therapy and require pancreatectomy to control the hypoglycemia and prevent permanent brain damage. The goal of this proposal is to elucidate the β-cell pathophysiology in KATPHI through the examination of fuel metabolism and stimulus-secretion coupling in islets isolated from children with KATPHI. Our overall hypothesis is that disturbances in KATP channels function result not only in dysregulation of the triggering pathway of insulin release, but also have secondary consequences that drastically disturb glucose and amino acid metabolism and alter fuel-stimulated insulin secretion through both the triggering and the amplification pathway. This hypothesis will be examined in three related and overlapping specific aims: Aim 1 characterizes fuel metabolism and fuel-mediated insulin release in human islets with inactivating mutations in KATP channels and examines the role that elevated cytosolic calcium plays in determining the fate of metabolic fuels in these islets. Aim 2 focuses on examining the metabolic and cAMP-mediated amplification of insulin secretion within the framework of energy production in human KATPHI islets. Aim 3 examines the differences in gene expression between KATPHI islets and normal islets and integrates the metabolic and transcriptional profile of these islets to understand the mechanisms underlying the differences in fuel metabolism and insulin secretion. KATPHI is a severe genetic disorder associated with high rates of neurodevelopmental impairment. It has been almost 20 years since the discovery of the molecular basis of this condition. However, the incomplete understanding of the pathophysiology underlying the dysregulated insulin secretion has precluded the development of effective therapies. Thus, outcomes with current treatment approaches continue to be suboptimal for children carrying the most severe mutations. Our study aims at examining the pathophysiology within the framework of the energy production/insulin secretion relationship to identify new targets for therapy. This study will improve our understanding of the mechanisms and second messengers mediating the amplifying pathway of insulin secretion, which in turn, will be helpful for understanding the mechanisms implicated in the progressive β-cell failure that leads to type 2 diabetes. Thus, these studies may lead to the identification of novel targets for therapy not only for hyperinsulinism but also for diabetes.

Project Number:	5R01DK092454-04	**Contact PI / Project Leader:**	DJAMALI, ARJANG
Title:	THE ROLE OF NOX2 IN CNI-INDUCED RENAL FIBROSIS	**Awardee Organization:**	UNIVERSITY OF WISCONSIN-MADISON

Abstract Text:

DESCRIPTION (provided by applicant): Despite the tremendous success of solid organ transplantation in past 20 years, long-term kidney outcomes have been limited by chronic calcineurin inhibitor (CNI)-mediated fibrosis. CNIs including cyclosporine A (CsA) and tacrolimus (TAC) are the backbone of anti-rejection therapy in transplantation. However, they represent a major public health concern since CNI-induced kidney fibrosis is an important cause of renal failure after solid organ transplantation. Increasing evidence suggests that Nox2 is at the crossroads of CNI-induced renal hypoxia and fibrosis. Nox2 is the classical phagocytic isoform of the NADPH oxidase enzyme responsible for "oxidative burst", the mechanism that eliminates internalized pathogens. We hypothesize that independent from its role in phagocytes, Nox2 is a key regulator of CNI-induced kidney hypoxia and fibrosis. In support of this hypothesis, observations from our laboratory demonstrate that (a) Nox2 is inducible in renal tubular epithelial cells during CsA-induced epithelial-to-mesenchymal transition (EMT) (b) tubulointerstitial Nox2 is upregulated in kidneys undergoing CsA-induced fibrosis (c) inhibition of Nox activity with apocynin and diphenyleneiodonium (DPI) is associated with prevention of CsA-induced fibrosis and hypoxia measured by blood oxygen-level-dependent MRI (BOLD MRI) in rats. Based on these observations, and the availability of Nox2 knockout mice to rigorously test our hypotheses, we propose the following studies. In Specific Aim 1, we will characterize the molecular mechanisms that regulate Nox2 activity during CNI-induced EMT and matrix remodeling in renal tubular epithelial cells. Next, we will define the specific role of Nox2 in CNI-induced renal fibrosis. We will perform these studies using wild type, Nox2, TGFb1 and Smad2/3-null mice and tubular cells. In Specific Aim 2, we will characterize the effects of chronic CsA therapy on medullary and cortical perfusion and oxygenation using noninvasive MR-imaging with BOLD and contrast-enhanced perfusion studies in mice. We will confirm these studies with molecular markers of tissue hypoxia including pimonidazole and HIF-1a. Last, we will determine if the absence of Nox2 improves CsA-induced hypoperfusion and hypoxia in mice. In Specific Aim 3, we will confirm the validity of the above molecular and small animal investigations in a pilot clinical study of 20 nonkidney organ transplant recipients. The study is designed to determine whether intrarenal Nox2 is associated with chronic CNI nephrotoxicity. The secondary objective is to determine whether intrarenal oxygenation measured by BOLD MRI can predict disease progression. In summary, we outline research studies that rigorously assess the role of Nox2 in CNI-induced renal fibrosis. In addition, will propose contemporary and complementary clinical and translational strategies to examine the molecular mechanisms that regulate Nox2 activity during CNI-mediated fibrogenesis. If successful, the results of our studies will provide a significant step forward in the design of new diagnostic, monitoring and treatment options aimed to offset the deleterious effects of immunosuppressant therapy and improve long-term kidney outcomes.

Project Number:	5R01DK091592-03	**Contact PI / Project Leader:**	DONG, X CHARLIE
Title:	REGULATION OF HEPATIC LIPID METABOLISM BY A NOVEL FOXO PATHWAY	**Awardee Organization:**	INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS

Abstract Text:

DESCRIPTION (provided by applicant): Proper regulation of hepatic lipid metabolism is critical to triglyceride homeostasis in the liver and blood circulation. However, the underlying mechanism of the regulation remains elusive. The long-term goal of this laboratory is to better understand the regulatory mechanism of hepatic lipid metabolism. The objective in this particular application is to illustrate the role of Forkhead transcription factor O subfamily members (Foxos) and their potential downstream effector(s) in the development of hepatic steatosis and hypertriglyceridemia. Foxos have been implicated in the regulation of hepatic lipogenesis and very-low-density lipoprotein (VLDL) secretion. However, the role of Foxos in these processes is still controversial. To clarify the physiological functions of Foxos in hepatic lipid metabolism, mouse models have been estabolished. The preliminary data suggest that a novel regulation is involved in hepatic lipid metabolism through Foxo-controlled expression of nicotinamide phosphoribosyltransferase (Nampt), the rate-limiting enzyme in the NAD biosynthesis. To test this hypothesis, two specific aims are designed: 1) To elucidate the molecular mechanisms of Nampt gene regulation by Foxos; 2) To determine the physiological role of the Foxo pathway in hepatic lipid metabolism. Under the first aim, mechanistic studies will be performed to illustrate the details of protein-DNA and protein-protein interactions in the regulation of the Nampt gene. Under the second aim, gene overexpression and knockout approaches will be used to delineate the physiological and pathological roles of the newly identified pathway in hepatic lipid homeostasis. This application is innovative, because new animal models will be utilized and a distinct pathway will be examined. The proposed research is also significant, because it is expected to advance and expand understanding of how hepatic lipid metabolism is regulated. Ultimately, such knowledge has a potential to advance the prevention and/or treatment of dyslipidemia and fatty liver disease.

Project Number:	5R01DK095069-03	**Contact PI / Project Leader:**	FORMAN, EVAN M
Title:	ACCEPTANCE-BASED BEHAVIORAL TREATMENT FOR OBESITY: MAINTENANCE AND MECHANISMS.	**Awardee Organization:**	DREXEL UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Obesity has become so prevalent it is now considered a national and global epidemic. The limitations of pharmacologic, surgical and environmental interventions point to the critical need for behavioral programs. However, standard behavioral treatments are only minimally effective in the long term, with most participants eventually gaining back their lost weight. Weight regain can be traced to participants' difficulty following recommended diet and physical activity prescriptions, which appears tied to immutable biological drives and internal (e.g., sadness, anxiety, cravings) and external (e.g., presence of delicious foods and labor- saving devices) cues. In our lab we have found that the ability to resist these cues is bolstered by interventions that increase distress tolerance (e.g., tolerance of negative effect, food cravings), present-moment awareness of internal states and how these may be affecting behavior (i.e., metacognitive awareness), and clarity about one's personal values. In particular, we have shown that acceptance-based behavioral interventions, which incorporate these strategies, have promise for weight control. Our NIH-funded pilot study demonstrated an especially strong effect of acceptance-based strategies on weight loss for participants who reported higher levels of depression, psychological responsivity to food, and internally and externally-cued eating. The primary goal of the proposed project is to evaluate the longer-term efficacy of ABT in relation to gold standard behavioral treatment for obesity. A secondary goal is to test hypothesized mechanisms of action of the two treatments, both during active intervention and during the post-treatment weight loss maintenance phase. Building on our recent work using lab-based behavioral measures and repeatedly-administered, ecological momentary assessment (EMA) to better understand the challenges of adopting and maintaining healthful behavior choices, we will use both these measurement strategies to most accurately capture causal pathways to in-the-moment eating and physical activity lapses. EMA offers considerable advantages over retrospective self-reports which are subject to inaccuracies and biases. We also aim to evaluate moderation hypotheses stating that the superiority of ABT will be especially pronounced for those with greater mood disturbance, sensitivity to the food environment, and internal and external disinhibited eating. Our aims work towards longer-range goals of using evidence to maximize the most effective components of interventions, matching patients to treatment type, and developing real-time interventions aimed at correcting problematic eating and physical activity decisions as they occur naturalistically. Accordingly, we will randomly assign 200 overweight participants to 24 sessions of ABT or SBT, delivered over one year. All participants will be followed until 36 months post-baseline. EMA and lab-based behavioral assessments will allow more valid measurement of moderating and mediating pathways including the relationship between internal states and their impact on behavior, and how these associations are affected by treatment.

Project Number:	5R01DK090316-04	**Contact PI / Project Leader:**	FORNONI, ALESSIA
Title:	NOVEL TARGETS OF RITUXIMAB IN FSGS	**Awardee Organization:**	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE

Abstract Text:

DESCRIPTION (provided by applicant): Recurrent focal segmental glomerulosclerosis (FSGS) after transplantation is a highly prevalent condition where rituximab (a monoclonal antibody against CD20) may have a potential indication. Besides CD20, rituximab has been shown to bind sphingomyelin-phosphodiesterase-like-3b-precursor (SMPDL-3b) and to regulate acid-sphyngomyelinase (ASMase). We tested the hypothesis that rituximab prevents recurrent FSGS after transplantation via preservation of podocyte SMPDL-3b expression and activity. Our preliminary study in 41 patients at high risk for recurrent FSGS demonstrated that rituximab treatment was associated with lower incidence of post-transplant proteinuria and with decreased eGFR. The number of SMPDL-3b positive cells in post-reperfusion biopsies was reduced in patients that would later develop recurrent disease. Rituximab partially prevented the SMPDL-3b down-regulation observed in podocytes treated with the sera of affected patients. Both rituximab and SMPDL-3b overexpression prevented the disruption of the actin cytoskeleton and the apoptosis induced by patient sera, an effect that was diminished in cells where SMPDL- 3b gene was silenced. Quantitative analysis of the disruption of stress fibers in vitro was associated with the degree of post-transplant proteinuria, suggesting the possibility of developing a prediction assay for recurrent FSGS. Our University offers one of the best clinical grounds for the recruitment of a large population of patients with FSGS. We propose to utilize a pilot study in all patients with primary FSGS who undergo kidney transplantation as a feeder for the experimental studies. We will collect clinical data that will serve as secondary exploratory analyses. Post-reperfusion kidney biopsies and pre-transplant sera will be collected per protocol in patients randomized to receive rituximab or placebo. SMPDL-3b expression in kidney biopsies and in cultured podocytes exposed to patient sera will be utilized to study disease mechanisms and to perform association studies with clinical outcomes. Cell cytoskeleton remodeling, cell viability, traditional slit diaphragm proteins expression and localization and cellular lipid composition will be utilized to study if rituximab protects podocytes in a SMPDL-3b dependent manner. Our study is highly significant because it has strong clinical implications, since it may lead to a change in the approved indications for rituximab treatment of FSGS as well as other proteinuric diseases. The proposed study is innovative because it will offer new insights into the role of shyngomyelin related enzymes in podocyte function, thus allowing the identification of novel targets for antiproteinuric drug development. Finally, our in vitro assay treating normal human podocytes with patient sera may become a pre-transplant assessment test for the identifications of patients at high-risk.

Project Number:	5R01DK085250-04	**Contact PI / Project Leader:**	FRAENKEL, PAULA GOODMAN
Title:	MODIFIERS OF HEPCIDIN EXPRESSION AS NEW THERAPIES FOR IRON OVERLOAD	**Awardee Organization:**	BETH ISRAEL DEACONESS MEDICAL CENTER

Abstract Text:

DESCRIPTION (provided by applicant): Iron overload syndromes remain important causes of heart and liver failure in patients with thalassemia or hereditary hemochromatosis, which are common genetic diseases worldwide. Current therapy for these conditions includes serial phlebotomy (hemochromatosis) or chelation therapy (thalassemia), both of which are associated with poor patient compliance because of inconvenience and significant side effects. Both thalassemia and hereditary hemochromatosis are associated with inappropriately low levels of hepcidin, the key regulator of intestinal iron absorption and cellular iron storage, resulting in excessive dietary iron absorption. Hepcidin, produced in response to tissue iron loading and inflammation, binds the iron exporter ferroportin1, causing internalization of both proteins and reduced iron release from enterocytes to the circulation and from macrophages to other tissues. We hypothesize that raising hepcidin expression will enhance the efficacy of chelation therapy in thalassemia by reducing dietary iron absorption and promoting storage of iron in the reticuloendothelial system and could eliminate the need for phlebotomy treatment in patients with hemochromatosis. We have previously demonstrated that ferroportin1 is required for iron export and iron cycling through enterocytes and macrophages in zebrafish. We have also demonstrated that the regulation of hepcidin expression in zebrafish embryos resembles that observed in mammalian systems, in that it is responsive to transferrin-bound iron and the BMP pathway. Recently, we have also discovered that treatment with the phytoestrogen, genistein, results in increased hepcidin transcript levels in zebrafish embryos and in human hepatocytes. We propose to screen for additional small molecules that regulate hepcidin expression by conducting a chemical screen in zebrafish embryos. To elucidate the mechanism of action of molecules identified in the screen, we will characterize the modulators' effects on mammalian cellular iron transport, chromatin immunoprecipitation, RNA expression, and signaling pathways. The best candidate regulators will be evaluated in mouse models of thalassemia and hemochromatosis for their effects on iron overload and erythropoiesis. These studies will lead to the identification of molecules and pathways that may be adapted to generate treatments for patients with thalassemia or hereditary hemochromatosis.

Project Number:	5R01DK095004-02	**Contact PI / Project Leader:**	FREY, MARK R
Title:	REGULATION OF COLON EPITHELIAL CELL SURVIVAL BY NRG4-ERBB4 SIGNALING	**Awardee Organization:**	CHILDREN'S HOSPITAL OF LOS ANGELES

Abstract Text:

DESCRIPTION (provided by applicant): The ErbB4 receptor tyrosine kinase is induced by inflammation in the colon epithelium, and ErbB4 overexpression promotes colonocyte survival in vitro without affecting proliferation or migration. Thus, ErbB4 induction may be a compensatory response meant to protect the epithelium. However, preliminary data developed for this application show that expression of the specific ErbB4 ligand neuregulin-4 (NRG4) is deficient in both human IBD and murine colitis. Furthermore, in murine colitis models, although ErbB4 expression is elevated, it is not phosphorylated/activated. These results suggest that, in the context of inflammation, NRG4 downregulation leads to deficient signaling despite ErbB4 upregulation. Additional preliminary studies show that exogenous NRG4 protects colonocytes from cytokine-induced apoptosis both in vitro and in vivo, and reduces the severity of acute murine DSS colitis. We propose therefore that NRG4 could be used to stimulate ErbB4 during colitis, and thus to inhibit colonocyte apoptosis and improve pathology. As ErbB4 (a) has ligand binding properties and downstream targets that are unique among tyrosine kinases, and (b) can directly associate with both anti-apoptotic signaling molecules (e.g., PI3K, Src) and inflammatory mediators (e.g., STAT1), it has significant potential as a novel and selective IBD therapeutic target. However, neither the role of ErbB4 in colon biology in vivo nor the colonic response to its selective activation has been defined. Therefore, this project is designed to test the hypothesis that downregulation of NRG4 worsens colitis, and thus exogenous NRG4 treatment may improve colitis by activating anti-apoptotic signaling in colon epithelial cells. Planned experiments will use coordinated cell culture, crypt culture, and in vivo models to (1) determine the effects of loss of NRG4-ErbB4 function on colitis and define the mechanisms of NRG4 loss, (2) test the effectiveness of exogenous NRG4 in colitis, and (3) define signaling pathways which are required for NRG4-induced colon epithelial cell survival. Together, these studies will investigate the exciting possibility that NRG4-ErbB4 signaling is a novel therapeutic avenue for IBD.

Project Number:	5R01DK084000-05	**Contact PI / Project Leader:**	FULKERSON, JAYNE ALLYN
Title:	HEALTHY HOME OFFERINGS VIA THE MEALTIME ENVIRONMENT (HOME) PLUS	**Awardee Organization:**	UNIVERSITY OF MINNESOTA

Abstract Text:

DESCRIPTION (provided by applicant): Childhood obesity is a serious public health problem with limited effective prevention strategies to date. Although previous nutrition and physical activity environmental approaches for obesity prevention show some promise, most studies have not shown reductions in excess weight gain. Moreover, few prevention studies significantly engage parents and focus on the home environment. To prevent childhood obesity it is essential to promote healthy behaviors in the home environment because parents are influential primary role models for healthy eating and sedentary behavior, and are gatekeepers for food and beverage availability and degree of inactivity within the home. Moreover, the home setting is where most of children's calories and energy dense foods are consumed and where children engage in much of their sedentary behavior, particularly screen time (e.g., television, computer, game system). The proposed study will test the efficacy of the Healthy Home Offerings via the Mealtime Environment (HOME) Plus program, a year-long, family-based health promotion intervention to prevent excess weight gain among 8-12 year old children. The program is based on Social Cognitive Theory and a socio-ecological framework and promotes both regular and nutritionally-sound snacks and meals in which family members eat together (i.e., family meals) and encourages reductions in sedentary behavior, particularly screen time among children in the home setting. The efficacy of the intervention will be tested in a randomized controlled trial with 160 families randomized to two conditions (intervention or attention- only control). Two cohorts of families, recruited from before- and after-school programs and community centers, will be followed for 2.5 years. The primary hypothesis is that, by the end of the 12-month intervention, target children in the intervention families, relative to children in the control families, will have significantly lower body mass index (BMI; primary outcome) after adjustment for baseline BMI values. Secondary outcomes include frequency of weekly family meals and number of healthful foods and beverages available in the home and served at family meals and snacks (as reported by parent), target children's daily intakes of healthful foods and beverages, and target children's minutes of sedentary behavior per week, particularly screen time. Child and parent measurement will occur in their homes at baseline, post-intervention (12-months post- randomization), and follow-up (9-months post-intervention) by trained research staff. The proposed study builds upon successful methods from our HOME pilot study (2006-2008; NIH R21-DK0072997) and is innovative as it actively engages entire families in experiential activities and capitalizes on the home setting. The study will provide important information on environmental and behavioral strategies that families can use at home to prevent excess weight gain. The intervention program has high translation potential and is likely to be immediately useful to families of school-age children because it will be tested in real-world community settings and sustained across the state of Minnesota by the University of Minnesota's Extension Service.

Project Number:	5R01DK090264-04	**Contact PI / Project Leader:**	GANIBAN, JODY M.
Title:	GENE-ENVIRONMENT INTERPLAY AND CHILDHOOD OBESITY: AN ADOPTION STUDY.	**Awardee Organization:**	GEORGE WASHINGTON UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): The number of obese children in the US has increased dramatically over the past thirty years. Most efforts to reverse this trend, however, have not been effective. Two factors may underlie their limited success. First, most programs do not take into account children's personal risk for obesity, including their genetic and prenatal risks. Second, there is little information about factors that predict weight trajectories during childhood. The proposed study tests a comprehensive developmental model of obesity that incorporates child-based (genetic, prenatal) and family-based (parenting practices and modeling) risk factors for obesity, and seeks to identify constellations of risk that predict unhealthy vs. healthy weight trajectories. Furthermore, the degree to which the postnatal environment mediates, mitigates or amplifies the expression of child-based risks for obesity is examined. As such, this study represents a first step in developing new prevention programs that can consider children's weight trajectories in light of their unique vulnerabilities and needs. The proposed research is an extension of the ongoing Early Growth and Development study (EGDS). EGDS is a prospective, longitudinal study of adoptive children, along with their birth parents and adoptive families. Because adoptive children's postnatal environments are distinct from their prenatal environments and genetic risk, the unique and interactive contributions of genes, prenatal, and postnatal factors to child development can be clarified in adoption studies. EGDS has focused on the origins of child emotional and behavioral problems and competence. This proposal seeks to extend the scope of EGDS to include childhood obesity EGDS is comprised of two participant cohorts, for a total sample of 561 sets of adopted children, and their birth and adoptive parents. Cohort I includes 361 sets (birth dates between January 2003 - January 2006; R01-HD042608, PI Leve), and Cohort II includes 200 sets (birth dates between May 2007 and May 2009; R01- DA020585, PI Neiderhiser). EGDS has been funded to assess Cohort I children and adoptive families from child age 9 months through 8 years, and Cohort II children and adoptive families from child age 9 months to 6 years (R01-MH92118, PIs Leve, Neiderhiser). Birth parents from both Cohorts have also been assessed on an ongoing basis since 3 months post-partum. The specific aims of the proposed extension of EGDS are to: (1) Identify genetic, prenatal, and postnatal environmental predictors of weight trajectories from 2-9 years of age; and (2) Test postnatal environmental mediation and moderation models for children's weight trajectories. The proposed research will use growth and prenatal data collected during previous assessments, and gather new data related to children's growth, and behavioral, genetic and postnatal family risks for obesity when children are between 7 and 9 years of age. Analyses will combine data from both Cohorts. This research will enhance understanding of the contributions of genetic, prenatal and postnatal risks to weight trajectories, and of postnatal environments that are most likely to foster healthy weights in the presence of genetic or prenatal risk.

Project Number:	5R01DK093832-03	**Contact PI / Project Leader:**	GAWEDA, ADAM E
Title:	COMPUTATIONAL APPROACH TO PERSONALIZED ANEMIA MANAGEMENT	**Awardee Organization:**	UNIVERSITY OF LOUISVILLE

Abstract Text:

DESCRIPTION (provided by applicant): Effective anemia management in End-Stage Renal Disease (ESRD) is a complex task due to large variation in erythropoietic response among the ESRD patients. Evidence shows that excessive doses of Erythropoiesis Stimulating Agents (ESA), used in hypo-responsive patients, coincide with increased cardiovascular complications. In addition to health risks, reimbursement restrictions imposed by Medicare demand additional vigilance in ESA administration. Iron is one of the most important elements affecting the erythropoietic response. The ongoing blood losses associated with hemodialysis treatments, increased risk of gastrointestinal bleeding, and access complications, as well as poor iron absorption lead to iron depletion in ESRD patients. Standard anemia management protocols do not fully address the synergistic nature of interactions between erythropoietin and iron. Personalized strategies for coordinated ESA and iron dosing are therefore necessary to achieve the desired clinical outcome, reduce patient risk exposure, and improve the cost-effectiveness of treatment. Our long-term goal is the advancement of biomedical computing to personalize medicine and pharmacologic management of chronic conditions. The objective of this project is to address the challenge of multiple drug dosing personalization with a specific application to ESA and iron management in anemia of ESRD. The central hypothesis is that a computational approach can be developed to perform coordinated personalized dosing of erythropoiesis stimulating agents and iron in order to achieve desired clinical outcomes and minimize patient exposure resulting in optimal care. The rationale behind the proposed research is that computational models quantifying the interaction between iron and erythropoietin can be applied through the principles of control theory and machine learning, to derive personalized dosing strategies for both agents. The main objective will be accomplished through three specific aims: 1) quantification of the erythropoietin-iron interaction through clinically relevant computational models, 2) application of such models to derive algorithms for coordinated personalized ESA and iron dosing, 3) validation of these algorithms through an "in sillico" trial for a wide range o simulated subjects and clinical conditions. The expected outcome of this project is a new systematic approach to the management of ESRD anemia using multiple agents resulting in improved patient care and decreased cost which will be broadly applicable to other therapeutic areas.

Project Number:	5R01DK090311-04	**Contact PI / Project Leader:**	GOESSLING, WOLFRAM
Title:	ESTROGEN REGULATION OF HEPATIC GROWTH	**Awardee Organization:**	BRIGHAM AND WOMEN'S HOSPITAL

Abstract Text:

DESCRIPTION (provided by applicant): Liver disease is a common cause of morbidity and mortality in the United States; approximately 400,000 patients suffer from chronic liver disease, caused by a variety of etiologies, and the incidence is rising. More than 25,000 patients die each year from complications of liver dysfunction, 1700 alone while awaiting liver trans- plant. Perturbations of liver growth can cause hepatic neoplasia. In addition, as the primary metabolic organ, the liver is exposed to both environmental and endogenous toxins, necessitating ongoing repair and regeneration. Using the zebrafish (Danio rerio) model, we have successfully elucidated a highly specific regulatory role for Wnt signaling in both liver development and regeneration, conserved across vertebrate species, and established a model to discover novel therapeutics for toxic liver injury. We recently completed a chemical genetic screen to identify regulators of liver development in zebrafish; we have successfully used this approach previously to elucidate conserved modifiers of hematopoiesis, one of which is currently in a phase I clinical trial. Through this screening methodology, we have discovered that estrogen is an important modifier of liver specification and growth. Estrogen is a well-characterized transcriptional regulator, which is frequently associated with cancer progression and may correspond with response to therapy. Furthermore, xenoestrogens, both naturally occurring and manufactured compounds that mimic the action of estrogen in the cell, have been shown to modulate the development and function of reproductive organs, as well as contribute to both cancer formation and therapy. Our long-term goal is to understand the molecular and cellular mechanisms by which estrogenic compounds affect the liver. Our objective here is to characterize the functional implications of estrogen exposure on liver growth during development, in regeneration after injury, and in carcinogenesis. Our central hypothesis is that estrogen exerts time and cell-type specific effects on the liver through interaction with other signaling pathways, particularly Wnt signaling. This hypothesis has been derived from our own screening results and subsequent preliminary data as well as clinical observations and cancer studies. The rationale for our work is that a detailed understanding of the impact of estrogen on liver growth will enable recommendations regarding nutrition and exposure during pregnancy and in early childhood, and reveal potential new targets for liver cancer prevention and treatment. In Specific Aim 1, we seek to define the role, timing, and targets of estrogen signaling during endoderm specification and liver formation; these studies will make use of both chemical and genetic modification of estrogen levels and signaling over the course of development, and utilize an extensive array of phenotypic, histological and functional methodologies. In Specific Aim 2, we will investigate whether estrogenic activity has an impact on organ regeneration and cancer growth; we will use previously devised surgical and chemical models of liver injury and a zebrafish liver cancer model to examine the effect of estrogen modulation on the recovery or destruction of hepatic structure and function.

Project Number:	5R01DK092485-04	**Contact PI / Project Leader:**	GONG, RUJUN
Title:	THERAPEUTIC TARGETING OF GSK3BETA: A NOVEL APPROACH FOR PODOCYTE PROTECTION	**Awardee Organization:**	RHODE ISLAND HOSPITAL

Abstract Text:

DESCRIPTION (provided by applicant): Proteinuria is an invariable finding in patients with most types of chronic kidney disease and it is one of the few modifiable risk factors for long-term prognosis and progression to end stage renal failure. Regardless of the original etiology, the pathologic basis for glomerular proteinuria is podocyte dysfunction or injury. Evidence suggests that glycogen synthase kinase (GSK) 3, a multi-tasking kinase, plays an important role in mediating acute and chronic injuries in multiple solid organs including the kidney through regulating multiple pathogenic cellular events, such as mitochondria permeability transition (MPT), proinflammatory NFB activation, and cytoskeleton disorganization. Inhibition of GSK3 prevents kidney injury and represents a novel renoprotective strategy. The studies proposed here will decipher the putative role of GSK3 in podocyte dysfunction and test the novel hypothesis that blockade of GSK3 protects podocyte from injury, improves proteinuria and slow progression of glomerulosclerosis. Aim 1 will examine the role of GSK3 in adriamycin induced podocyte injury in cultured podocytes. GSK3 activity in podocytes will be specifically manipulated by RNA interference or ectopic expression of either inactive or non-inhibitable mutant GSK3. The regulatory effect of GSK3 on adriamycin induced podocyte injuries will be assessed, including MPT and the ensuing podocyte death, proinflammatory NFB activation and de novo expression of the costimulatory molecule B7-1, an NFB target gene, as well as podocyte shape changes and the underlying cytockeleton disorganization; Aim 2 will determine the effect of doxycycline inducible podocyte specific GSK3 knockout on adriamycin induced podocytopathy and proteinuria in adult mice. These studies are essential to conclusively elucidate the role of GSK3 in podocyte injury in vivo because selective GSK3 inhibitors may have nonspecific effects and podocyte specific blockade of GSK3 is impossible pharmacologically. Pathogenic mechanisms identified in Aim1 by which GSK3 promotes podocyte injury will be validated in vivo in the knockout mice. Aim 3 will test the preventive and rescue effects of TDZD-8, a novel non-ATP competitive small molecule inhibitor of GSK3 on adriamycin induced nephropathy. The efficacy of TDZD-8 will be compared with low dose lithium, a safe and effective FDA approved drug that possesses potent GSK3 inhibitory actions, already exists for decades and could be used for clinical trials years before kidney specific GSK3 blockade is possible. The effects of TDZD-8 or lithium on adriamycin induced podocyte injury and related mechanisms will be delineated. Collectively, these studies should allow rapid progress to clinical trials of existing drugs with GSK3 inhibitory activities to improve podocyte injury, induce proteinuria remission, and slow progression of glomerulosclerosis in man.

Project Number:	5R01DK099108-02	**Contact PI / Project Leader:**	GRANT, RICHARD W
Title:	PRE-VISIT PRIORITIZATION FOR COMPLEX PRIMARY CARE PATIENTS WITH DIABETES	**Awardee Organization:**	KAISER FOUNDATION RESEARCH INSTITUTE

Abstract Text:

DESCRIPTION (provided by applicant): Patients with type 2 diabetes are increasingly living with multiple concurrent conditions and complicated medical regimens. For these patients, diabetes management decisions and treatment goals must be addressed within the larger context of other competing health concerns. In parallel, clinical advances have led to a substantial increase in the number of tasks that primary care providers must perform during each visit. These twin trends of patient and visit complexity present a formidable challenge to effective diabetes primary care. Although there are a variety of non-visit strategies that can and are being instituted to address these issues, the primary care visit remains a vital opportunity for catalyzing changes in diabetes care. To achieve this change, efficient and scalable tools to support more productive primary care encounters are needed. We hypothesize that among patients with type 2 diabetes and elevated HbA1c, a systematic approach that enables patients to explicitly prioritize their top diabetes and non-diabetes related health concerns before the primary care visit will result in more effective diabetes care over time. To test this hypothesis, our proposal's aims are to:1) Design and implement a web-based tool linked to the electronic medical record that will enable complex patients to indicate, and PCPs to review, patients' top health priorities for their upcoming visit; 2) Conduct a randomized clinical trial among patients with type 2 diabetes and elevated HbA1c testing the impact on intermediate care outcomes (medication adherence, medication intensification) compared to usual care and HbA1c (primary clinical outcome), blood pressure, and lipid control (secondary clinical outcomes) compared to usual care; 3) Among a sub-set of intervention participants (patients and PCPs), use mixed qualitative and quantitative methods to examine the impact of pre-visit prioritization on the content of subsequent visit discussions and examine the influence of patient and PCP factors on these discussions. The key conceptual innovation of this study is to test a replicable, low-cost approach to improving diabetes primary care that explicitly integrates non-diabetes problems into the process of diabetes management. We will implement an easy-to-use web-based tool linked to our EPIC(R)-based electronic medical record. This patient-centered care model has the potential to significantly improve the design of primary care systems responsible for providing patient-centered care and offers an innovative approach to improving the care of increasingly complex patients with type 2 diabetes. This study addresses the three NIH priorities of translating evidence into practice, improving medication adherence, and understanding health care disparities. If successful, we will work to actively disseminate the tool throughout our system and to other U.S. care organizations.

Project Number:	5R01DK094004-02	**Contact PI / Project Leader:**	GUERTIN, DAVID A
Title:	MECHANISTIC TARGET OF RAPAMYCIN PATHWAYS IN METABOLISM AND ENERGY EXPENDITURE	**Awardee Organization:**	UNIV OF MASSACHUSETTS MED SCH WORCESTER

Abstract Text:

DESCRIPTION (provided by applicant): The long-term goal of this proposal is to elucidate the mechanisms that regulate cellular energy balance. Here, we are focusing on energy regulation in adipose tissue with a weighted focus on brown fat. Interest in brown fat bioenergetics is rapidly gaining momentum because of the recent realization that adult humans possess a significant quantity of brown fat or brown fat-like cells that may exhibit metabolically favorable "fat burning" properties. It is speculated that therapeutically increasing brown fat energy expenditure could defend against obesity. Importantly however, very little is known about the molecular signals that control energy expenditure in adipose tissue, or brown fat differentiation and function. The objective of this proposal is to test the hypothesis that the mechanistic target of rapamycin complex 2 (mTORC2) is a critical regulator of metabolism and energy expenditure in brown fat. To test this, we are taking a multidisciplinary approach utilizing genetically engineered mice, primary cell lines, and pharmacological agents to study the mechanisms by which mTORC2 and its substrates regulate energy balance in adipose tissue. Our work is yielding very interesting and unexpected preliminary findings that suggest inhibiting mTORC2 reprograms cellular metabolism and may increase brown fat activity. In Specific Aim 1, we elucidate the mechanism by which mTORC2 reprograms metabolism. In Specific Aim 2, we test the in vivo relevance of our hypothesis and our preliminary findings using novel mouse models. In Specific Aim 3, we ask if pharmacologically inhibiting mTORC2 can treat pathological fat accumulation. Elucidating the metabolic regulatory circuits under mTORC2 control in brown fat will have important implications in advancing therapies targeting cellular bioenergetics.

Project Number:	5R01DK095118-03	**Contact PI / Project Leader:**	GUO, SHAODONG
Title:	TRANSCRIPTIONAL REGULATION OF METABOLIC AND HEPATIC HOMEOSTASIS BY FOXO SIGNALING	**Awardee Organization:**	TEXAS A&M UNIVERSITY HEALTH SCIENCE CTR

Abstract Text:

DESCRIPTION (provided by applicant): This proposal "Transcriptional Regulation of Metabolic and Hepatic Homeostasis by FoxO Signaling" addresses the fundamental mechanism of diabetes by studying fuel hormone's action in the liver. Elevated blood glucagon levels and defective insulin action in patients with type 2 diabetes are responsible for hyperglycemia, but the molecular mechanisms remain elusive. Glucagon and insulin reciprocally control metabolic and cellular homeostasis, in which the liver is a major organ that executes their cellular functions. In the fasting liver, glucagon stimulates gluconeogenesis, degrades macromolecules including glycogen, lipid, and protein, and promotes the autophagic pathway that regulates cellular organelle turnover. In the feeding liver, insulin reverses the catabolic metabolism of glucagon. The metabolic and cellular adaptation from fasting to feeding requires a tight control of gene transcription by opposing effects of the two hormones, and the failure of the adaptation causes hyperglycemia in diabetes. The forkhead transcription factor Foxo1 that regulates multiple biological processes is inhibited by insulin signaling. Insulin phosphorylates Foxo1 at Ser253 in mice or S256 in humans via PKB activation, and triggers Foxo1 nuclear export and cytoplasmic sequestration for ubiquitination. Conversely, glucagon promotes Foxo1 protein stability in the fasting liver or the liver of diabetes when insulin level is decreased or insulin resistance occurs. Foxo1 can mediate the effect of cyclic AMP, the second messenger of glucagon, on expression of gluconeogenic enzymes and autophagic genes, but the role of Foxo1 and its regulation by glucagon, particularly in concert with insulin resistance, in metabolic regulation and cellular function is completely unclear. In Aim 1, we will use Foxo1 liver-specific knockout mice and examine whether Foxo1 is a key mediator in glucagon signaling to regulate hepatic glucose production, glycogenolysis, lipid and protein homeostasis, mitochondrial turnover and function, autophagy and survival, whereas disruption of Foxo1 prevents the glucagon-induced biological processes that promote the development of diabetes. In Aim2, we will use mass-spectrometry and phospho-specific antibodies to determine whether Foxo1 phosphorylation at S153 by glucagon and protein kinase PKA promotes nuclear targeting and whether phosphorylation at S276 enhances transcriptional activity in cells. In Aim 3, we have generated Foxo1- S253A mutant mice mimicking insulin resistance at the Foxo1 level in vivo. Using this unique mouse model, we will determine whether glucagon stimulates the effect of dephosphorylated Foxo1, disrupting metabolic and cellular homeostasis and liver function. In overall, we use Foxo1 gene loss- and gain-of-function approaches to investigate the physiological role of Foxo1 in glucagon action and identify novel molecular mechanisms of Foxo1 activation, which will advance our understanding of the mechanism of diabetes and help develop strategies detecting and inhibiting the glucagon->Foxo1 pathway to control the disease.

Project Number:	5R01DK092421-04	**Contact PI / Project Leader:**	HABTEZION, AIDA
Title:	ROLE OF HEMEOXYGENASE-1 IN EXPERIMENTAL ACUTE PANCREATITIS	**Awardee Organization:**	STANFORD UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Acute pancreatitis (AP) remains a challenging clinical problem, particularly in patients with severe disease. Despite its disease burden, therapy remains supportive at best coupled with removal of precipitating factors that may include alcohol or biliary obstructing calculi. Previously we showed a protective effect of hemin (hemoglobin prosthetic moiety that upregulates hemeoxygenase-1, HO-1) in experimental AP via recruitment of HO-1+ F4/80+ cells to the pancreas. More recently, we showed that Panhematin (PH, an FDA-approved water soluble formulation of hemin) induces rapid HO-1+ cell recruitment and treats ongoing experimental AP. Given these results, we propose to test the hypothesis that HO-1 downstream effectors and hemin primed cell- based transfers offer alternative therapeutic means for treating AP. Furthermore, we propose to define the source, characteristics, and mechanisms for monocyte recruitment and acinar cell protection. The specific aims of our proposal are: Aim 1: Determine the therapeutic role of HO-1 downstream effectors and evaluate the role for cell-based therapy in experimental acute pancreatitis. We propose to define the therapeutic role of HO-1 downstream effectors and PH-primed cells in treating AP. Aim 2: Characterize HO-1+ monocytes/macrophages recruitment to the inflamed pancreas following hemin treatment. We propose to characterize the monocytes recruited to the pancreas following PH treatment and assess their polarization into macrophages using phenotypic and functional assays. Aim 3: Define the mechanism of HO-1+ monocyte protection against pancreatic acinar cell injury. We propose here to determine mechanisms via which HO-1+ monocytes interact and protect against acinar cell injury. Aim 4: Characterize molecular and cellular determinants via which HO-1+ monocytes are recruited to the inflamed pancreas. In this aim, we propose to define trafficking molecule expression and then assess their functional role using blocking antibodies and/or mice genetically deficient in specified trafficking receptors. Evaluation of PH/HO-1 downstream effectors and interaction of PH-primed monocytes with acinar cells should help define PH's mechanism of action and offer alternate means of treating AP. Relative to lymphocyte trafficking, monocyte recruitment to various inflammatory sites is not as well-defined, and even less so to the pancreas. Findings from this project could lead to a better understanding of disease pathogenesis and mechanisms for immune cell recruitment to the inflamed pancreas.

Project Number:	5R01DK090769-04	**Contact PI / Project Leader:**	HAMMES, MARY SUSAN
Title:	A CLINICAL AND COMPUTATIONAL STUDY TO IMPROVE BRACHIOCEPHALIC FISTULA OUTCOMES	**Awardee Organization:**	UNIVERSITY OF CHICAGO

Abstract Text:

DESCRIPTION (provided by applicant): Significance: The care and outcome of the patient with end stage renal disease (ESRD) on chronic hemodialy- sis is directly dependent on their hemodialysis access. Regional and national indicators promote the placement of arteriovenous fistulae (AVF). However, there are numerous complications of AVF, with cephalic arch stenosis (CAS) one of the leading causes of access failure in patients with a brachiocephalic fistula (BCF). Objectives: The long-term goal is to develop methods and procedures that will improve dialysis access by improving the patency of BCF and reducing the number of post-fistula procedures required to maintain such access. The immediate goal is to determine the factors that lead to the development of CAS in ESRD patients with BCF. A better understanding of these factors will 1) guide alternative designs for BCF that minimize risk of CAS, 2) guide clinical management to minimize the risk of hemodynamic parameters causing CAS, 3) establish a surveillance protocol to detect early signs of CAS or changes in hemodynamic parameters that would foster CAS, and 4) identify patients for whom BCF would not be ideal. Methods: Using a combined clinical and computational investigation, a means of predicting the risk of CAS in patients with planned fistula access is sought. Patients with ESRD requiring BCF access will be enrolled by written consent with baseline and then protocol venograms and Dopplers done at approximately 12 month intervals up to 36 months. Hemodynamic parameters (HDP) will be obtained using computational fluid dynam- ics (CFD) to determine which correlate with the development of CAS. The feasibility of this approach has been demonstrated in carrying out the preliminary studies. The results of the study will be interpreted by comparing wall shear stress (WSS), and other HDP, and geometry between those that do, and do not, develop CAS using life table and regression analysis. Other co-variates that will be analyzed include diabetes, age, sex, type and characteristics of anastomosis. The specific aims are: Aim 1: Observe a cohort of BCF subjects over time with protocol venograms and Dopplers and calculate WSS, along with other HDP, using CFD in order to perform a life table analysis to estimate the effect of WSS on time to CAS. Because diabetes may affect this outcome, diabetic and non-diabetic patients will be studied. The large-scale prospective study will be augmented by a small-scale sub study involving a subset of the larger cohort. These patients will be subject to more detailed imaging and CFD in order to elucidate the mechanisms leading to IH and venous remodeling in the cephalic arch. The prospective design of the trial with arteriovenous fistulae (AVF) placement will allow cephalic vein tissue samples to be saved for pathologic review of histology and assay for cytokines and growth factors in a subsequent study. Aim 2: In the same subjects as Aim 1, measure venous radius and cephalic arch angle over time and derive predictive functions of time, inlet pressure, anastomosis type, and initial arch angle.

Project Number:	5R01DK095879-03	**Contact PI / Project Leader:**	HERING-SMITH, KATHLEEN S
Title:	A NEW TARGET FOR KIDNEY STONE PREVENTION: CALCIUM-SENSITIVE TRANSPORT OF CITRATE	**Awardee Organization:**	TULANE UNIVERSITY OF LOUISIANA

Abstract Text:

DESCRIPTION (provided by applicant): Kidney stones are a common & serious illness. Urinary citrate is the most important inhibitor of calcium stones by keeping calcium soluble. The regulation of citrate transport in the kidney has received inadequate investigation & remains poorly understood. A single transporter NaDC1 has been assumed to be responsible for intestinal & renal citrate reabsorption. However we have recently identified a novel calcium-sensitive citrate transport process. The overall objective of this application is to determine the mechanisms & regulation of kidney proximal tubule apical citrate transport via a novel apical calcium-sensitive transporter, & the relative roles of NaDC1 & NaDC3. Our central hypothesis is that the novel citrate reabsorptive process functions to limit citrate transport in the proximal tubule when calcium is increased. Elucidation of previously unidentified citrate transporters can potentially lead to new treatments to increase urinary citrate. Aims are: 1) Define the novel calcium-sensitive citrate transporter & its role in the proximal tubule. Our working hypothesis, based on data in three proximal tubule cell lines, is that in addition to NaDC1, a novel calcium- sensitive dicarboxylate transporter is present on the apical side of the proximal tubule. We will use knockdown of NaDC1 in these cell lines to demonstrate this. Also we will determine citrate transport rates & the extracellular calcium-sensitivity for the remaining citrate transport process found in proximal tubule cells grown from dissected proximal tubule segments from knockout mice. 2) Determine the role of NaDC3 in proximal tubule reabsorption of citrate. Based on our surprising preliminary data, we will determine if NaDC3 is expressed on the apical membrane & accounts for calcium- sensitive citrate reabsorption. We will determine the localization of NaDC3 in the proximal tubule & determine the calcium sensitivity on the apical surface. We will also determine the role of basolateral NaDC3. 3) Determine the role of NaDC1 in renal reabsorption & intestinal absorption of citrate. Our working hypothesis is that NaDC1 is not the exclusive mechanism of citrate transport in the kidney & intestine. Other apical mechanisms may both be important in conditions such as acidosis & hypercalciuria. We will use NaDC1 knockout mice & compare renal citrate reabsorption in the -/- to +/+ mice both under baseline & conditions of acidosis & hypercalciuria. We will also determine intestinal citrate absorption in NaDC1 knockout mice. These studies will establish new paradigms in understanding citrate reabsorption in both the kidney proximal tubule & the intestine, & how these paradigms are impacted in acidosis & hypercalciuria. These outcomes are expected to have an important impact since understanding the regulation of citrate transport in the proximal tubule will dramatically improve strategies in the prevention of calcium stones.

Project Number:	5R01DK095413-02	**Contact PI / Project Leader:**	HOUSEKNECHT, KAREN L.
Title:	PHARMACOLOGY OF RISPERIDONE EFFECTS ON BONE REMODELING AND ENERGY METABOLISM	**Awardee Organization:**	UNIVERSITY OF NEW ENGLAND

Abstract Text:

DESCRIPTION (provided by applicant): Second generation anti-psychotics (SGAs) are widely prescribed to treat psychiatric disorders in adults and children and are among the 10 top selling medications world-wide. The pharmacology of SGAs is complex: they potently antagonize multiple G protein coupled receptors (GPCRs) including dopamine, serotonin, alpha- adrenergic and histamine receptors. Side effects of SGAs include increased incidence of obesity and type 2 diabetes among both acute and chronic users. Recent evidence indicates that SGAs are also associated with increased fracture risk and reduced bone mineral density; however the underlying molecular and pharmacological mechanisms leading to these severe endocrine side effects are unknown. Children and adolescents are the most susceptible to metabolic side effects, and in this proposal we hypothesize, that the skeleton is also vulnerable during the time of peak bone accrual. Thus the over-arching goal of this proposal is to elucidate the cellular/pharmacological mechanisms underlying SGA-induced bone loss, using the most widely prescribed, SGA, risperidone (RIS). Our novel central hypothesis is that RIS therapy is associated with significant bone loss, and this adverse side effect occurs via multiple mechanisms: 1) by directly interacting with bone cells and uncoupling bone remodeling; [2) via hyper-prolactinemia induced hypogonadism] and 3) by modulating the sympathetic nervous system output to bone. The goals of this project are to 1) determine whether SGAs have direct effects on osteoclast and osteoblast biology; 2) to examine the effect of RIS treatment in vivo on the skeletal-energy metabolism network, 3) determine if effects are mediated, at least in part by the sympathetic nervous system (SNS) and/or hypogonadism; and 4) to determine if detrimental effects of RIS on bone can be ameliorated with mechanism-directed co-therapy. To achieve these goals we will employ a pharmacologic approach to explore the functional consequence of specific receptor binding effects of RIS, and prolactin-sparing SGAs olanzapine and clozapine, using osteoblast and osteoclast culture in vitro, and in vivo by using established mouse models of RIS-induced bone loss. We will also explore whether β-blocker or bisphosphonate co-therapy can alter adverse effects of RIS on bone and energy metabolism. Finally, an important part of our strategy involves continuous monitoring of drug exposure (RIS and its active metabolite, 9-OH RIS) in plasma and bone marrow in order to gain understanding of the pharmacokinetic/pharmacodynamic relationships associated with adverse endocrine side effects of RIS therapy. These studies are both innovative and collaborative, capitalizing on the complementary strengths (pharmacology, drug metabolism, endocrinology, bone biology, diabetes, and neuroscience) of our interdisciplinary research team. Results of these novel mechanistic pharmacology studies may help inform public health policy concerning SGA prescribing and patient monitoring practices and may help inform strategies for prescribing co-therapies in order to minimize side effects in vulnerable patient populations.

Project Number:	5R01DK096239-03	**Contact PI / Project Leader:**	HUANGFU, DANWEI
Title:	UNDERSTANDING PANCREATIC PROGENITORS FOR DIABETES CELL-REPLACEMENT THERAPY	**Awardee Organization:**	SLOAN-KETTERING INST CAN RESEARCH

Abstract Text:

DESCRIPTION (provided by applicant): Diabetes mellitus is an escalating global health problem. Both Type 1 and Type 2 diabetes lead to the gradual loss of insulin-producing beta cells. Our long-term goal is to develop beta cell replacement strategies to overcome the insulin deficiency in diabetic patients. To achieve this goal, we have developed novel, safer approaches to convert patient fibroblasts to induced pluripotent stem cells (iPSCs) using chemicals together with genetic factors. These iPSCs can be differentiated into multipotent pancreatic progenitors, the precursors to beta cells, using protocols developed for human embryonic stem cells (hESCs). However, our understanding of the basic biology of pancreatic progenitor cells is still rudimentary, which presents hurdles in the development of effective strategies to expand and further differentiate these progenitor cells for therapy. Evidence emerged from our own studies and from those of other laboratories suggests that pancreatic progenitor cells are heterogeneous, and likely consist of subpopulations with different physiological functions. Yet, molecular and functional distinctions between these subpopulations are poorly understood. It is unclear which subpopulation(s) in the developing pancreas is(are) capable of generating functional beta cells, and to which extent a specific subpopulation is capable of self-renewal. Even less is known about the physiological functions and self-renewal properties of pancreatic progenitor cells differentiated from hESCs. We aim to address these critical questions in this proposal. We hypothesize that the pancreatic progenitor cell compartment in vivo contains heterogeneous subpopulations: (i) a common multipotent pancreatic progenitor responsible for generating all three pancreatic lineages; and (ii) distinct lineage-specific progenitors responsible for generating one or two specific pancreatic lineages. Based on this hypothesis, the overall objective of this proposal is to define pancreatic progenitor subpopulations in terms of their molecular characteristics and physiological functions, as well as to identify mechanisms for self-renewal. We anticipate that our study will yield the following outcomes. Aim 1 will reveal the presence of distinct pancreatic progenitor subpopulations both during embryo development and in hESC differentiation culture. This will identify the progenitor subpopulation(s) capable of generating functional β cells. Aim 2 will identify cell surface markers for enrichment of the appropriate progenitor subpopulation(s) for further differentiation into β cells, and set the stage for studies on expansion of progenitor cells. Aim 3 will elucidate the mechanism of self-renewal of distinct progenitor subpopulations, which are critical for the development of novel, effective strategies to expand pancreatic progenitors for beta cell replacement therapy. Additionally, the ability to generate a large quantity of human pancreatic progenitor cells will provide a new way to study the biology of these cells to complement mouse genetics approaches. Broadly, the proposed research will lead to novel findings to fill in critical gaps in our current knowledge of human pancreatic development.

Project Number:	5R01DK091240-04	**Contact PI / Project Leader:**	HUSS, WENDY JOY
Title:	DIFFERENTIATION SIGNALING IN PROSTATE STEM CELLS	**Awardee Organization:**	ROSWELL PARK CANCER INSTITUTE CORP

Abstract Text:

DESCRIPTION: Prostate stem cells maintain self-renewal and inhibit differentiation to remain in the stem cell state. In the prostate the mechanisms required to maintain stem cell properties can be therapeutically targeted to eliminate the stem cell compartment to reduce the number of new cells. Our long-term goal is to understand how an unregulated stem cell compartment contributes to prostatic diseases and determine if they can be a therapeutically targeted. The ABC transporters protect stem cells from xenobiotics. Prostate and hematopoietic stem cells can be enriched based on the high efflux capacity of Hoechst dye, defined as the side population. The ABC transporter ABCG2, is required for the side population phenotype. While it has long been appreciated that the side population is enriched for stem cells, and ABCG2 is required for the side population, it is unknown if ABCG2 function maintaining the stem cell state. Our data suggests ABCG2 effluxes androgen. The overall objective of this proposal is to determine whether the inhibition of ABCG2 can force accumulation of androgen resulting in stem cell differentiation. The central hypothesis is that ABCG2 efflux of androgen inhibits prostate stem cell differentiation to maintain stem cell properties. The rationale for the proposed research is to determine whether forcing prostate stem cells to differentiate is a therapeutic option for prostatic diseases that are caused by an unregulated stem cell niche including benign prostatic hyperplasia (BPH). The hypothesis is tested in three specific aims: 1. Determine the mechanism of androgen efflux to maintain stem cell properties. 2. Identify regulators of the side population phenotype that contribute to maintaining prostate stem cell properties. 3. Determine the effect of abrogated ABCG2 function on the prostate stem cell niche. The proposed studies are anticipated to demonstrate that: ABCG2 mediated androgen efflux inhibits AR induced prostate stem cell differentiation; Prostate stem cells within the side population require ABCG2 expression; and ABCG2 inhibition depletes stem cell compartment and the prostate is unable to serially regenerate. This contribution is significant because the proposed studies seek to determine whether prostate stem cells can be eliminated by inhibition of ABCG2 function. The research described in this proposal is innovative because we are functionally targeting the biology of the stem cell without the necessity of identifying prostate stem cell markers. Thus, this proposal exploits the biology of the phenotype of the prostate stem cell.

Project Number:	5R01DK098378-02	**Contact PI / Project Leader:**	IVANOV, IVAYLO IVANOV
Title:	MECHANISMS OF MUCOSAL TH17 CELL INDUCTION BY SEGMENTED FILAMENTOUS BACTERIA	**Awardee Organization:**	COLUMBIA UNIVERSITY HEALTH SCIENCES

Abstract Text:

DESCRIPTION (provided by applicant): In this proposal we will investigate the mechanisms by which an individual commensal bacterial species induces generation of a specific effector CD4 T cell subset in the intestinal lamina propria. Commensal bacteria represent a diverse microbial community that permanently resides in the intestines of all mammals. As a community, commensals are known to affect multiple aspects of host immunity. Perturbations in the composition of this community are important determinants of disease pathogenesis in many autoimmune conditions, e.g. inflammatory bowel diseases (IBD), diabetes, arthritis. However, how individual microbiota members modulate host immunity in order to provide protection or exacerbate disease is unclear, which has impeded identification of participating molecular mechanisms. We identified a commensal, segmented filamentous bacteria (SFB), that can specifically induce Th17 cells in the gut. Th17 cells are pro-inflammatory cells that play important protective roles against bacterial and fungal pathogens while at the same time contribute to autoimmunity, including IBD and colitis, in susceptible hosts. We showed that presence of SFB in mice specifically induces Th17 cells and leads to increase in mucosal protection against intestinal infections and exacerbation of autoimmunity. Presently, SFB are the only known commensal that induces Th17 cells. We propose to identify host cells responsible for detecting SFB and presenting antigens in order to induce Th17 cells. We will examine the role of intestinal dendritic cells (iDCs), which have been implicated in gut Th17 cell induction. We have discovered that genetic ablation of one iDC subset, the CD103+CD11b+ DCs, leads to a decrease in Th17 cells. We will examine whether CD103+CD11b+ DCs are required for SFB-mediated effects in the gut. We will also examine if SFB antigens are directly sampled to induce SFB-specific Th17 cells. We will utilize a collection of genetic models that we have re- derived SFB-free and Th17 cell-free. This will allow us to colonize these models with SFB and assess the role of the corresponding mechanisms specifically in SFB-mediated Th17 cell induction. Understanding the mechanisms by which commensals modulate T cell homeostasis, and in particular Th17 cell induction will allow for the development of therapies to mimic or antagonize such mechanisms for the directional regulation of inflammatory T cell responses for the boost of mucosal protection in the case of intestinal infections or the decrease in inflammation in the case of IBD.

Project Number:	5R01DK091845-02	**Contact PI / Project Leader:**	JEREMIC, ALEKSANDAR MILORAD
Title:	MOLECULAR MECHANISIMS OF AMYLIN TRAFFICKING AND TOXICITY IN HUMAN PANCREATIC ISLE	**Awardee Organization:**	GEORGE WASHINGTON UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Human amylin, a pancreatic peptide hormone, is the principal constituent of amyloid deposits in the pancreas, a hallmark of type-2 Diabetes Mellitus (T2DM). Aggregation of human amylin into small soluble oligomers and β-sheet-enriched fibrils is linked to dysfunctions of beta (β)- and other islet cells and pathogenesis of T2DM. Although much progress has been made in understanding the actions of amylin oligomers and aggregates, the cellular events and factors that contribute to amylin oligomerization, aggregation and toxicity in the pancreas remain largely unknown. The overarching goal of this proposal is to elucidate factors regulating amylin oligomerization and aggregation in the pancreatic human islet cells, and to determine the underlying mechanisms of amylin-mediated islet cell death. Our published and preliminary results suggest that plasma membrane (PM) cholesterol and endocytosis play a key role in amylin turnover and toxicity in the human islet cells. In the proposed studies, we will test the hypothesis that the amylin receptor (AM-R), clathrin and v- SNARE/Rab endocytotic proteins mediate amylin uptake and degradation in lysosomes, the impairment of which stimulates amylin oligomerization and aggregation, oxidative stress and consequently apoptosis of human islet cells. To test this idea, amylin trafficking, degradation and toxicity pathways in cultured human islet cells will be explored by combinations of atomic force microscopy (AFM), confocal microscopy, spectroscopy and biochemical approaches. The objectives of the proposal are to: (1) elucidate amylin trafficking and degradation pathways in human islet cells, and determine the extent to which they contribute to formation and accumulation of toxic amylin oligomers and aggregates, (2) determine the causal relationship between amylin turnover and toxicity in human islet cells, and (3) determine the mechanisms by which amylin oligomers and/or aggregates stimulate oxidative stress in human islet cells and thereby activate redox-sensitive stress kinases, apoptosis signal-regulating kinase 1 (ASK-1) and c-Jun N-terminal kinase (JNK). These studies should provide a better understanding of the molecular and biochemical events leading to formation of amyloid aggregates and soluble toxic amylin oligomers, knowledge which is critical for the development of novel therapeutics for the treatment of T2DM.

Project Number:	5R01DK097441-03	**Contact PI / Project Leader:**	KAJIMURA, SHINGO
Title:	MOLECULAR CONTROL OF BROWN ADIPOSE CELL FATE AND ENERGY METABOLISM	**Awardee Organization:**	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Abstract Text:

DESCRIPTION (provided by applicant): Obesity develops when energy intake chronically exceeds total energy expenditure. Currently, most anti- obesity medications act to repress energy intake, either by suppressing appetite or by inhibiting intestinal fat absorption. However, due to side effects including depression, oily bowel movements and steatorrhea, there is an urgent need for alternative approaches. Because brown adipose tissue (BAT) dissipates energy to produce heat as a defense against cold and obesity, altering the molecular pathway to increase the amount or thermogenic activity of BAT may lead to an alternative and effective therapeutic intervention to counteract human obesity and metabolic disorders. Our long-term goals are to understand the molecular circuits that regulate the fate specification of brown adipose cells and to investigate their physiological roles in energy homeostasis. We have previously shown that brown adipocytes arise from a subset of dermomytomal precursors through the action of a transcription factor, PRDM16; however, it remains unclear how the PRDM16 action in the myoblast-to-brown fat switch is regulated. We identified a lysine methyltransferase, EHMT1 as a critical component of the PRDM16 transcriptional complex. EHMT1 is expressed at its highest in BAT and is highly induced by PRDM16. Notably, EHMT1 appears to act as a developmental switch of brown adipocytes versus myocytes. Importantly, loss of the EHMT1 gene is associated with obesity in mice and in humans; however, its underlying mechanism remains completely unknown. Our current objective is thus to investigate the physiological function and mechanism of EHMT1 that controls brown adipose cell fate in vivo. Based on our preliminary data, we will test the hypothesis that EHMT1 plays a pivotal role in energy homeostasis as a developmental switch that controls brown adipose cell fate through modulating the function of the PRDM16 complex. To test this hypothesis, we will pursue the following specific aims: In Aim1, we will determine the genetic requirement of EHMT1 in the fate specification and maintenance of brown adipose cells in vitro and in vivo. In Aim2, we will analyze the metabolic phenotypes of adipose-specific EHMT1 knockout mice and EHMT1 heterozygous null mice and critically characterize EHMT1's physiological role in controlling energy expenditure and glucose homeostasis in vivo. In Aim3, we will conduct biochemical analyses and use cultured cells to elucidate the mechanism by which EHMT1 acts as a developmental switch of brown fat lineage. The expected outcome of these studies is to characterize a completely novel upstream regulatory pathway of brown adipose cell fate specification. Our findings will have a significant impact, because, to our knowledge, this study will characterize the first enzyme that controls the cell fate switch between brown adipose versus skeletal muscle. The identified mechanism will allow us to manipulate this developmental pathway by pharmacological approaches, which may provide a possible therapeutic target.

Project Number:	5R01DK094062-03	**Contact PI / Project Leader:**	KATSANOS, CHRISTOS S.
Title:	REGULATION OF MUSCLE ATP SYNTHASE BETA SUBUNIT METABOLISM IN OBESITY	**Awardee Organization:**	ARIZONA STATE UNIVERSITY-TEMPE CAMPUS

Abstract Text:

DESCRIPTION (provided by applicant): Obesity is associated with reduced adenosine triphosphate (ATP) turnover in skeletal muscle. This condition results in unfavorable outcomes, proposed to range from decreased capacity for physical activity, to impaired activation of physiological mechanisms associated with cell function, to increased oxidative stress and the development of insulin resistance. The abundance of the beta subunit of the ATP synthase (β-F1-ATPase) in muscle mitochondria is decreased in obese, insulin-resistant individuals. β-F1- ATPase makes up the catalytic site of the ATP synthase, and it is a rate-limiting component of ATP synthesis. We propose that muscle β-F1-ATPase synthesis is reduced in obesity. Because measurement of stable isotopic enrichment of individual proteins is not practical using traditional gas chromatography-mass spectrometry approaches for proteins that are found in small amounts in skeletal muscle, we have developed an approach to quantify the isotopic enrichment of in vivo labeled muscle β-F1-ATPase using HPLC-ESI-MS/MS. It is based on the quantification of the isotopic enrichment of a unique peptide of muscle β-F1-ATPase. Using this approach we will test the hypothesis that the rate of muscle β-F1-ATPase synthesis is reduced in obese individuals. We also intend to investigate the effects of increased plasma amino acid concentrations as well as exercise on stimulating the synthesis rate of β-F1-ATPase in skeletal muscle of both obese and non-obese individuals. Muscle β-F1-ATPase synthesis, which is the main end-point of this proposal, will be determined using an intravenous constant infusion of d9-leucine in obese and non-obese subjects, and by measuring the d9-leucine enrichment of a β-F1-ATPase peptide. The following conditions will be tested: saline infusion (control), amino acid infusion, aerobic exercise, and a combination of aerobic exercise with amino acid infusion. These studies will for the first time determinate the rate of synthesis of muscle β-F1-ATPase in humans in vivo, and how it is altered by interventions known to promote muscle protein anabolism. Overall, the results of these studies will lead to better understanding of the mechanisms regulating the abundance of β-F1-ATPase in skeletal muscle in both obese and non-obese individuals. Further, they will provide scientific knowledge to base lifestyle interventions to improve muscle ATP turnover in obese individuals.

Project Number:	5R01DK097830-03	**Contact PI / Project Leader:**	KELLY, ANDREA BRIDGET
Title:	EVALUATION OF THE ENTERO-INSULAR (INCRETIN) AXIS IN CYSTIC FIBROSIS	**Awardee Organization:**	CHILDREN'S HOSP OF PHILADELPHIA

Abstract Text:

DESCRIPTION (provided by applicant): CFRD is associated with worse nutritional status, greater pulmonary function decline, and increased mortality. CFRD arises primarily from compromised insulin secretion--traditionally considered a by- product of pancreatic exocrine tissue damage and fibrosis. Recent developments in the field of type 2 diabetes (T2D) are propelling a re-examination of this basic explanation. For example, islet cell amyloid, a feature of T2D and a marker of endoplasmic reticulum stress, is found in pancreatic islets in CF. Genome-wide association studies have associated genetic variants in TCF7L2, a transcription factor implicated in enteroendocrine function, with increased susceptibility to T2D and CFRD. Decreased secretion of GLP-1 and decreased responsiveness of insulin secretion to GIP, both incretins, have been identified in T2D, but have received minimal attention in CFRD. Moreover, the mechanisms underlying CFRD development have been minimally explored. We hypothesize that 1) acute incretin exposure and chronic incretin-based therapy will improve β-cell sensitivity to glucose in patients with early glucose abnormalities and in patients with CFRD, 2) incretin-based therapy with sitagliptin (a T2D therapy that inhibits breakdown of incretins) will improve insulin secretion and glucose excursion during a mixed meal, and 3) insulin secretory capacity, β-cell sensitivity to glucose, and incretin secretion are decreased in non-diabetic CF subjects homozygous for the T2D-risk conferring TCF7L2 allele vs the wildtype TCF7L2 allele. We propose cross sectional and 6-month intervention studies to test these hypotheses. Forty-five CF adolescents and adults with Indeterminate glucose tolerance, impaired glucose tolerance, and CFRD will undergo Glucose Potentiated Arginine Tests (GPA, which measures β-cell secretory capacity and sensitivity to glucose); these will be performed in the presence and absence of acute incretin (GIP or GLP-1) exposure. The impact of six months of incretin-based therapy (sitagliptin) upon glucose excursion and incretin and insulin secretion during the Mixed Meal Tolerance Test, and β-cell secretory capacity and sensitivity to glucose during the GPA will be tested. Similar studies will be completed in thirty non-diabetic children and adults homozygous for the T2D-risk conferring TCF7L2 allele vs the wildtype TCF7L2 allele. We anticipate that in CF disturbed incretin secretion contributes to impaired insulin secretion, that incretin-based therapy can improve insulin secretion, and that the T2D-conferring genotype is associated with aberrant incretin regulated insulin secretion. Such sophisticated phenotyping of insulin and incretin secretion has not previously been undertaken. The knowledge gained will better define the mechanisms responsible for insulin secretion defects in CF, identify potential interventions to interrupt progressive insulin deficiency, and may uncover early insulin secretion disturbances that will predict not only progression to CFRD but concurrent risk of worsening pulmonary status.

Project Number:	5R01DK091658-03	**Contact PI / Project Leader:**	KESELOWSKY, BENJAMIN GEORGE
Title:	DENDRITIC CELL-TARGETING MICROPARTICLES FOR SUBCELLULARLY-TARGETED DELIVERY OF IN SULIN PEPTIDE, VITAMIN D3, TGFb1 AND GM-CSF FOR TYPE-1 DIABETES	**Awardee Organization:**	UNIVERSITY OF FLORIDA

Abstract Text:

DESCRIPTION (provided by applicant): Type 1 diabetes (T1D) develops as a result of insufficient insulin being produced due to a self-destructive immune response against insulin producing beta cells. Although a number of factors are known to promote advantageous immune cell responses in experimental systems for T1D, systemic intravenous delivery of these agents often results in significant harmful off-target effects due to the uncontrolled dosing of bystander cells, tissues and organs. This project focuses on the targeted in vivo delivery of pro-tolerance factors and insulin antigen, in particulate form, targeted to a key immune cell type, dendritic cells (DCs). Dendritic cells, critical for maintenance and initiation of immunity to foregn antigens and tolerance to self-antigens, are phagocytic, antigen presenting cells. This makes DCs an ideal recipient for the targeted delivery of agents provided in particulate form. Moreover, exogenous conditioning of DCs with certain immunomodulatory agents has been shown to induce a pro-tolerance DC phenotype as well as ameliorate T1D. Vaccination with DC-targeting microparticles (MPs) holds promise to correct T1D autoimmune responses, critically, without the costly ex vivo manipulations required of DC-based cellular therapy. This enables the potential for widespread use. Micron-sized biodegradable polymeric particles are phagocytosable, which effectively promotes delivery of encapsulated factors to intracellular sites of DCs over non-phagocytes. These phagocytosable particles can be further targeted to DCs by surface immobilizing molecules targeting DC receptors. Larger (but still small enough to be injectable), non-phagocytosable biodegradable polymeric particles provide controlled release of encapsulated factors to the local extracellular environment at the subcutaneous injection site. Encapsulated factors in these large particles consist of bioactive factors for which DCs have the cognate cell-surface receptors. The objective of this proposal is to engineer a subcutaneously injectable dual MP vaccine system consisting of i.) Phagocytosable DC-targeting MPs delivering antigen and immunomodulatory factor (insulin and vitamin D3) to intracellular sites; and ii.) Non-phagocytosable MPs to deliver, extracellular, factors (GM- CSF and TGF-b1) for DC recruitment and tolerance induction. We expect to effect a pro-tolerogenic DC phenotype and promote induction of regulatory T-cells, suppression of auto-reactive T-cells, and prevent and reverse diabetes in non-obese diabetic (NOD) mice. We hypothesize that the combination of the multiple components in the dual MP system will more effectively provide robust, durable antigen-specific immune suppression than single-component formulations, either in MPs or in soluble form. Aim 1 is to formulate the dual MP system, test it in vitro by characterizing DC phenotype (activated, immature or tolerogenic) and T-cell response (stimulation, Th1, Th2, Treg, or Th17). Aim 2 is to evaluate the ability of the dual MP formulation in vivo, aiming to prevent and reverse diabetes in NOD mice. This novel and innovative approach holds promise for correcting autoimmune responses in T1D and represents a simple, clinically translatable system.

Project Number:	5R01DK095207-03	**Contact PI / Project Leader:**	KNUTSON, KRISTEN
Title:	HOME SLEEP AND CIRCADIAN PHASE: MEDIATORS OF RACIAL DISPARITIES IN DIABETES RISK	**Awardee Organization:**	UNIVERSITY OF CHICAGO

Abstract Text:

DESCRIPTION (provided by applicant): Summary African Americans are at significantly greater risk of developing type 2 diabetes than non-Hispanic whites. Despite the long-standing recognition of this racial disparity and attempts to eliminate it, it persists. Diabetes is associaed with reduced quality of life, decreased life expectancy and increased economic burden, and therefore African Americans experience a greater health burden than non-Hispanic whites. Thus, more efforts to combat this disparity in diabetes is urgently needed in order to achieve health equity for African Americans. Laboratory and observational studies have observed (1) significant associations between deficient sleep and increased diabetes risk and (2) shorter sleep durations and poorer sleep quality in African Americans compared to whites. No research to date, however, has explicitly examined whether deficient sleep partially accounts for the increased diabetes risk in African Americans. Therefore, we propose to examine sleep duration, sleep quality and circadian disruption as novel biobehavioral mediators of the racial disparity in diabetes risk. Indeed, despite it being well-recognized that (1) short sleep durations alter circadian phase, (2) circadian disruption produces metabolic disturbances, and (3) the melatonin rhythm directly impacts beta-cell function, circadian disruption has not previously been considered as a key mediator between sleep and diabetes risk. Thus the 3 primary goals of this study are to (1) conduct comprehensive and ecologically-valid assessments of sleep in people's homes, (2) assess circadian phase in the home environment by objectively controlling for light exposure and timing of sample collection and (3) determine if differences in home sleep and circadian measures partially explain differences in diabetes risk factors between African Americans and non- Hispanic whites. Our primary marker of diabetes risk will be the Matsuda Index of insulin sensitivity, estimated from a frequently-sampled oral glucose tolerance test. Secondary outcomes will include area-under-the-curve of glucose levels, disposition index, and a marker of inflammation (C - reactive protein), blood pressure, heart-rate variability, and lipid profiles. We plan to study 72 African Americans and 72 non-Hispanic whites without diabetes or sleep disorders. We have preliminary data that 1) support the existence of racial differences in the duration, structure and timing of sleep, (2) support our hypothesis that deficient sleep may mediate some health disparities, (3) support the existence of racial differences in circadian timing, (4) demonstrate the feasibility of conducting unattended in-home PSG, (5) demonstrate the feasibility and validity of data from at- home circadian phase assessments and (6) demonstrate the feasibility of the complete shortened protocol to be used in this study. This important multidisciplinary project will yield unique insights into the bio behavioral mechanisms underlying increased diabetes risk in African-Americans and will likely lead to the development of novel targeted interventions for diabetes including bedtime extension or regularity and chrono-therapeutic treatments. This application is in response to PA-09-262 "Health Disparities in NIDDK Diseases".

Project Number:	5R01DK101593-02	**Contact PI / Project Leader:**	KOHL, HAROLD WILLIS
Title:	EFFECTS OF LIGHT RAIL TRANSIT ON PHYSICAL ACTIVITY: A NATURAL EXPERIMENT	**Awardee Organization:**	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON

Abstract Text:

DESCRIPTION (provided by applicant): Physical inactivity is a known risk factor for obesity and related chronic diseases, including cardiovascular disease and certain cancers. Substantial variations exist in physical activity and obesity by various factors such as socioeconomic status and race/ethnicity. Recent research has clarified the multiple domains of physical activity (discretionary, household, transport-related and occupational) as well as the role that the built environment can play in supporting or impeding physical activity. It is now clear that transport-related physical activity, i.e. activity undertaken to get to a destination, can help play a major role in achieving recommended levels of physical activity. Public transit is a natural candidate for study in this regard because use of transit almost invariably requires some degree of activity to travel to and from the stops, such as walking or biking. The purpose of the proposed time-sensitive project is to evaluate, in the context of a natural experiment, the short and long-term effect of a new light rail transit (LRT) system on adult's physical activity in Houston, Texas. We are particularly interested in understanding this effect in the low-income, ethnically diverse adul population residing along the LRT line. This study is possible because of an ongoing expansion of the city's LRT system. To accomplish this goal, we propose the following three specific aims in 1,400 residents living within a half-mile of the new rails lines and 500 living beyond walking distance of the lines: (1) Evaluate the short-term (<12 months) and long-term (24 & 36 months) impact of accessibility to a new LRT line on LRT and overall transit use; (2) Evaluate the short- and long-term impact of LRT use on transit-related and overall physical activity levels; and (3) Using travel choice modeling techniques, examine the factors (such as demographic, socioeconomic, and environmental factors) influencing individuals' LRT mode choice decision, as well as the relation between individuals' LRT mode choice and active-travel behavior choices. We will assess typical travel patterns and transit use with travel diaries; self-reported physical activity; measure resident perceptions of the neighborhood environment; conduct on-the-ground neighborhood audits; and develop GIS-based profiles of the built environment of study neighborhoods. A subgroup of 1000 participants (500 each in intervention and control areas) will wear accelerometers for one week to provide a direct measure of physical activity. Baseline data will be collected prior to the lines' opening in late December 2013, with follow-up occurring once a year for three years. This proposed project improves substantially upon related prior studies. First, with a follow-up of three years post-LRT opening, we will be able to determine sustainability of changes to physical activity. Second, our target population is primarily minority and lower income, a collectively understudied group regarding physical activity. The population is also representative of demographic changes projected to occur in the rest of the Unites States. Third, we have a strong interdisciplinary team of consisting of specialists in epidemiology and public health, biostatistics, behavioral science and transportation engineering.

Project Number:	5R01DK083345-04	**Contact PI / Project Leader:**	KRENDEL, MIRA
Title:	ROLE OF MYOSIN 1E IN PODOCYTE BIOLOGY AND RENAL FILTRATION	**Awardee Organization:**	UPSTATE MEDICAL UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): In order to improve prevention and treatment of chronic kidney disease, a major public health concern in the US and worldwide, it is essential to identify proteins that are necessary for normal glomerular functions. Identification of proteins that are critical for glomerular filtration will help pinpoint molecular targets of disease pathways that lead to renal dysfunction. The goal of this research project is to identify the roles of an actin-dependent molecular motor myosin 1e (myo1e) in normal kidney functions and in development of kidney disease. Myosin 1e is expressed in glomerular podocytes, specialized kidney epithelial cells that play a critical role in selective renal filtration. We have found that myo1e knockout mice are viable but exhibit severe defects in glomerular filtration and organization. This project focuses on identification of the intracellular functions of myo1e in podocytes and analysis of the role of myo1e in maintaining normal renal filtration. These studies will help determine how changes in myo1e activity may contribute to progression of kidney disease. We propose a hypothesis that myo1e motor activity is required for its role in normal podocyte functions. In order to test this hypothesis, we will pursue the following specific aims. Aim 1. Analyze the effects of mutations in myo1e on its functions in podocytes. In this aim we will determine the role of myo1e motor activity in regulation of podocyte migration and cell shape. Aim 2. Determine how intracellular signaling pathways in podocytes are affected by the loss of myo1e activity and analyze regulation of myo1e motor functions by podocyte signaling. Aim 3. Test the ability of myo1e mutants to rescue the defects in glomerular filtration in mice lacking myo1e.

Project Number:	5R01DK097865-02	**Contact PI / Project Leader:**	KUMAR, MATAM VIJAY
Title:	ROLE OF LIPOCALIN 2 INFLAMMATORY BOWEL DISEASE	**Awardee Organization:**	PENNSYLVANIA STATE UNIVERSITY-UNIV PARK

Abstract Text:

DESCRIPTION (provided by applicant): Inflammatory bowel disease (IBD) is the collective term for chronic idiopathic inflammatory diseases of the intestine, most notably Crohn's Disease (CD) and Ulcerative Colitis (UC), which together affect 1.4 million people in the US and 2.2 million people in Europe. IBD is associated with elevated levels of a number of acute phase proteins (APP) that drive or dampen the inflammatory response. Exploration of the biologic activities of APP has resulted in the development of targeted biological therapeutic agents. Indeed, agents that directly antagonize pro-inflammatory mediators or mimic anti-inflammatory molecules are currently being used and/or developed to treat IBD. However, the biologic activity, and thus therapeutic potential, of some of the most dynamically regulated APP remain unexplored. For example, while levels of the APP lipocalin-2 (Lcn2) increase by several log orders of magnitude in various inflammatory conditions, including murine colitis and human IBD, the extent to which Lcn2 drives or dampens gut inflammation remains unexplored. In addition to its elevated expression being associated with colitis, the multifaceted biologic activity of Lcn2 (as well as that of its human ortholog, Neutrophil Gelatinase-Associated Lipocalin) or NGAL suggests it may play a central role in IBD. Specifically, Lcn2 exerts potent antibacterial activity mediated by sequestering bacterial siderophores and thereby preventing bacteria from scavenging iron from lower affinity host proteins. In addition, Lcn2 participates in iron transport stabilizing highly reactive catalytic iron by chelation. Accordingly, it has been shown that Lcn2 deficient mice are highly susceptible to bacterial and LPS-induced sepsis. We hypothesize that Lcn2's control over iron homeostasis is not limited to the extreme events such as sepsis but, rather, that the dynamic regulation of Lcn2 from low-grade inflammation to acute and chronic colitis plays an important role in preserving gut neutrophil function as well as iron/microbiota homeostasis. Consequently, the goal of this proposal is to investigate the role and mechanism of action of Lcn2 in intestinal inflammation. Establishing the role of this dynamically regulated protein will advance our knowledge of pathogenesis and perhaps allow development of novel therapeutic strategies to treat human IBD. We anticipate that these studies will demonstrate a key role for Lcn2 in protecting the gut. Given its small size, simple structure and biologic activiy in the absence of post-translational modification, Lcn2 may be exploitable as a treatment for intestinal inflammation.

Project Number:	5R01DK092776-03	**Contact PI / Project Leader:**	KURPIOS, NATASZA A
Title:	MECHANISMS UNDERLYING ASYMMETRIC ROTATION AND VASCULAR DEVELOPMENT OF THE MIDGUT	**Awardee Organization:**	CORNELL UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Early in development, the midgut must rotate so that its ventral margin shifts to the left; failure to do so results in a malrotation and can lead to catastrophic midgut volvulus. It has long been assumed that gut rotation is intrinsic to the tube itself; however, my research has demonstrated that rotation is instead determined by asymmetric cellular changes within the dorsal mesentery that suspends the gut. This mesentery has four juxtaposed yet distinct cellular compartments distributed along its left-right axis, and changes in each are required for correct gut rotation. Combined with the unique accessibility of the chicken egg, this cellular architecture has established the dorsal mesentery as a powerful model system to define, in vivo, the fundamental genetic and cellular mechanisms through which organs acquire their spatial organization, which is a prerequisite for normal functioning. The genesis of gut rotation traces its origins to the early left-right symmetry-breaking transcription factor Pitx2. In mice and birds, Pitx2 is necessary and sufficient to produce the leftward tilt, and this rotation is randomized in embryos deficient for Pitx2 activity. However, th mechanisms by which this transcription factor directs downstream cellular changes necessary to cause gut rotation remain unknown. To identify cellular targets of Pitx2 in each of the four compartments, we employed laser capture microdissection to isolate then catalog the genes expressed in each cellular compartment at the time of the leftward tilt. Using these data, the firs aim pursues cascades involving subsets of genes that are critical for signaling, for recognizing extracellular cues, and for remodeling cytoskeletal architecture. The roles of key players will be assessed by introducing gain- or reduction- of function gene constructs into each compartment. In our second aim, we address previously unknown asymmetries in the formation of intra-mesenteric arteries that bring blood to the gut, using experimental approaches similar to the first aim but assaying for positive and negative regulators of vasculogenesis. In our third aim, we expand our studies using mouse models of asymmetric organ development and use chromatin immunoprecipitations in vivo to identify bona fide Pitx2 transcriptional targets. Lessons learned from these experiments will impact the study of other regions of the gut, and of tubular organs in general, some of which share strikingly similar features of morphogenesis and genetic patterning with the vertebrate midgut.

Project Number:	5R01DK089211-04	**Contact PI / Project Leader:**	LEE, ANN HWEE
Title:	REGULATION OF TRIGLYCERIDE METABOLISM BY THE TRANSCRIPTION FACTOR CREB-H	**Awardee Organization:**	WEILL MEDICAL COLL OF CORNELL UNIV

Abstract Text:

DESCRIPTION (provided by applicant): CREB-H is an endoplasmic reticulum (ER)-bound transcription factor that is highly and selectively expressed only in the liver and the small intestine. CREB-H activation requires a sequential cleavage of its precursor protein by Golgi proteases that liberate the mature N-terminal portion of the protein, which localizes to the nucleus to act as a transcriptional transactivator. CREB-H is induced by fatty acids, the fatty acid oxidation regulator PPAR1, and fasting in the liver, suggesting that it might participate in nutrient and energy metabolism. We demonstrated that CREB-H is required for the maintenance of normal trigylceride (TG) levels in vivo. CREB-H is induced in the liver by fasting and controls a subset of genes that are critical for TG and lipoprotein metabolism. CREB-H deficient mice displayed severe hypertriglyceridemia secondary to inefficient TG clearance catalyzed by lipoprotein lipase (LPL). Genetic profiling revealed that CREB-H deficiency was associated with decreased expression of the LPL coactivators, Apoc2, Apoa4, and Apoa5 apolipoproteins and concurrent augmentation of the LPL inhibitor, Apoc3. Multiple nonsynonymous mutations in CREB3L3 that produced hypomorphic or nonfunctional CREB-H protein were identified in patients with extreme hypertriglyceridemia. We establish CREB-H as a novel transcription factor that governs TG metabolism in rodents and humans. The current proposal aims to further investigate the function and mechanism of action of CREB-H in lipid metabolism. We propose to address the following questions: Aim 1. What is the organ specific function of CREB-H in liver and small intestine, as assessed using conditional CREB-H knock-out mice that selectively lack CREB-H in these organs? Aim 2 and 3. CREB-H and PPAR1 share common target genes that are involved in fatty acid oxidation. What is the functional relationship between CREB-H and PPAR1? Does CREB-H play a role in hepatic steatosis? Given the induction of PCPCK by CREB-H, is CREB-H required for glucose homeostasis? What is the universe of CREB-H targets genes in the liver and intestine? What nutritional and hormonal signals regulate CREB-H, and how CREB-H activation can be achieved at multiple levels, which include transcriptional activation, Golgi translocation, and other post-translational modifications. The mode of CREB-H activation appears be distinct in liver and small intestine, and we will further investigate the precise mechanisms that account for this. Given that CREB-H deficiency resulted in hyperlipidemia, would the augmentation of CREB-H activity be beneficial in the treatment of dyslipidemia? We will address this question by inducible overexpression of constitutively active CREB-H. Aim 4. Finally, what is the molecular mechanism for hypertriglyceridemia caused by mutations in CREB3L3 in patients? We envision that these studies will uncover novel signaling pathways that may lead to the discovery of potential targets for developing novel therapeutics for dislipidemia.

Project Number:	5R01DK093774-02	**Contact PI / Project Leader:**	LEE, YOON-KWANG
Title:	HEPATIC LIPID MOBILIZATION BY NUCLEAR HORMONE RECEPTORS	**Awardee Organization:**	NORTHEAST OHIO MEDICAL UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Hepatic steatosis is associated with nonalcoholic fatty liver disease (NAFLD), which can progress to nonalcoholic steatohepatitis (NASH). NAFLD is also a leading risk factor for the development of impaired fasting glucose and type 2 diabetes. Small heterodimer partner (SHP, NR0B2) belongs to the nuclear hormone receptor superfamily. Earlier molecular studies suggested that SHP plays a role in glucose and lipid metabolism. Our studies with congenic SHP-/- mice showed that SHP regulates hepatic triglyceride (TG) storage in response to excess dietary fat ingestion, and its deficiency protects against development of hepatic steatosis. This protection against fatty liver development in SHP-/- mice results in part from elevated-fatty acid oxidation due to derepression of PPARα transcriptional activity, but also to lower expression of PPARγ2, a major lipogenic transcription factor. Marked elevation of hepatic PPARγ expression has been observed in numerous mouse models of NAFLD and human patients with the disorder. Integrating our own preliminary results with published studies, we have identified a novel transcriptional cascade in which SHP regulates PPARγ expression. In this new regulatory pathway, SHP represses the ability of the retinoic acid receptor (RAR) to activate expression of hairy and enhancer split 6 (Hes6) a transcriptional corepressor that has recently been reported to repress PPARγ2 via inhibition of HNF4α transactivation. In accord with this, we have shown that RAR activation by its natural ligand all-trans retinoic acid (atRA) alleviates hepatic steatosis. Thus we hypothesize that SHP and atRA/RAR can function coordinately to regulate hepatic lipid accumulation. In order to critically test the significance o our proposed regulatory cascade, we will 1) define the regulatory role of SHP and atRA in the expression of Hes6, then 2) examine the functional interactions of SHP and atRA/RAR in modulating fat accumulation in mouse models of NAFLD, and finally 3) test the linkage between Hes6 and fat mobilization using Hes6 overexpression or silencing. Our studies of this novel transcriptional regulatory network will provide insights into the development of hepatic steatosis and crucial avenues into the prevention and treatment of a disorder that is a major contributor in the development of the metabolic syndrome.

Project Number:	5R01DK093586-03	**Contact PI / Project Leader:**	LINDE, JENNIFER A
Title:	WEIGHT TRACKING AND WEIGHT LOSS OUTCOMES: ESTABLISHING THE STANDARD OF CARE	**Awardee Organization:**	UNIVERSITY OF MINNESOTA

Abstract Text:

DESCRIPTION (provided by applicant): Given the pernicious reach of obesity and the evidence that current behavioral treatments are modestly effective at changing weight, efforts to refine behavioral recommendations in order to improve weight loss interventions are crucial. Frequency of tracking body weight presents itself as a prime target for behavioral enhancement during weight loss. Daily self-monitoring (e.g., of dietary intake and physical activity) is alread well-established as a central component of the behavioral weight loss process. However, the current standard of care in behavioral weight loss with regard to weighing is weekly tracking of weight, and some programs caution against any weight tracking. It has been suggested that frequent weight tracking may have a negative impact on mental health and outcomes during weight loss, but there are minimal data that address this concern experimentally in the context of an active weight loss program. Observational evidence from behavioral weight control trials and community studies suggests that greater frequency of tracking weight is associated with better weight outcomes. Stronger experimental evidence is needed to establish a causal link between weight tracking and weight outcomes and to elucidate the impact on mental health during weight loss. To achieve the long-term goal of strengthening behavioral weight loss programs, the purpose of this project is to test an enhanced, daily weight tracking instruction against the current standard of care (weekly weight tracking) and an alternate model of care with very limited data (no weight tracking). In pursuit of study goals, 336 overweight and obese adults will be recruited and randomized to one of three 12-month weight loss interventions with a 12-month follow-up (24 month study endpoint): the standard of care (weekly weight tracking during weight loss), an enhanced condition (daily weight tracking during weight loss), or a comparison condition (no weight tracking during weight loss). The rationale behind this proposal is that within the context of social ecology and a social-cognitive framework of behavior change, enhancement of this key environmental feature (i.e., the weight tracking environment) during weight loss will contribute to success by promoting self-efficacy for this critical behavior. Speciic aims of the study will seek to determine the effects of weight tracking frequency on the weight loss process and outcomes, as well as to elucidate the effects of weight tracking frequency on mental health during weight loss. This study will have the expected outcome of enhancing the standard of care for weight loss, leading to better weight control for overweight and obese adults and thus directly mitigating the public health impact of the obesity crisis.

Project Number:	5R01DK090305-04	**Contact PI / Project Leader:**	MA, XIAOCHAO
Title:	MECHANISMS OF ADVERSE EFFECTS OF ANTI-TUBERCULOSIS DRUGS	**Awardee Organization:**	UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Abstract Text:

DESCRIPTION (provided by applicant): Drug-induced liver injury is a major safety issue in anti-tuberculosis (TB) chemotherapy. The long- term goal of our research is to improve the safety profile of medication with anti-TB drugs. The objective of this application is to determine the mechanism of liver injury associated with rifampicin and isoniazid co-therapy. Extensive studies have been conducted previously to investigate the liver injury caused by rifampicin and isoniazid in mice or rats; however, none of these studies mimicked the hepatotoxicity in humans. Species differences between rodents and humans in responding to rifampicin and/or isoniazid are expected. Pregnane X receptor (PXR) is a transcription factor regulating a gene network involved in the metabolism of xenobiotics and endobiotics. The ability of chemicals to activate PXR is species- dependent. Rifampicin is a human specific PXR activator, which strongly activates human PXR, but has a very weak effect on mouse PXR. To overcome the species differences in ligand-dependent PXR activation, we generated a PXR-humanized mouse model. By using these PXR-humanized mice, we noted that rifampicin and isoniazid-induced liver injury is human PXR-dependent. However, rifampicin- mediated PXR activation does not alter isoniazid metabolism. By using a metabolomic approach, we found that rifampicin and isoniazid co-treatment caused protoporphyrin IX (PP-IX) accumulation, specifically in liver, and this is human PXR-dependent. PP-IX is an intermediate in porphyrin synthesis, and has been shown to be hepatotoxic in previous studies. Based upon our preliminary data and previous reports, we hypothesize that rifampicin and isoniazid co-treatment disturbs porphyrin synthesis, and the accumulation of PP-IX in liver mediates the hepatotoxicity. To test our hypothesis, we will pursue the following two specific aims: (1) identify the toxic mediator(s) in the liver injury caused by rifampicin and isoniazid co-therapy. Our working hypothesis is that the accumulation of PP-IX in liver is the key mediator of the hepatotoxicity caused by rifampicin and isoniazid co-therapy; and (2) determine the human PXR-dependent pathway(s) responsible for the hepatotoxicity in rifampicin and isoniazid co- therapy. Our working hypothesis is that human PXR-mediated up-regulation of aminolevulinic acid synthase 1, the rate-limiting enzyme in porphyrin synthesis in liver, is critical in the hepatotoxicity caused by rifampicin and isoniazid co-therapy. The results from these studies are expected to provide a new paradigm for the mechanistic understanding of rifampicin and isoniazid-induced hepatotoxicity. Novel strategies, based upon human PXR, aminolevulinic acid synthase 1, and PP-IX, can be developed to predict, prevent, and treat the liver injury caused by rifampicin and isoniazid co-therapy.

Project Number:	5R01DK097271-03	**Contact PI / Project Leader:**	MANICASSAMY, SANTHAKUMAR
Title:	REGULATION OF ORAL TOLERANCE AND INTESTINAL INFLAMMATION BY BETA-CATENIN/TCF PATH	**Awardee Organization:**	GEORGIA REGENTS UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Crohn's disease and ulcerative colitis (inflammatory bowel disease, IBD) are important clinical problems, but molecular targets for therapeutic immune intervention remain elusive. Intestinal dendritic cells (DCs) and macrophages (Mϕs) play a pivotal role in mediating mucosal tolerance and suppressing inflammation. In IBD, these cells lose their tolerogenic properties resulting in uncontrolled intestinal inflammation. However, the molecular pathways that program these cells to a tolerogenic state rather than to an inflammatory state are not known. We have identified a new and previously unsuspected role for the β-catenin signaling pathway as a key molecular regulator of tolerogenic phenotype in intestinal DCs and Mϕs. β-catenin is downstream of three sets of ligands widely expressed in the gut (TLR ligands, wnt ligands and E-cadherin), and ablation of β-catenin in these cells causes loss of tolerance. The current proposal will focus on the mechanistic role of the β-catenin pathway in regulating key downstream effector mechanisms, and test its relevance in in vivo models of colitis and oral tolerance. Specific aims in the current proposal are (i) to understand the molecular mechanisms by which β-catenin/TCF pathway regulates the expression of three key immune regulatory genes - IL-10, RALDH and IDO - in intestinal DCs and Mϕs (Aim 1), (ii) to understand the functional and biological role of this pathway in intestina DCs and Mϕs in T regulatory cell differentiation and expansion (Aim 2), and (iii) their ability to limit intestinal inflammation and promote oral tolerance (Aim 3). The successful completion of the proposed studies will provide new mechanistic insights into how the β-catenin/TCF pathway in intestinal DCs and Mϕs regulates a balance between tolerance and inflammatory responses, and will provide a mechanistic rationale for targeting this pathway in IBD. Pharmacological activators of β-catenin pathway already exist, and more are in development and the proposed studies will provide a rationale for the development of an entirely new class of agents that may have significant therapeutic impact in treating IBD.

Project Number:	5R01DK097107-02	**Contact PI / Project Leader:**	MANNON, PETER
Title:	ULCERATIVE COLITIS - REGULATION OF THE IL-13 RECEPTOR SYSTEM	**Awardee Organization:**	UNIVERSITY OF ALABAMA AT BIRMINGHAM

Abstract Text:

DESCRIPTION (provided by applicant): Dysregulation of IL-13 and the IL-13 receptor pathway is the most defining cytokine abnormality of ulcerative colitis (UC). The significance of this finding is established not only by the observed toxicity exerted by IL-13 on the colonic epithelium in vitro and the successful treatment of murine oxazalone colitis by anti-IL-13 strategies, but also by results of a recent trial of interferon-beta in UC that showed significant post-treatment decreases in IL-13 production that were restricted to the clinical responders. Because multiple novel therapies targeting IL-13 activity at various points in the ligand-receptor-signaling pathway are currently in development, identifying the predominant mechanism of dysregulation of the IL-13 receptor system in UC will lead to optimized clinical trial design through choice of agent and monitoring for effect. The preliminary data for this proposal show striking upregulation of the decoy IL13Ralpha2 receptor in the epithelium and excess production of IL-13 by lamina propria mononuclear cells in many, but not all, active ulcerative colitis patients and are absent in healthy controls and active Crohn's disease. These findings provide the innovation for new and critical questions about UC: is the epithelial IL13Ra2 expression protective or injurious in active UC, is the heterogeneity of IL-13 production related to NKT versus innate lymphoid cell production, and are there IL-13 expression-based endotypes of UC that can predict response to IL-13-targeted therapies? Using primary gut tissue, methods to measure regulation of receptor expression, IL-13 signaling and receptor activity, and phenotypes of the cells producing IL-13 and expressing IL-13 receptors will allow comparison between subsets of UC patients, Crohn's and healthy controls. These studies will define the relevant cell source of IL-13 in UC, the regulation of its production and the sites and mechanisms of action among and within different strata of UC disease activity. The results will be applicable to other mucosal inflammatory diseases like allergic asthma and eosinophilic esophagitis where IL-13 also drives disease and new therapies targeting IL-13 are needed.

Project Number:	5R01DK090364-04	**Contact PI / Project Leader:**	MASHEK, DOUGLAS G
Title:	ROLE OF ATGL IN HEPATIC ENERGY METABOLISM	**Awardee Organization:**	UNIVERSITY OF MINNESOTA

Abstract Text:

DESCRIPTION (provided by applicant): Non-alcoholic fatty liver disease (NAFLD), defined by triacylglycerol (TAG) accumulation, is a prevalent disorder that is involved in the etiology of numerous metabolic diseases including obesity, diabetes and cardiovascular disease. Despite the importance of TAG metabolism and the advancements into our understanding of the TAG synthetic pathway, the mechanisms regulating hepatic TAG hydrolysis and their effects on disease etiology are unknown. The objective of this application is to define the role of adipose TAG lipase (ATGL) in hepatic lipid metabolism and signaling, the etiology of insulin resistance and in mediating diet-specific effects. The hypothesis of the proposed studies is that ATGL is a prominent hepatic lipase that elicits wide-ranging effects on energy metabolism by altering FA channeling and signaling. We base this hypothesis on Preliminary Studies from our laboratory showing that ATGL alters partitioning of hydrolyzed FA between anabolic and catabolic pathways, regulates PPAR-1 activity, uncouples insulin resistance from NAFLD and selectively hydrolyzes TAG. The rationale for the proposed research is that identifying the role of ATGL in mediating hepatic TAG metabolism will provide significant insight into the etiology of NAFLD and related comorbidities, thereby, advancing the possibilities for development of nutritional or pharmaceutical therapies. The hypothesis will be tested using three specific aims: 1) to characterize the ATGL and PPAR-1 signaling axis and its role in hepatic energy metabolism, 2) to define the role of hepatic ATGL in regulating hepatic and whole-body insulin resistance and 3) to characterize the effect of hepatic ATGL on hydrolyzing distinct TAG pools and mediating subsequent FA channeling and signaling. Under the first aim, ATGL gain or loss-of-function studies in mouse models will define the relationship between ATGL and PPAR-a. Additionally, in vitro studies will define the mechanisms through which ATGL regulates PPAR-1 activity. The second aim will employ both in vitro and in vivo methodologies along with stable isotope techniques to characterize how ATGL uncouples hepatic TAG accumulation from insulin resistance and its role in the formation of lipid signaling molecules. The third aim will define how hepatic ATGL regulates the signaling and channeling of TAG-FA derived from different substrates and mediates diet-specific effects on metabolism. These studies are innovative because they approach NAFLD and its comorbidities from the understudied and often ignored pathway of TAG hydrolysis. Understanding how hepatic TAG hydrolysis is regulated is significant because it not only impacts TAG accumulation, but also dictates the metabolic fate and signaling properties of the hydrolyzed FA that can ultimately influence a multitude of biological processes.

Project Number:	5R01DK091281-03	**Contact PI / Project Leader:**	MCCOLE, DECLAN
Title:	A NOVEL ROLE FOR PTPN2 IN INTESTINAL EPITHELIAL BARRIER REGULATION	**Awardee Organization:**	UNIVERSITY OF CALIFORNIA RIVERSIDE

Abstract Text:

DESCRIPTION (provided by applicant): Increased intestinal permeability plays a crucial role in a number of chronic intestinal inflammatory conditions including Type 1 Diabetes (T1D), celiac disease, as well as Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as inflammatory bowel disease (IBD). More than 1.4 million Americans suffer from IBD. While the exact cause(s) of IBD are unknown, there is considerable evidence that a permeability defect in the intestinal epithelial layer plays a major role in the development of IBD. The intestinal epithelial lining is a single layer of cells that forms the interface between the bactera that reside in the intestine (intestinal microbiota), and the rest of the body. During inflammation the epithelium is exposed to high levels of inflammatory mediators such as interferon-g (IFNg). These mediators activate signaling pathways that alter various functions of the epithelium, such as barrier maintenance. Termination of these signals is mediated largely by the activity of phosphatases. One such phosphatase, protein tyrosine phosphatase non-receptor type 2 (PTPN2), negatively regulates IFNg signaling in non-epithelial cells. However, little is known about the function of PTPN2 in the intestinal epithelium. Recently, single nucleotide polymorphisms (SNP) in the PTPN2 gene have been identified as a genetic marker associated with Crohn's disease, UC, T1D and celiac disease. Thus, these diseases share a common gene association and an elevation in intestinal permeability. We have recently identified a completely novel involvement of PTPN2 in the regulation of epithelial barrier function. Therefore, the specific objectives of this proposal are to understand the role of PTPN2 in regulating intestinal barrier function, and to identify how PTPN2 may be involved in the pathogenesis of chronic intestinal inflammatory diseases. This will be addressed in three specific aims. Aim 1 will investigate how PTPN2 modulates inflammation-induced intestinal barrier dysfunction by determining how PTPN2 restricts intestinal epithelial barrier dysfunction caused by inflammatory cytokines. Aim 2 will identify how the expression, activity and cellular localization of PTPN2 are regulated by inflammatory cytokines. Aim 3 will identify how PTPN2 regulates intestinal permeability in vivo using PTPN2-deficient mice. Expected Outcomes & Impact: These studies will provide fundamental insights into the role of PTPN2 in the regulation of intestinal barrier function, the effect of inflammatory mediators on PTPN2 expression and activity, and the functional consequences of a loss of PTPN2 on epithelial cytokine signaling. On a broader scale, we will identify a unifying link for a gene (PTPN2) and a pathophysiological phenomenon (increased intestinal permeability) that are both fundamentally involved in CD, UC, Type 1 diabetes and celiac disease. These studies may also identify new diagnostic and treatment approaches for IBD patients expressing a PTPN2 SNP.

Project Number:	5R01DK097084-02	**Contact PI / Project Leader:**	MILJKOVIC, IVA
Title:	ECTOPIC ADIPOSITY IN BLACK MEN WITH HIGH TYPE 2 DIABETES RISK	**Awardee Organization:**	UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Abstract Text:

DESCRIPTION (provided by applicant): Obesity and type 2 diabetes (T2D) disproportionately affect black individuals. Generalized obesity and other established risk factors do not explain the racial disparity in T2D, and this is particularly evident among men. Emerging evidence indicates that fat accumulation in non-adipose tissues (referred to as ectopic adiposity) may be associated with T2D, independent of general obesity. Compared to white men, both obese and lean black men have less visceral and liver adiposity, while in contrast, they paradoxically have more skeletal muscle adiposity. Skeletal muscle is crucial for maintaining glucose homeostasis, and thus, skeletal muscle adiposity may be the key adipose tissue depot contributing to increased T2D risk in blacks. However, much remains to be learned about the epidemiology of skeletal muscle adiposity, particularly among high-risk black populations. Through the K01 (DK083029) and R03 (DK092348) funded pilot studies for new investigators, the applicant has begun to investigate the epidemiology of skeletal muscle adiposity and other ectopic adipose tissue depots in a well-characterized, large cohort of black men from the Tobago Health Study. This cohort offers a unique opportunity to study a black population with low levels of total adiposity, and low prevalence of other potential confounding variables, but with a high prevalence of T2D, especially among non- obese men. We are proposing to continue and expand upon our preliminary research on ectopic adiposity in this cohort. We will take advantage of our unique resource of archived computed tomography (CT) scan image files from over 1500 black men, aged 40 years and above, to analyze skeletal muscle adiposity changes over an average of nearly 7 years, and characterize the natural history of skeletal muscle adiposity changes with aging in black men, and the temporal relationship of these changes with glucose and insulin homeostasis. We will also use archived biological specimens to measure physiologic markers of potential importance for skeletal muscle adiposity, and test several compelling hypotheses about the etiology and consequences of skeletal muscle adiposity. In addition, we will obtain new CT measures of visceral, liver, abdominal muscle and pericardial adiposity, and will test for an association of abdominal skeletal muscle adiposity with measures of glucose and insulin homeostasis, and determine if these associations are independent of liver, visceral and pericardial adiposity. The proposed study will greatly advance our understanding of ectopic adiposity and its role in T2D among high risk black men.

Project Number:	5R01DK096030-02	**Contact PI / Project Leader:**	MIYAZAKI, MAKOTO
Title:	MOLECULAR PATHOGENESIS OF CHRONIC KIDNEY DISEASE-DEPENDENT VASCULAR CALCIFICATION	**Awardee Organization:**	UNIVERSITY OF COLORADO DENVER

Abstract Text:

DESCRIPTION (provided by applicant): The long term objective of this research proposal is to determine the molecular mechanisms of vascular calcification in order to identify novel target(s) for the treatment of chronic kidney disease (CKD)-dependent vascular calcification. Vascular calcification is closely associated with cardiovascular morbidity and mortality in patients with CKD. In fact, more than half of all deaths in CKD subjects can be attributed to cardiovascular diseases. We hypothesized that a central event in the pathogenesis of CKD-dependent vascular calcification is increased expression of phosphorylated activating transcription factor 4 (ATF4). ATF4 is a member of the cAMP-responsive element-binding protein (CREB) family of basic zipper-containing transcription factors that regulates osteogenesis and also mediates unfolded protein response (UPR) in the endoplasmic reticulum (ER). Our hypothesis is based on the following evidence derived from a series of preliminary results from our lab: 1) total and phosphorylated ATF4 protein levels were induced by a number of positive regulatory factors for vascular calcification, such as inorganic phosphate, inflammatory cytokines (TNFa) and saturated fatty acids through the activation of the PERK-elF2a axis of the UPR in vascular smooth muscle cells (VSMCs); 2) adenovirus-mediated overexpression of ATF4 induced mineralization of VSMCs; 3) ATF4 knockdown, on the other hand, attenuated vascular calcification; 4) serine-phosphorylation of ATF4 (p-ATF4) was induced by PKA activation by forskolin, which is known to promote vascular calcification; 5) PKA and ERK inhibitors inhibited the phosphorylation of ATF4, resulting in the reduction of vascular calcification; 6) Total ATF4 and p-ATF4 proteins were increased in the aortas of murine models of atherosclerotic calcification such as ApoE knockout mice with 5/6 nephrectomy (5/6 nx), and medial calcification such as DBA2/J mice with 5/6 nx and klotho knockout mice; 7) ATF4 targets (CHOP and GADD34) increased in these models and 8) ATF4 regulates the expression of Pit-1, a major phosphate transporter in VSMCs. To determine the pivotal role of ATF4 in the pathogenesis of vascular calcification, we propose three specific aims. Specific Aim 1: Determine whether global ATF4 deficiency and overexpression modulate CKD-dependent medial and atherosclerotic calcification. Specific Aim 2: Determine whether VSMC-specific activation and inhibition of ATF4 influence CKD-dependent medial and atherosclerotic calcification. Specific Aim 3: Elucidate molecular mechanisms by which ATF4 regulates osteoblastic differentiation and mineralization of VSMCs.

Project Number:	5R01DK097423-02	**Contact PI / Project Leader:**	MRUG, MICHAL
Title:	MECHANISMS OF C3 EFFECTS IN ARPKD PATHOGENESIS	**Awardee Organization:**	UNIVERSITY OF ALABAMA AT BIRMINGHAM

Abstract Text:

DESCRIPTION (provided by applicant): This grant application addresses the role of complement component 3 (C3), an axial component of complement pathway, in the pathogenesis of autosomal recessive polycystic kidneys disease (ARPKD), the most severe form of polycystic kidney disease (PKD). In line with paradigm shifts resulting from discoveries of novel essential roles of local C3 production, our studies point to intra-renal production of C3 as a regulator of a cystogenic pathway that dictates the pace of ARPKD progression. We formulated this hypothesis based on our genome-wide expression analyses of kidneys with rapid verses slow pace of cystogenesis in Cys1cpk/cpk model which phenocopies ARPKD. We supported this hypothesis by demonstrating: (i) increased content of biologically active split C3 fragments in kidneys from ARPKD and its orthologous model; (ii) presence of C3 mRNA and protein in renal cystic and pericystic cells; and (iii) strong association between renal C3 expression and pace of renal cystogenesis that we validated in crosses of C3 deficient (C3-/-) mice with Cys1cpk/+ mice. In addition, cystogenesis is attenuated in Pkhd1pck rats' introgressed to a strain with low C3 expression. While C3 may act through different pathways, we have found consistent association of accelerated cystogenesis specifically with the pathway regulated by complement receptor CR3. CR3 (or Mac-1), a major receptor for C3 fragment iC3b, which is highly abundant in cystic kidneys, plays a central role in differentiation, attachment and survival of monocytes/macrophages. While we have identified C3, macrophage marker CD14 and C3-inducible factor MCP-1 as candidate predictors of PKD outcomes, others have demonstrated that macrophage depletion attenuates cystogenesis in orthologous models of autosomal dominant PKD by reducing the proliferation of cystic tubules. CR3 may also induce pro-cystogenic TNF release and directly activate c-Src in renal tubule cells. Consistent with essential and novel effects of local complement factor production, the capacity of renal tubule cells to produce and activate C3 and dysregulation of this process by a cystogenic defect, we suggest that the C3 effects in ARPKD increase as cystic tubules dilate, forming a vicious cystogenic cycle. Specifically, we hypothesize that C3 pathway activation accelerates cyst formation in ARPKD through a CR3 dependent process. We address this hypothesis in three inter-related aims: 1) Dissect mechanisms underlying cystogenic effects of C3; 2) Determine whether C3 production by Pkhd1-expressing cells modulates ARPKD pathogenesis; and 3) Determine the role of complement component receptor CR3 (or Mac1) in renal cystogenesis. Objectives of these Aims will be accomplished by integrating: (i) highly innovative study design of interrogating novel regulatory mechanisms of renal cystogenesis with (ii) generation of novel state of the art reagents (e.g., for conditional C3 targeting). Achieving these aims will: (i) allo integration of existing knowledge by linking established and novel cystogenic pathways to the C3-CR3 nexus, and (ii) provide a new direction in ARPKD research that may lead to development of novel prognostic and therapeutic strategies.

Project Number:	5R01DK092587-03	**Contact PI / Project Leader:**	MUENZBERG-GRUENING, HEIKE
Title:	LEPTIN AND CENTRAL CONTROL OF THERMOREGULATION	**Awardee Organization:**	LSU PENNINGTON BIOMEDICAL RESEARCH CTR

Abstract Text:

DESCRIPTION (provided by applicant): The ongoing dramatic rise in obesity and the lack of efficient intervention strategies to treat obesity demonstrates the need to better understand mechanisms to maintain energy homeostasis. Thermogenesis is necessary to maintain body temperature, but also affects energy expenditure and body weight. Thermogenesis controls heat production in peripheral tissues, particularly the brown adipose tissue (BAT). BAT thermogenesis is also functional in adult humans and despite controversial opinions on the importance of BAT function to control body weight, BAT size correlates negatively with body mass index and thus central regulators of BAT thermogenesis are potential targets for anti-obesity drugs. Leptin regulates body weight in part via thermoregulatory mechanisms including BAT heat production. Indeed, hypothalamic leptin responsive neurons (e.g. in the DMH/DHA) recapitulate known central thermoregulatory pathways, that we hypothesize to mediate food-intake independent body weight regulation. The proposed experiments investigate the role of DMH/DHA leptin action in thermogenesis and energy homeostasis, emphasizing physiological function, regulation of central and peripheral signaling pathways and neuronal connectivity of DMH/DHA neurons (inhibitory/excitatory LepRb inputs to the DMH/DHA). The proposed study of leptin receptor (LepRb) neurons in mice allows the use of several molecular biological state-of-the-art tools (cre/loxP technology, neuron specific tracing and reporter expression), that have not been used in the thermoregulation research field, yet. In Aim 1 we will study the physiological importance of thermoregulatory DMH/DHA leptin action on body weight control by using DMH/DHA specific leptin or LepRb antagonist injections, or by in vivo modulation of neuronal activity in DMH/DHA LepRb neurons using DREADD technology. Thermoregulatory leptin action in wildtype or leptin deficient ob/ob mice is monitored by temperature transmitters, VO2/CO2 exchange, protein markers of BAT function and effects on body weight as well as other peripheral tissues (e.g. muscle and white fat) are investigated for leptin induced changes (e.g fat oxidation, mitogenesis). In Aim 2 will identify inhibitory/excitatory (GABA-/glutamatergic inputs to the DMH/DHA (e.g. from the POA) and their response to leptin. Furthermore, we will study mice with loss of glutamate in LepRb DMH/DHA to test the physiological consequence for thermoregulation and body weight control. In Aim 3 we identify the neuronal connectivity of LepRb DMH/DHA neurons. We will use site and neuron- specific tracing techniques (stereotaxic injection of cre-inducible viral tracers) to visualize GABA-/glutamatergic projections (axonal EGFPf) and their 2nd order target neurons (transsynaptic tracing). In leptin deficient ob/ob mice with LepRb-driven cre/EGFP expression potential thermoregulatory defects (e.g. LepRb expression, neuronal projections) in POA & DMH/DHA neurons are investigated.

Project Number:	5R01DK097760-02	**Contact PI / Project Leader:**	MUTHUMALAIAPPAN, KUZHALI
Title:	MECHANISMS OF IMPAIRED ERYTHROPOIESIS IN POST BURN ANEMIA OF CRITICAL ILLNESS	**Awardee Organization:**	LOYOLA UNIVERSITY CHICAGO

Abstract Text:

DESCRIPTION (provided by applicant): Anemia in burn patients is largely multifactorial requiring multiple transfusions. Emerging evidences around the globe indicate transfusion risks outweigh benefits in the critically ill. Transfusions greater than four units of blood are an independent risk factor for morbidity, mortality and systemic infections in burn patients. Reduced erythrocyte production due to lack of erythropoietin (Epo) could contribute to anemia. Nevertheless, unlike in patients with kidney failure and patients after chemotherapy, Epo administration to burn patients fails to alleviate anemia. Our recent studies demonstrate that resistance to Epo in experimental burn is due to decrease in the number of bone marrow erythroid progenitors and that beta-adrenergic blockade following burn significantly improves the bone marrow erythroid cells. We have also established that burn injury offsets the balance between erythroid specific and monocyte specific transcription factors in multi potent stem cells. Taken together, our overarching hypothesis states that post burn anemia of critical illness is due to impaired erythropoiesis, which is orchestrated by a combination of dysregulated hematopoietic transcription factors and burn environment. We seek to test this hypothesis through the 3 specific aims. In aim 1) we will study the transcriptional regulation of impaired lineage commitments causing anemia of critical illness post burn with and without beta-blockade. First, we will delineate the role of hemopoietic transcription factors MafB and GATA-1 in regulating the impairment of bone marrow erythropoiesis after burns through intervention using loss of function and gain of expression studies and later evaluate the gain of Epo responsiveness after beta-blocker treatment. In aim 2) we will investigate the signaling mechanisms that determine impaired erythroid commitments following burn injury where, the intracellular signaling mediators that inhibit erythroid commitment and promote monocyte commitments will be addressed. We will define the crosstalk between lineage commitment associated cell signals and the catecholamine mediated signals following burn injury in an attempt to restore the erythroid progenitor differentiation in hemopoietic stem and progenitor cells. In aim 3) we will interrogate temporal and mechanistic defects during erythropoietic development in burn patients and evaluate the efficacy of beta-blockade where we will establish that PBMC derived erythroid progenitors and the sequential distribution of erythroblast sub sets are disrupted following burn as a read out to bone marrow erythropoiesis. Next, we will evaluate the balance between MafB and GATA-1 expressions and the signaling mechanisms that dictate PBMC derived CD34+ hematopoietic stem cells and erythroid progenitors from burn patients with and without beta-blockade. Results gleaned from the experimental model combined with clinical data will provide the mechanistic insight into post burn anemia, which will pave the way for potential therapeutic interventions to treat anemia of critical illness.

Project Number:	5R01DK099317-02	**Contact PI / Project Leader:**	NAKAYAMA, MAKI
Title:	MOLECULAR DISSECTION OF INSULIN TARGETING IN ANTI-ISLET AUTOIMMUNITY	**Awardee Organization:**	UNIVERSITY OF COLORADO DENVER

Abstract Text:

DESCRIPTION (provided by applicant): The major histocompatibility complex (MHC) class II locus is strongly associated with the risk of type 1 diabetes, and tissue specificity of the autoimmunity causing diabetes is likely to be determined by the trimolecular complex composed of an MHC molecule, an antigen, and a T cell receptor (TCR). We hypothesize that the interactions between components of this trimolecular complex, all of which are encoded in the germline, determines the nature of T cells involved in the development of type 1 diabetes. Targeting of an insulin B chain 9-23 amino acid peptide (insulin B:9-23) is highly likely to be an essential determinant in the initiation of islet inflammation in the spontaneous diabetes animal model, NOD mouse. We recently discovered that TCRs containing the germline-encoded variable gene (Vgene) sequence called "TRAV5D-4" play a critical role to induce anti-islet autoimmunity via the recognition of insulin B:9-23 peptide. Thus, the trimolecular complex consisting of the insulin B:9-23 peptide and TRAV5D-4 TCR alpha chain plays a key role in developing anti-islet autoimmunity; however, how T cells expressing TRAV5D-4 TCRs contribute to the initiation and development of the disease remains to be elucidated. Given evidence that the DQ8 diabetes- susceptible HLA class II molecule is an ortholog of NOD I-Ag7 presenting the insulin B:9-23 peptide and that T cells expressing TRAV13-1 (human ortholog of TRAV5D-4) TCR alpha chains dominantly exist in the pancreas of a type 1 diabetes patient having DQ8, the ultimate goal of this proposal is to verify a proof of concept that insulin targetig by a specific germline-encoded TCR Vgene motif plays a critical role in the development of islet autoimmunity. In this proposal, we aim to determine the molecular mechanism of how TCRs, in particular those containing TRAV5D-4, target the critical peptide, insulin B:9-23, to initiate isle inflammation using the NOD mouse model (Aim 1), and to determine whether T cells expressing TRAV5D-4 are essential for diabetes development in NOD mice (Aim 2). If the development of anti-islet autoimmunity is completely suppressed in the absence of TRAV5D-4, targeting only T cells expressing such essential TRAV genes will enable us to develop a robust immunotherapy with the minimum of side effects. Finally, we will pursue the hypothesis that there is a conceptually similar interaction in the human trimolecular complex consisted of the insulin B:9-23 peptide and TRAV13-1 TCR Vgene motif underlying susceptibility to human type 1 diabetes (Aim 3). Findings from this proposal will provide a deeper understanding of the principles underlying the initiation of islet autoimmunity via the interaction within the insulin trimolecular complex, which will ultimately to be applied to design antigen-based immunodiagnostic and immunotherapeutic clinical studies for type 1diabetes in humans!

Project Number:	5R01DK094841-03	**Contact PI / Project Leader:**	NEELON, SARA ELIZABETH
Title:	EARLY CHILD CARE AND RISK OF OBESITY	**Awardee Organization:**	DUKE UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): The need to prevent childhood obesity extends down to our youngest children. Obesity and excessive weight gain in the first year of life are independently associated with higher blood pressure, recurrent wheezing, higher hospital admission rates, and other adverse physical and psychosocial health conditions in childhood. Thus, effective approaches to obesity prevention in early childhood are needed. Because nearly two-thirds of U.S. children under 6 years of age are routinely cared for outside of the home, organized child care is an important setting for obesity prevention. Recent studies suggest that children who attend child care are more likely to be obese than children cared for at home by a parent or other caregiver, and younger children might be most at risk. Our own research found that infants who spent time in child care during the first 6 months of life were heavier at one yea and still heavier at 3 years of age than children cared for at home. These previous studies identified a relationship between child care and obesity, but failed to pinpoint specific causal pathways. The proposed longitudinal study will examine factors contributing to the development of obesity that may be influenced by the child care setting, including dietary behaviors, physical activity and inactivity, stress, and sleep duration and quality. To accomplish these aims, we propose a diverse southern cohort of 800 black, white, and Latino/a infants in various child care arrangements, followed regularly from birth to 12 months of age. Frequent in-home assessments throughout infancy will help pinpoint exactly when children begin to gain weight excessively and will identify risk factors related to energy intake, energy expenditure, stress, and sleep associated with obesity. To mitigate participant burden and enhance retention, we will use Interactive Voice Response (IVR) technology to supplement in-person visits through innovative telephone-administered assessments with parents and child care providers. Results of this study will provide new information on the relationship between child care attendance and obesity and may help determine causality in instances where the associations between these variables have been unclear. Findings will inform state and federal policy governing child care settings and will also guide intervention efforts to help prevent obesity in young children in chil care.

Project Number:	5R01DK095233-03	**Contact PI / Project Leader:**	NEWTON, ROBERT LEE
Title:	AEROBIC PLUS RESISTANCE TRAINING TO INCREASE INSULIN SENSITIVITY IN AFRICAN AMERI	**Awardee Organization:**	LSU PENNINGTON BIOMEDICAL RESEARCH CTR

Abstract Text:

DESCRIPTION (provided by applicant): To date, there has not been a large-scale, randomized, controlled study examining the benefits of exercise training the diabetes risk factor, mainly insulin resistance, in African American males. National standardized estimates show that between 15% and 20% of all African Americans aged twenty and older have diabetes (including both diagnosed and undiagnosed). Regular physical activity is a modifiable risk factor for the development of diabetes. Although it has been shown that exercise training results in a reduction of diabetes in Caucasian adults, it cannot be assumed that the benefits derived in Caucasian adults apply to men of other ethnic groups. These types of studies are typically conducted at the university setting, which can be a barrier for African American participants compared to a community-based program. Therefore, we proposed to a randomized community-based trial assessing the effect of regular exercise on risk factors for diabetes in an exclusively African American male cohort. This proposal is entitled Aerobic Plus Resistance Training to Increase Insulin Sensitivity in African American Men (ARTIIS). The study group will consist of sedentary, healthy African American men aged 35 to 70 years. At this age group, we are recruiting men who are at the highest risk of developing diabetes and therefore, the group who is likely to benefit from an exercise program. Males in the exercise training group will engage in 150 minutes of aerobic activity, as well as 2 days of strength training. The target exercise intensity is 50-70% of VO2 max (aerobic) and 50-80% of 1RM (strength). This exercise dose is consistent with the current national physical activity recommendations, and therefore, ARTIIS will assist in determining if the current recommendations result in health benefits for African American males. We recognize that African American males are a difficult-to-reach population. In order to ensure successful participation we will utilize community-based fitness facilities to deliver the program. Thus males in the exercise training group will be able to exercise in their community. Primary outcome measures are risk factors for diabetes including insulin response to a glucose load, fasting insulin, and c-peptide. Secondary outcomes are cardiovascular fitness, muscular strength, body weight and composition, and psychological outcomes.

Project Number:	5R01DK089182-04	**Contact PI / Project Leader:**	NUNEMAKER, CRAIG S.
Title:	LOW-GRADE INFLAMMATION, CYTOKINES, AND BETA-CELL DYSFUNCTION IN TYPE 2 DIABETES	**Awardee Organization:**	UNIVERSITY OF VIRGINIA

Abstract Text:

DESCRIPTION (provided by applicant): The long-term goal of this research is to identify the early mechanisms of pancreatic beta-cell dysfunction in development of diabetes. Evidence suggests that inflammation, mediated by at least in part by cytokines, is a key component in both type 1 diabetes (T1D) and type 2 diabetes (T2D). In T1D, the current consensus is that cytokines produced locally within the islets at very high doses by immune cells play a critical role in the destruction of pancreatic beta cells. In T2D, circulating cytokine levels are elevated early in the development of the disease due to low-grade systemic inflammation. However, circulating cytokine levels associated with low- grade systemic inflammation are ~100-1000x lower than seen within the islet during direct immune cell infiltration associated with T1D. To date, the effects of these low-level cytokines on beta-cells have not been systematically examined, particularly in models of obesity and T2D. Our preliminary data show for the first time that specific cytokine combinations, present at concentrations found in the blood of obese and diabetic individuals, are sufficient to induce excess basal intracellular free calcium, reduce endoplasmic reticulum (ER) calcium storage, and impair insulin secretion in pancreatic islets. Furthermore, these cytokine effects are more severe in islets from pre-diabetic db/db mice, a mouse model of T2D. The hypothesis for this proposal is that circulating cytokines at concentrations typical of low-grade systemic inflammation directly cause beta-cell dysfunction by disrupting intracellular calcium handling in diabetes-prone individuals. Using molecular, electrophysiological, and imaging-based approaches, we will test this hypothesis by addressing three specific aims: (I) Compare the effects of low-grade inflammation on islet calcium handling and markers of cell stress in islets from normal and diabetes-prone mice, (II) Determine the cellular sites of cytokine-induced dysfunction in beta-cells, (III) Determine the in vivo effects of low-grade inflammation in normal vs. diabetes-prone or obese mice. Collectively, these studies will elucidate novel aspects of cytokine action at concentrations present in the systemic circulation in obese and diabetic individuals. Identifying early stages in cytokine-mediated beta-cell dysfunction will open new avenues of therapeutic intervention to prevent beta-cell dysfunction in early T2D.

Project Number:	5R01DK091353-04	**Contact PI / Project Leader:**	OLUMI, ARIA F.
Title:	REDUCED LEVELS OF 5-ALPHA REDUCTASE 2 IN ADULT PROSTATE TISSUE AND BPH THERAPY	**Awardee Organization:**	MASSACHUSETTS GENERAL HOSPITAL

Abstract Text:

DESCRIPTION (provided by applicant): 5-1 reductase 2 inhibitors are commonly used for medical management of patients with obstructive uropathy secondary to benign prostatic hyperplasia (BPH). Finasteride, the most commonly used 5-1 reductase inhibitor, is prescribed to 8.2 million American men. Based on our preliminary results, we estimate that 2.37 million of those men are resistant to its therapeutic action, because they do not express its intended target enzyme, 5-1 reductase 2, accounting for $640 million in annual health care spending. Despite its common use, mechanisms accounting for resistance to Finasteride are not understood. To explore why some patients are resistant to the widely used 5-1 reductase type 2 inhibitor, we evaluated the degree of expression of 5-1 reductase 2 in human prostate tissues. We found that there is a wide variability of expression of 5-1 reductase 2 in human prostate samples with 30% of different samples lacking expression of the protein. Since methylation of the CpG dinucleotide islands in the promoter region of genes has been associated with regulation of genes, we investigated whether the 5-1 reductase gene contains CpG islands. We found that the 5-1 reductase 2 promoters contains a rich CpG island and in fact the CpG island is methylated in many prostate cell lines which do not express 5-1 reductase 2. In addition, there is a strong correlation between methylation of 5-1 reductase 2 promoter regions and absence of 5-1 reductase 2 in human prostate samples. Therefore, we hypothesize that methylation of the promoter region of 5-1 reductase 2 gene is associated with reduced expression of the protein, which can lead to stagnant or suppressed prostatic growth in adulthood, and possibly accounting for resistance to 5-1 reductase 2 inhibitor therapies. This clinical study is designed to explore the heterogeneous growth pattern of adult human prostates as related to expression of 5-1 reductase 2, and to evaluate the mechanisms of resistance to 5-1 reductase 2 inhibitions. The specific aims are: Specific Aim #1. To determine whether methylation of 5-1 reductase 2 promoter region is associated with repression of 5-1 reductase 2 protein in human prostate tissue. Specific Aim #2. To determine whether methylation of 5-1 reductase 2 promoter is associated with decreased prostatic growth rates. Specific Aim #3. To determine whether methylation of 5-1 reductase 2 promoter and reduced expression of 5-1 reductase 2 is associated with resistance to Finasteride in management of BPH. Our proposal is well-aligned with NIH/NIDDK's Prostate Research Strategic Plan. The findings will have broad implications for chronic use of 5-1 reductase 2 inhibitors for BPH, and also in newly suggested strategies for chemoprevention of prostate cancer. Recognition of mechanisms that regulate expression of 5-1 reductase 2 will lead to identification of newer compounds and better targeted therapies for BPH and reduce the rates of invasive therapies for this benign condition.

Project Number:	1R01DK100868-01	**Contact PI / Project Leader:**	OOTTAMASATHIEN, SIAM
Title:	TREATMENT OF BLADDER PAIN BY NOVEL GLYCOSAMINOGLYCAN DERIVATIVES	**Awardee Organization:**	UNIVERSITY OF UTAH

Abstract Text:

PROJECT SUMMARY/ABSTRACT Interstitial cystitis (IC)/painful bladder syndrome (PBS) is a debilitating chronic urologic condition. Over 3 million women above the age of 18 in the U.S. suffer from unrelenting pelvic pain, significant urinary symptoms, recurring urinary infection, bladder fibrosis, and renal failure. In 2007, the cost and disease burden associated with IC/PBS was analyzed by the Urologic Diseases in America Project and found to exceed $750 million annually. We have developed a mouse model of inflammatory cystitis utilizing LL-37, a natural anti-microbial peptide produced in the genitourinary system. Our model recapitulates key aspects of IC/PBS including the induction of profound bladder inflammation, production of bladder-specific pain, urothelial cell injury, glycosaminoglycan (GAG) layer dysfunction, and accumulation of mast cells. To further establish the physiologic relevance of LL- 37 induced cystitis, our group has shown that human urinary LL-37 levels were significantly elevated in pediatric spina bifida patients. In addition within our mouse model, we've demonstrated LL-37 could elicit profound dose dependent bladder inflammation involving the urothelium. Furthermore, the propagation of inflammation involves mast cells in a dose dependent fashion. Mast cells have been well described to be a central cell type mediating pain in patients with IC/PBS. The exact role of mast cell mediated bladder pain in LL-37 induced cystitis remains unclear and will be further investigated in the proposed research. We hypothesize that LL-37 induced cystitis pain intimately involves mast cells. This hypothesis will be tested in Specific Aim 1, by elucidating mast cells as a key effector cell type utilizing our surrogate model. From a therapeutic standpoint, our group has developed novel patented compounds known as semi-synthetic glycosaminoglycan ethers (SAGEs) that attenuates the inflammatory effects of LL-37 by direct immune modulation and interference with mast cell activation. Our preliminary data suggests treatment with SAGE compounds truncates both inflammation and pain observed in LL-37 induced cystitis. The exact mechanism behind how our SAGEs inhibit mast cell derived bladder pain remains unclear and will be further investigated in the proposed research. We hypothesize that mast cell mediated cystitis pain can be attenuated with SAGE compounds. This hypothesis will be tested in Specific Aim 2, investigate SAGE attenuation of mast cell mediated bladder pain. This integrated proposal is innovative with high impact because it will further define mast cell driven cystitis pain and provide detailed knowledge about the pain attenuation properties of our SAGE compounds. These data also provide significant opportunity with a high likelihood of success to further develop novel SAGE compounds as potential pharmaceutical interventions to attenuate not only inflammation associated with IC/PBS but inhibit mast cell mediated bladder pain.

Project Number:	5R01DK096263-03	**Contact PI / Project Leader:**	PASK, ANDREW J
Title:	NEW PLAYERS IN URETHRAL CLOSURE; DEFINING THE ROLE OF A NOVEL LONG NONCODING RNA	**Awardee Organization:**	UNIVERSITY OF MELBOURNE

Abstract Text:

DESCRIPTION (provided by applicant): Hypospadias (the abnormal placement of the urethral opening) is one of the most common birth defects in the USA, affecting approximately 1 in every 140 live male births. Despite its high incidence, relatively little is known about the causes of this common disease. A few genes have been isolated that predispose the penis to hypospadias. However, genetic causes alone cannot explain a doubling in the reported rate of hypospadias in the USA between 1970-1993. Since inappropriate estrogen exposure or inhibition of androgen signaling have both been shown to induce hypospadias, its increase has been attributed to environmental factors, with environmental endocrine disruptors (EEDs) being prime candidates. Thus, understanding the interplay between hormones and the critical molecular pathways regulating urethral closure is essential to define the causes of hypospadias and potential targets for the clinical management of this disease. In this proposal we will define the function of a novel long noncoding RNA molecule (lnc353) that is necessary for urethral closure in mice. Deletion of lnc353 causes a complete failure of urethral closure resulting in a severe penoscrotal hypospadias, mirroring human severe hypospadias phenotypes. We have shown that lnc353 is flanked by multiple androgen and estrogen receptor response elements suggesting it is under direct hormonal control and a potential target of endocrine disruption. Furthermore, lnc353 is unusually highly conserved in the human genome both at the nucleotide level (>80%) and in its physical location, suggesting an important developmental function. In this proposal we will define the function of lnc353 in urethral closure, its interaction with know and novel penile patterning networks, its hormonal control and potential for endocrine disruption. In future work, we will determine if mutations in lnc353 are associated with severe hypospadias in humans. This work will characterize a critical new player in normal urethral closure and penile development. Our findings will provide much needed information on the genetic and hormonal causes of this common disease and aid in the development of new ways to diagnose and treat this condition. Such studies are fundamental before we can assess clinical management of this disease and the potential reasons for the dramatic increase in hypospadias incidence over recent decades. This research is inline with the missions of the NIH, specifically by Improving the health of the Nation by conducting and supporting research in the causes, diagnosis, prevention, and cure of human diseases; in the processes of human growth and development; and in the biological effects of environmental contaminants.

Project Number:	5R01DK095803-02	**Contact PI / Project Leader:**	QIN, LING
Title:	ROLE OF EGFR SIGNALING IN BONE FORMATION AND THE ANABOLIC ACTIONS OF PTH	**Awardee Organization:**	UNIVERSITY OF PENNSYLVANIA

Abstract Text:

DESCRIPTION (provided by applicant): Intermittent parathyroid hormone (PTH) injection is one of the most effective anabolic treatments for osteoporosis because of its remarkable actions on bone formation. Osteoblasts are derived from mesenchymal progenitors, including mesenchymal stem cells (MSCs) and committed osteoprogenitors. Multiple mechanisms have been proposed to explain how PTH exerts its beneficial effects, but whether these effects include, or are mediated by, a stimulation of bone marrow mesenchymal progenitor activities, is not clear. Our new data support this mechanism by demonstrating the presence of a functionally distinct population of mesenchymal progenitors within the trabecular bone that are very responsive to PTH. PTH strongly stimulates the expression of amphiregulin, an epidermal growth factor receptor (EGFR) ligand, in osteoblasts and osteocytes. EGFR is highly expressed in mesenchymal progenitors and its activation stimulates proliferation, survival, and migration of these cells. Our preliminary data show that blocking EGFR activity in mice leads to defective bone formation and an osteopenic phenotype which are accompanied by a reduction in the number of mesenchymal progenitors. Interestingly, conditioned media from PTH-treated osteoblastic cells chemoattract mesenchymal progenitors in an amphiregulin-EGFR-dependent manner. Moreover, mice with deficient EGFR activity in osteoblast lineage cells have a poor anabolic response to PTH injection. These and other data lead to our central hypothesis that EGFR signaling is an essential regulator of bone marrow mesenchymal progenitors and mediates at least in part the anabolic effects of intermittent PTH administration. We will test our central hypothesis by pursuing the following aims: 1) investigate whether EGFR inactivation in MSCs inhibits bone formation and the anabolic response to PTH by assessing skeletal phenotypes of conditional EGFR knockout mice with a nestin promoter-driven inducible Cre with or without PTH treatment; 2) elucidate whether EGFR plays a critical role in maintaining the bone marrow mesenchymal progenitor population under conditions of normal and PTH-induced bone formation. We will use animal models with deficient EGFR activity in mesenchymal progenitors at different stages of lineage commitment to investigate the relationship between EGFR activity and mesenchymal progenitor populations residing in different regions of the long bone. We will also use cell culture approaches to determine whether a group of transcription factors, Egrs, mediates and regulates EGFR-stimulated proliferation and survival of mesenchymal progenitors; 3) determine whether EGFR signaling activated by PTH injection recruits mesenchymal progenitors toward the bone surface by using an in vivo transplantation approach, in which GFP-labeled mesenchymal progenitors can be visualized. Completion of these three aims will enable us to determine for the first time the role of EGFR in bone formation and the anabolic response of bone to the osteoporosis therapy PTH. Long-term, we seek to determine whether we can target EGFR signaling as a novel anabolic strategy to treat osteoporosis and other bone-related diseases.

Project Number:	5R01DK096982-02	**Contact PI / Project Leader:**	REEDS, DOMINIC N
Title:	TAUROURSODEOXYCHOLIC ACID FOR PROTEASE-INHIBITOR ASSOCIATED INSULIN RESISTANCE	**Awardee Organization:**	WASHINGTON UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): The introduction of protease-inhibitor based antiretroviral therapy (PI-ART) has reduced the mortality associated with HIV infection (HIV+). Unfortunately, PI-ART use is a major risk factor for insulin resistance, an important risk factor fr diabetes and coronary heart disease (CHD). Tauroursodeoxycholic acid (TUDCA), a naturally occurring bile salt, improves insulin sensitivity in insulin resistant people who do not have HIV. We have found that TUDCA markedly ameliorates ritonavir-induced insulin resistance in human myotubes and mice. The mechanism(s) responsible for these TUDCA-induced metabolic improvements are unclear, but could be related to: 1) TGR5 receptor activation, which upregulates cellular factors in muscle, including type 2 deiodinase (which increases intracellular triiodothryonine) and PGC-1 that increase mitochondrial biogenesis and fatty acid oxidation and/or 2) acting as chaperones that reduce endoplasmic reticulum (ER) stress by assisting protein folding. Initiation of ritonavir-boosted PI-ART worsens insulin sensitivity in HIV+ people and induces markers of ER stress in adipose tissue. We propose to perform a double-blind, randomized, controlled trial to determine if TUDCA improves insulin sensitivity in insulin-resistant, HIV+ people receiving PI-ART and to clarify the molecular mechanisms responsible for these improvements. We will randomly assign 48 insulin- resistant, HIV+ subjects to either placebo or TUDCA (1.75g/day x 30 days) and will measure multi-organ insulin sensitivity before and after the intervention by using a multistage hyperinsulinemic euglycemic clamp with infusion of stable isotope labeled tracers. To clarify the mechanisms responsible for the anticipated improvements in insulin sensitivity, we will examine the effect of TUDCA on TGR5 activation (type 2 deiodinase expression) in skeletal muscle biopsies and on ER stress by measuring Grp78 in adipose tissue biopsies taken before and after TUDCA administration. The results from this study will determine not only whether TUDCA may be effective for treatment of PI-associated insulin resistance but is also expected to identify new pathways by which TUDCA exerts insulin sensitizing effects. In addition to improving clinical care of people with HIV, the findings of this study may allow development of new drugs for treatment of type 2 diabetes.

Project Number:	5R01DK094886-03	**Contact PI / Project Leader:**	RO, SEUNGIL
Title:	ROLES OF DNA METHYLATION IN GASTROINTESTINAL SMOOTH MUSCLE CELLS	**Awardee Organization:**	UNIVERSITY OF NEVADA RENO

Abstract Text:

DESCRIPTION (provided by applicant): Gastrointestinal (GI) neuromuscular disorders (motility disorders) are characterized by dysfunctions of three types of key cells: interstitial cels of Cajal (ICC), enteric nervous system (ENS), and smooth muscle cells (SMCs), which cooperatively control SM motility in the GI tract. ENS and ICC generate complex rhythmic motor behavior and spontaneous electrical slow waves, respectively, both of which control SMCs, the final effectors for muscle contraction and muscle relaxation. Although there has been a significant amount of work investigating the effects of ENS and ICC dysfunction in GI motility disorders, the dysfunction of SMCs has received much less attention. The gap in the knowledge of SMC dysfunction needs to be addressed, since the three types of cells are physically associated and functionally working together: dysfunction of one cell type can affect the other two. This present project seeks to uncover a molecular mechanism for understanding how SMCs are remodeled during the development of GI motility disorders. We have recently reported that GI SMCs require microRNAs (miRNAs) for the development and survival of animals, and that the phenotypes of GI SMCs are controlled by serum response factor (SRF)-dependent microRNAs. In addition, our preliminary study suggested that the phenotypic change (hypertrophy) of SMCs is linked to dysregulation of a unique set of SRF-dependent miRNAs which are regulated by epigenetic DNA methylation. To study this new molecular mechanism, we generated six transgenic animal models that display abnormal phenotypes of SMCs during the embryonic and post-natal development of the cells. In this project, we propose three specific aims: define the roles of SRF-dependent miRNAs during the development of GI SMCs, define the roles of DNA methylation during the development of GI SMCs, and discover the roles of DNA methyltransfertase (Dnmt1)-targeting miRNAs that regulate GI SMC hypertrophy. Completion of the specific aims of this project will provide an exciting new mechanism for understanding how the SRF-dependent miRNA genes are epigenetically reprogrammed in the SMCs of GI neuromuscular disorders. Identifying the epigenetic changes will aid not only in the development of a diagnostic tool for hypertrophy-related diseases, but also of a therapeutic target that has the potential to reverse the epigenetic changes that are responsible for these pathological conditions, and thus possibly reverse some of the unwanted pathological changes that occur in these disorders.

Project Number:	5R01DK093729-03	**Contact PI / Project Leader:**	SANTY, LORRAINE C.
Title:	CYTOHESIN DEPENDENT ARF TO RAC SIGNALING IN HGF MEDIATED MOTILITY	**Awardee Organization:**	PENNSYLVANIA STATE UNIVERSITY-UNIV PARK

Abstract Text:

DESCRIPTION (provided by applicant): Acute kidney injury is a common hospital complication that leads death or long-term kidney damage if recovery is not complete. Hepatocyte growth factor (HGF) promotes the recovery from kidney damage at multiple steps. While many of the proximal signals activated by HGF and the downstream targets that remodel cell shape in response to HGF are known, the details of the circuits that link them together are unclear. This limits the possibility of selectively modulating HGF signaling without impacting the actions of other growth factors. Work in the applicant's lab has recently demonstrated that protein- protein interactions are critical for building a pro-migratory circuit that links activatin of Arf6 by cytohesin-2 to the downstream activation of Rac by Dock180. Preliminary data suggest that this signaling circuit is required for HGF-stimulated Rac activation and migration. The overall objective of this application is to determine the molecular details of this cytohesin-dependent Arf-to-Rac signaling module and to test the degree to which it mediates HGF-induced motility and the recovery from acute kidney injury. This is the next step toward the long-term goal of understanding the initiation of motility in epithelial cells by small GTPase cascades. This application will test a hypothesized model for the cytohesin-dependent Arf-to-Rac signaling module. This module will be tested by pursuing 4 specific aims: 1) Determine how cytohesin-2 activity is controlled; 2) Determine the mechanism of interaction of cytohesin-2 and Dock180 and test the degree to which this interaction mediates HGF dependent Rac activation; 3) Determine the role of active Arf6 in cytohesin-dependent Rac activation; 4) Determine the extent to which cytohesin-dependent Rac activation regulates HGF-stimulated wound healing and recovery of the kidney from ischemia reperfusion injury. Aim 1 will test the hypothesis that cytohesin-2 intramolecular interactions prevent its interaction with membranes until these interactions are disrupted by phosphorylation. Aim 2 will use mutagenesis to identify the regions necessary for the interaction of the cytohesin-binding scaffold GRASP with Dock180. The importance of this interaction for HGF- induced Rac activation will be tested using knockdown of GRASP and expression of GRASP mutants. Aim 3 will test the hypothesis that Arf6-dependent lipid modifications promote activation of Rac by Dock180. Aim 4 will use siRNA, mutant and pharmacologic modulation of cytohesin-dependent Arf-to- Rac signaling to test its involvement in HGF-stimulated wound healing and recovery of the kidney from ischemia reperfusion injury. A proven model of this pro-migratory circuit will allow the design of interventions to modulate this circuit without impacting other Arf6 or Rac-dependent functions. Such treatments could promote or inhibit HGF-dependent migration without disrupting the actions of a broad range of growth factors.

Project Number:	5R01DK096008-02	**Contact PI / Project Leader:**	SEGEV, DORRY
Title:	LONG-TERM HEALTH OUTCOMES AFTER LIVE KIDNEY DONATION IN AFRICAN AMERICANS	**Awardee Organization:**	JOHNS HOPKINS UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Every year, over 6000 healthy individuals donate a kidney in the United States to benefit a loved one or even a stranger. Currently, approximately 100,000 individuals are living post-nephrectomy. Live kidney donors gain no medical benefit from donation, nor do they expect to. However, live donors do expect the medical community to understand the long-term risks of kidney donation, for the purposes of donor selection, informed consent, and post-donation care. For African American kidney donors, we have thus far failed in this regard. The largest cohort study of kidney donors, from which the transplant community's assessment of the safety of kidney donation has been primarily derived, was comprised of less than 1% African American donors. Yet 13% of live donors in the US are African American, and our preliminary findings suggest that rates of death, hypertension, chronic kidney disease, and end-stage renal disease following donation are significantly higher in African Americans. It is critical to not only estimate the risk of these diseases, but to understand the risk attributable t donation; however, no study to date has captured appropriate non-donor controls that are necessary for this estimation. Furthermore, many African American donors, particularly young donors, have limited access to healthcare, and it is important to elucidate potential disparities i the management of post- donation consequences such as hypertension and decline in kidney function. In light of a significant knowledge gap regarding long-term outcomes and medical care following kidney donation in African Americans, we propose to estimate the incidence and consequences of hypertension and kidney disease in African American versus Caucasian donors. More importantly, we will determine how much of that risk is attributable to donating a kidney (rather than population-based differences in underlying risk) by comparing donors to healthy non-donors. We will also evaluate the reliability of administrative data sources in capturing and studying post-donation morbidity, and seek to better understand racial differences in treatment patterns for donors who develop hypertension or chronic kidney disease. We will accomplish these goals by recruiting the largest primary cohort of African American donors (over 4000 donors from the top 13 centers in the US), a comparison cohort of Caucasian donors, and healthy non-donors who met eligibility criteria for donation but did not actually donate. We will supplement these cohort with linkage of national registry data to Medicare, Medicaid, and private payer claims and pharmacy data. Our findings will have a direct impact on the practice of live kidney donation among African Americans in the US, informing critical aspects of donor selection, informed consent for donation, and post-donation care. In addition, this research will create an important resource from which several future ancillary projects are foreseeable, including genotyping to risk stratify potential donors, evaluating the effects of acut kidney injury and nephrotoxic drugs after donation, and estimating lifetime healthcare costs and utilization for kidney donors.

Project Number:	5R01DK088902-04	**Contact PI / Project Leader:**	SINGH, AMAR B
Title:	ROLE OF CLAUDIN-2 IN INFLAMMATORY DISEASES AND COLON CANCER	**Awardee Organization:**	VANDERBILT UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Increased mucosal permeability is a key characteristic of the inflammatory bowel disease (IBD). The claudin family of proteins constitutes the tight junctions (TJs), which are the sole determinants of the paracellular permeability in an intact epithelium. Importantly, a common finding from the analysis of the IBD (Crohn's and Ulcerative Colitis) patient samples and related animal models is that claudin-2 expression is highly upregulated in the IBD. In the claudin family, Claudin-2 is unique as its expression correlates with the epithelial leakiness. However, it is also noteworthy that the colonic claudin-2 is expressed among the undifferentiated colonocytes at the crypt base, the proliferative zone. Furthermore, outcome from our preliminary studies and recently published studies from other labs suggest potential correlation of claudin-2 expression with the colonic epithelial cell proliferation and/or migration. It is further noteworthy that claudin-2 is a target of the Wnt/β-catenin signaling. However, role of claudin-2 in the pathogenesis of IBD is not known. To investigate, we generated Villin-claudin-2 transgenic (Cl-2Tg) mice that overexpress claudin-2 in the colon, a condition similar to the IBD. Our studies using these mice have provided novel outcomes: 1) Colonic epithelial permeability in Cl-2Tg mice is significantly increased compared to the WT littermates ($p<0.05$); 2) the colon and crypt lengths in Cl-2Tg mice are significantly increased compared to the wild type (WT) littermates ($p<0.001$ for both); and 3) Cl-2Tg mice are significantly protected from experimental-colitis [induced using dextran sodium sulfate (DSS, 4% w/v in drinking water)] compared to WT littermates ($p<0.001$). Our further data show sharp decreases in the DSS-induced expressions of proinflammatory cytokines including IL-1α, IL- 1β, TNF-α in Cl-2Tg mice compared to the WT littermates. On the other hand, gene expressions related with proliferation were upregulated in the DSS-treated Cl-2Tg mice compared to the DSS-treated WT littermates. Taken together, we postulate that claudin-2 plays an important role in the regulation of colonic homeostasis. We further hypothesize that immune adaptation/tolerance due to the constitutive increase in the mucosal permeability and/or modulations of the colonic epithelial cell proliferation/apoptosis or combination of both underlie the protection from DSS-colitis in Cl-2Tg mice. To test our hypothesis, we have proposed following specific aims: 1) To determine whether claudin-2 TG mice are protected against mucosal inflammation and disease; 2) To determine the role of claudin-2 in colitis-associated regeneration, repair and colitis-associated cancer; and 3) To determine the cellular and molecular mechanism/s underlying protection from colitis in claudin-2 TG mice. We anticipate that our studies will provide valuable and clinically relevant information that will have direct impact upon the understanding of the regulation of IBD pathogenesis and its progression to cancer, and will create potential new opportunities for therapeutic interventions.

Project Number:	5R01DK093462-04	**Contact PI / Project Leader:**	SISKIND, LEAH J
Title:	ROLE OF CERAMIDE-INDUCED KIDNEY CELL DEATH IN ACUTE KIDNEY INJURY	**Awardee Organization:**	UNIVERSITY OF LOUISVILLE

Abstract Text:

DESCRIPTION (provided by applicant): Acute kidney injury (AKI) is a devastating disease with a high mortality rate. Apoptosis and necrosis play major roles in AKI, but there is a fundamental knowledge gap of the factors regulating their induction in AKI. Continued existence of this gap represents a significant problem as AKI has a high mortality rate and there are very few therapeutic interventions to alter the clinical course of this disease. The long-term goal is t uncover mechanisms involved in AKI for the development of novel therapeutics to protect the kidney. Ceramides regulate apoptosis and necrosis and are elevated in the kidney in several models of AKI. The factors that regulate production of ceramides during kidney apoptosis and necrosis and whether ceramides lead to apoptotic versus necrotic kidney cell death are completely unknown. Likewise, there are many different ceramide species and the roles for particular ceramide species in AKI have not been determined. This proposal will answer these questions to achieve the objective of developing ceramides as novel therapeutic approaches for the treatment of AKI. Preliminary data demonstrate that: (i) long-chain ceramides (C16 - C20- ceramides) are generated via de novo synthesis during kidney cell apoptosis and blocking their generation inhibits apoptosis; (ii) the pro-apoptotic BCL-2 protein BAK is a key regulator of ceramide synthases (CerS) and long-chain ceramide generation during kidney cell apoptosis; (iii) acid sphingomyelinase (aSMase) generated very long-chain ceramides (C24-C26-ceramides) occurs in kidney cell necrosis; (iv) kidney cortical CerS and acid SMase are activated and specific ceramides elevated several-fold in in vivo rodent models of AKI (cisplain nephrotoxicity and rhabdomyolysis-induced AKI); and (v) mice given inhibitors of enzymes responsible for ceramide synthesis are protected from cisplatin-induced AKI. This expanding and developing body of work has led us to propose the following hypothesis: nephrotoxic stimuli elevate specific species of kidney ceramides through CerS and SMase-mediated pathways, inducing kidney cell death and ultimately kidney failure. This hypothesis will be tested with three specific aims: (1) determine the mechanism by which BAK regulates CerS activity and generation of specific long-chain ceramides during kidney cell apoptosis; (2) determine the contribution of SMase-generated ceramide to kidney cell necrosis; and (3) determine the in vivo contribution of CerS and aSMase to cisplatin-induced AKI in mice. The approach is innovative because it will identify the mechanism by which BAK regulates ceramide synthases as well as the specific role of individual ceramide species in vivo in AKI. The proposed research is significant as it advances our current knowledge of mechanisms of kidney cell death AKI. Ultimately such knowledge has the potential to greatly improve the treatment of AKI.

Project Number:	5R01DK095804-02	**Contact PI / Project Leader:**	SRINIVASAN, SUPRIYA
Title:	G PROTEIN-MEDIATED INTEGRATION OF OXYGEN SENSING AND ENERGY BALANCE IN C. ELEGANS	**Awardee Organization:**	SCRIPPS RESEARCH INSTITUTE

Abstract Text:

DESCRIPTION (provided by applicant): Sensory perception plays an important role in maintaining energy balance and normal body fat content. Despite its significance, there is a major gap in our understanding of the molecular mechanisms that link specific sensory modalities, to energy balance circuits in the brain. Our long-term goal is to identify the molecula mechanisms that integrate sensory signals in the nervous system with intrinsic cues to regulate body fat, and the defects in this process that lead to obesity. The objective of the proposed research is to determine the role of the Gα protein GPA-8 in C. elegans, a powerful and tractable model system for the study of energy balance circuits. GPA-8 is homologous to the mammalian α-gustducin Gα protein, and is expressed in oxygen-sensing neurons in C. elegans. The central hypothesis of the proposed research is that GPA-8 signaling from sensory neurons integrates oxygen sensing with body fat content. We expect that understanding the mechanism of action of GPA-8 in C. elegans will be a critical step toward identifying the neural circuits and conserved molecular mechanisms by which oxygen sensation in the nervous system influences body fat content. Our Specific Aims are to: I. Identify the GPA-8-expressing neurons that regulate body fat. Using neuron-specific promoters, we will restore GPA-8 expression in subsets of neurons in gpa-8 mutant animals to define the precise anatomical sites of GPA-8 action in regulating body fat. II. Define the intracellular mode of action for GPA-8. GPA-8 is a Gα protein suggesting that loss of G protein signaling in oxygen-sensing neurons regulates body fat. We will test the effects of loss of G protein activation cycle genes specifically in oxygen-sensing neurons, to determine the intracellular mode of action of GPA-8. III. Determine the mechanisms of integration of oxygen sensation with fat stores. We will test a candidate genetic pathway involved in cGMP signaling and in oxygen-sensing for changes in body fat under different oxygen concentrations, to delineate the neural mechanisms underlying the integration of oxygen-sensing and body fat content. With respect to expected outcomes, the completion of the proposed work will enable the first insights into the neural circuits and molecular mechanisms that connect oxygen-sensing in the nervous system, with body fat content. Importantly, our findings will allow us to identify signaling paradigms underlying the gut-brain axis that controls energy balance. Because all of the genes under study have clear mammalian orthologs, our contribution here will have a positive impact on rapidly identifying new molecular targets for combating obesity and its associated illnesses. The proposed research is significant because a molecular connection between neural oxygen sensing and body fat content provides a new dimension to our understanding of organismal energy balance and the causes underlying obesity.

Project Number:	5R01DK098542-02	**Contact PI / Project Leader:**	STEGER, DAVID J.
Title:	TRANSCRIPTIONAL AND EPIGENOMIC CONTROL OF ADIPOSE TISSUE DEVELOPMENT AND FUNCTION	**Awardee Organization:**	UNIVERSITY OF PENNSYLVANIA

Abstract Text:

DESCRIPTION (provided by applicant): A major goal of this research is to understand the complex interplay between transcription factors and epigenomic modification that regulates gene expression programs establishing and maintaining adipocyte cells. We recently identified the glucocorticoid receptor (GR) and CAAT/enhancer binding protein β (CEBPβ) as critical transcriptional regulators that activate the adipogenic program by co occupying thousands of specific sites in the genome during early adipogenesis. We hypothesize that GRCEBPβ bound regions, the majority of which are positioned far away from active genes, control transcription by forming long-range associations with core promoter elements occupied by the transcription initiation apparatus. Specific Aim 1 will identify GR and CEBPβ direct gene targets and determinants of long-range chromatin interactions on a genome wide scale during mouse adipocyte cell differentiation. Preliminary results from chromatin interaction analysis by paired end tag sequencing (ChIAPET) demonstrate the feasibility of detecting long-range associations for CEBPβ that globally link distal binding sites with regulated genes. Chromatin conformation capture (3C) validates a loop spanning 170 kilobases of DNA, suggesting that the ChIAPET data are robust and informative. Determinants of DNA looping will be examined by gain and loss of function studies targeting sequence specific factors and coregulator activities. Specific Aim 2 will identify on a genome wide scale the GR and CEBPβ adipogenic targets that are conserved between human and mouse. Preliminary chromatin immunoprecipitation sequencing (ChIPseq) results reveal that only a small minority of bound sites is shared in both species, and we hypothesize that comparison of the GR and CEBPβ chromatin interactomes in human and mouse will uncover the direct transcriptional pathways driving adipocyte differentiation. This will be tested by performing ChIAPET for GR and CEBPβ during adipocyte differentiation of human mesenchymal stem cells (hMSCs). Specific Aim 3 will identify GR and CEBPβ direct gene targets on a genomewide scale in mouse adipose and liver tissues. Preliminary ChIPseq results reveal extensive colocalization of GR and CEBPβ in either adipose or liver, but only a minority of bound sites is shared in both tissues. We predict that comparison of the chromatin interactomes from adipose and liver tissues will reveal fundamental mechanisms controlling cell type specific gene expression by GR and CEBPβ in vivo. As a whole, these studies use an innovative approach that will increase understanding of the development and function of adipose tissue, which normally benefits health, yet in excess as in obesity, is a strong risk for metabolic diseases including diabetes, hyperlipidemia, hypertension and heart disease.

Project Number:	5R01DK098398-02	**Contact PI / Project Leader:**	TANG, VIVIAN
Title:	DISRUPTING FSGS1-ASSOCIATED ACTIN ASSEMBLY IN GLOMERULOSCLEROSIS	**Awardee Organization:**	UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN

Abstract Text:

DESCRIPTION (provided by applicant): Interaction of cell-cell adhesion molecules with the actin cytoskeleton is critical for the maintenance and stability of the glomerular filtration barrir formed by the slit diaphragm. Disrupting this interaction is intimately coupled to the initiation o proteinuria and progression of nephrotic syndromes in general. Many forms of glomerulosclerosis including focal and segmental glomerulosclerosis (FSGS) are characterized by reorganization of the actin cytoskeleton resulting in loss of cell-cell adhesion and displacement of the slit diaphragm. Most studies had focused on global regulation of the actin cytoskeleton without considering the possibility that perturbing actin assembly directly at sites o cell-cell adhesion might be the key to disrupting slit diaphragm stability. Recently, we found that FSGS1/α-actinin-4 is required for actin assembly at cell-cell contacts. Furthermore, a mutation of FSGS1/α-actinin-4 K255E that links to a dominant form of FSGS specifically inhibits actin assembly at sites of cell-cell adhesion without compromising the overall actin cytoskeletal organization. Therefore, disruption of actin assembly locally at adhesive contacts might be a convergent pathway that leads to break down of the slit diaphragm filtration barrier. Given the complexity of the slit diaphragm, dissecting the structural-functional relationships of its molecular components would be essential to revealing the mechanism behind development of proteinuria and FSGS. Aim 1. Determine how FSGS1/α-actinin-4 and its disease mutation regulate actin dynamics at membrane adhesion complex. We will use our newly developed reconstitution biochemical assays, in combination with actin reporter assays, to assess the role of FSGS1/α-actinin-4 in actin assembly. First, we will define the molecular function of the wild-type FSGS1/α-actinin-4. Second, we will analyze how to the disease mutant K255E inhibits actin assembly. Lastly, we will develop high throughput assays to screen for inhibitors of K255E mutation. Aim 2. Characterize FSGS1/α-actinin-4-associated actin regulatory machine. We developed a novel target-based crosslinking to identify six proteins in complex with FSGS1/α-actinin-4. We will dissect the molecular and cellular functions of these junctional components using in vitro biochemical and cellular approaches (shRNA and mutant expression) as well as high-resolution imaging techniques. Aim 3. Develop a novel "pressure chamber" apparatus to investigate the role of hydraulic pressure in the development of proteinuria. Actin assembly at cell-cell contacts is necessary for proper cell-cell adhesion to withstand normal and hypertensive pressure. We will use a new "pressure chamber" to perform functional analysis under different hydraulic pressure treatments to elucidate the causative role of disease susceptible genes in the initiation and progression of permeability barrier disruption.

Project Number:	5R01DK084064-04	**Contact PI / Project Leader:**	TAVAKKOLI, ALI
Title:	SURGICAL MODULATION OF INTESTINAL NUTRIENT TRANSPORT	**Awardee Organization:**	BRIGHAM AND WOMEN'S HOSPITAL

Abstract Text:

DESCRIPTION (provided by applicant): Roux-en-Y gastric bypass (RYGB) is the gold standard therapy used in the fight against the worsening obesity and type 2 diabetes mellitus (T2DM) epidemics. An impressive observation has been the rapid resolution of T2DM within days of surgery and before any substantial weight loss. In fact many specialists recommend RYGB as a 'cure' for T2DM. Unfortunately 70% of diabetic patients do not qualify for weight loss surgery based on the current surgical guidelines. We have been intrigued by the observation that RYGB leads to a rapid resolution of T2DM, and to help us develop a less invasive approach that can be offered to a wider population, have focused our attention on the impact of this procedure on the intestinal Na+/glucose cotransporter SGLT1. SGLT1 is a major intestinal transporter that is responsible for most luminal sugar absorption, and is overexpressed in T2DM and obesity. Interestingly, luminal exposure to glucose leads to an acute and profound increase in intestinal SGLT1 expression, referred to as Intestinal Sweet Sensing (ISS). Several studies have confirmed a critical role for duodenal isolation to the success of RYGB, by a mechanism not related to malabsorption. We contend that duodenal isolation, by blunting ISS alters the absorptive capacity of the remaining intestine to delay the temporal appearance of nutrients and gut hormones in the circulation. Thus, the post-RYGB metabolic benefits arise because nutrient influx is slowed without being prevented. To develop a less invasive alternative to blunt ISS, we have targeted vagal afferent fibers. We hypothesize that blunting of ISS by selective vagal deafferentation with capsaicin (a naturally occurring pepper derivative) will rapidly improve glucose homeostasis, similar to RYGB, and lead to resolution of T2DM and weight loss. We will test this in the following aims: 1. Characterize the mechanism for ISS and assess its dysregulation in disease. 2. Assess ISS function and vagal signaling after duodenal isolation by vagus-sparing RYGB. 3. Study the long term effects of vagal deafferentation on weight and glucose homeostasis. We believe that selective vagal deafferentation will modulate intestinal SGLT1 expression and function, and could enhance or possibly replace current surgical interventions for weight loss and T2DM. The ability to reproduce the success of RYGB with a lower morbidity profile would provide immense benefit to numerous individuals at risk.

Project Number:	5R01DK091466-04	**Contact PI / Project Leader:**	THI, MIA M
Title:	EFFECTS OF HIGH GLUCOSE ON BONE CELL MECHANOSENSING, TRANSDUCTION, AND SIGNALING	**Awardee Organization:**	ALBERT EINSTEIN COLLEGE OF MEDICINE

Abstract Text:

DESCRIPTION (provided by applicant): Patients with insulin dependent diabetes mellitus (IDDM; Type 1 diabetes) display higher bone loss and increased risk for osteoporosis and related bone fractures. However, the mechanisms that underlie bone loss in IDDM are still not fully understood. It is well established that bone mass is maintained by bone remodeling, a process that involves formation of new bone by osteoblasts and osteocytes and resorption of existing bone by osteoclasts. Bone remodeling is regulated by mechanical stimuli imposed continuously to the skeleton by physical activity, and proper response of osteocytes/osteoblasts to mechanical loading is thus essential for maintenance of bone function and skeletal integrity. The main goal of this R01 application is to test the novel hypothesis that altered expression of components of bone mechanosensory and transduction systems is a central mechanism leading to bone cell dysfunction and higher bone loss in IDDM. For this we will use comprehensive in vitro studies with bone cell lines that will be uniquely combined with in vivo bone physiology and in situ bone tissue analysis on the Type 1 diabetic Akita mouse model. The proposed in vitro studies will provide mechanistic insights into effects of high glucose on bone cell detection and response to mechanical stimuli. The in vivo and ultimate in situ studies with control age- matched and Akita mice treated with or without insulin will determine the impact of diabetes and associated high glucose on bone formation in response to mechanical loading, and evaluate the contribution of altered bone mechanosignaling to the higher bone loss in diabetes. These studies will be directed by a new investigator who has a background in biomedical engineering and has begun a first faculty appointment in a Department of Orthopaedic Surgery. Studies will combine the broad expertise of junior and senior researchers in the areas of biomedical engineering, pharmacology, physiology and molecular biology, and state-of-the-art biochemical, live cell imaging, histomorphometric studies and non-invasive in vivo whole animal bone imaging. The proposed studies are not only expected to advance understanding of mechanisms underlying diabetic osteopenia, highlighting the deleterious effects of high glucose on bone mechanosensory/transduction systems, but will also bring awareness to the importance of an early and tight glycemic control to prevent and reverse bone loss in diabetes.

Project Number:	5R01DK092605-03	**Contact PI / Project Leader:**	TONG, QINGCHUN
Title:	SIM1 NEURONS AND BODY WEIGHT REGULATION	**Awardee Organization:**	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON

Abstract Text:

DESCRIPTION (provided by applicant): Mutations in the genes encoding single-minded 1 (Sim1) and the melanocortin receptors 4 (MC4Rs) cause severe obesity in humans. In agreement, mice with Sim1 haploinsufficiency or PVH lesion are obese. Importantly, specific genetic restoration of MC4R in Sim1 neurons reduces obesity resulted from MC4R null mice by 60-70%, demonstrating a critical role for MC4Rs in Sim1 neurons in body weight regulation. However, despite the well established importance of Sim1 neurons in both humans and rodents, our understanding of Sim1 neural pathway is still limited to the level of Sim1 neurons. Downstream of Sim1 neurons, the identity of the neurotransmitters that mediate their action is not clear. Studies have been focused on the roles of neuropeptides released from Sim1 neurons (e.g. corticotrophin-releasing hormone, thyrotrophin-releasing hormone and oxytocin). However, knockout of each of these neuropeptides produced little or limited defects in feeding or body weight, suggesting a role for additional neurotransmitters. Sim1-expressing regions contain abundant vesicular glutamate transporter 2 (Vglut2, required for presynaptic glutamate release), indicating that the majority of Sim1 neurons are glutamatergic. Upstream of Sim1 neurons, how the activity of Sim1 neuron is regulated remains largely unknown. With the exception of the melanocortin input, the function of synaptic inputs is unknown. Electrophysiological data have suggested an important role for GABAergic input to PVH Sim1 neurons. However, the physiological significance of the GABAergic input is yet to be demonstrated. Aim 1 will test the hypothesis that glutamate release mediates the action of Sim1 neurons in body weight regulation using mice with specific loss of glutamate release from Sim1 neurons. Aim 2 will test the hypothesis that glutamate release mediates the action of MC4Rs expressed in Sim1 neurons in body weight regulation using mice with concurrent re-expression of MC4Rs and disruption of glutamate release restricted to Sim1 neurons on MC4R null background. Aim 3 will determine the function of GABAergic input to adult Sim1 neurons on body weight regulation using a mouse model in which only GABA-A receptors in Sim1 neurons will be sensitive to Zolpidem (a specific benzodiazepine mimicking GABA-A agonist), but those in all other brain neurons will not. GABA-A receptors in all neurons will respond normally to GABA, thus these mice will behave normally except for Zolpidem action. Effects of specific activation of GABAergic input on body weight, food intake and energy expenditure will be examined by administering Zolpidem in a temporally controlled and reversible fashion. These studies will reveal the function of glutamate release, an important downstream mediator, and GABAergic input, an important upstream regulator, of Sim1 neural pathway, thus representing a significant step in our understanding of brain neurocircuitry on body weight regulation.

Project Number:	5R01DK092238-04	**Contact PI / Project Leader:**	VORUGANTI, VENKATA SAROJA
Title:	COMPREHENSIVE SNP DISCOVERY IN SLC2A9, A CANDIDATE GENE FOR URIC ACID NEPHROPATHY	**Awardee Organization:**	UNIV OF NORTH CAROLINA CHAPEL HILL

Abstract Text:

DESCRIPTION (provided by applicant): Increased serum uric acid (SUA) or hyperuricemia is a metabolic problem that is associated with increased renal disease risk and has been increasing in prevalence worldwide. As with other renal disease risk factors, hyperuricemia also has a strong genetic basis, and its pattern of inheritance suggests that it may be influenced by several genes. In a recently conducted genome-wide association study in the San Antonio Family Heart Study (SAFHS), we found a strong association between polymorphisms in solute carrier family 2, member 9 (SLC2A9) and SUA levels in Mexican Americans. This is a replication of published work by others that has shown association of variants in the SLC2A9 gene with SUA levels in European Caucasian populations. Therefore, we propose to conduct a detailed and comprehensive inventory of variation in SLC2A9 in the SAFHS cohort and then to use the identified SNPs for replication efforts in another group of Mexican Americans from the San Antonio Family Gall Bladder study (SAFGS), American Indians of the Strong Heart Family Study (SFHS) and from the Genetics of Kidney Disease in Zuni Indians (GKDZI) and Alaskan Eskimos from the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study. SLC2A9 encodes a transporter that plays a major role in urate homeostasis, specifically in urate secretion and reabsorption in proximal convoluted tubule of kidneys in humans and our preliminary data in SAFHS shows that SLC2A9 polymorphisms have significant influence on the phenotypic variation observed in renal phenotypes in addition to SUA. However in order to account for all polymorphisms in the SLC2A9 gene and capture the maximum variance due to all SNPs we propose the following specific aims: 1) to identify all variation in the SLC2A9 gene and investigate which are associated with SUA and renal phenotypes in Mexican Americans 2) to resequence SLC2A9 gene (all exons, conserved introns and regulatory regions) for SNP/polymorphism discovery in 1122 founders in American Indians of the SFHS, genotype significant SNPs in all participants, test for association with SUA and other renal disease risk factors and pursue replication in another group of American Indians of the GKDZI and Alaskan Eskimos of the GOCADAN study; 3) to validate the functionality of most significantly associated variants in Mexican Americans, American Indians and Alaskan Eskimos. With the application of high-throughput sequencing technology and powerful statistical and functional methodologies, we intend to achieve a detailed understanding of the genetic architecture of SLC2A9 and its association with SUA and renal disease risk in non-European populations, including resequencing and replication and confirmation in two populations (Mexican Americans and American Indians) and generalization to a distinct population (Alaskan Eskimos).

Project Number:	5R01DK096021-02	**Contact PI / Project Leader:**	WAITZFELDER, BETH E.
Title:	HAWAII ASIAN AND PACIFIC ISLANDER DIABETES STUDY	**Awardee Organization:**	KAISER FOUNDATION RESEARCH INSTITUTE

Abstract Text:

DESCRIPTION (provided by applicant): Asians and Pacific Islanders as a whole bear a disproportionate burden of diabetes, both in terms of higher prevalence and rates of diabetes-related complications. Asian and Pacific Islander populations are the fastest growing populations in the United States (US), increasing by 43 percent and 35 percent respectively during the past decade. Despite obvious and important differences among Asian and Pacific Islander subgroups, the relatively small size of these populations included in diabetes studies has resulted in the "lumping" of these heterogeneous populations of Asian groups and Pacific Islanders in diabetes studies, masking potentially important differences. The study of these groups is also complicated by a relatively high proportion of individuals with mixed race/ethnicity. As a consequence, little is known about diabetes prevalence, treatment patterns and outcomes among Asian and Pacific Islander (API) populations, or importantly, about underlying factors contributing to differences among these populations. Diabetes prevalence, and particularly outcomes, is influenced by many individual, treatment and environmental factors. The objective of this study is to utilize electronic medical record (EMR) data, patient survey data and geocoded census data to comprehensively assess differences in diabetes prevalence, intermediate clinical outcomes and prevalence of diabetes-related complications among ten well-defined populations in a large integrated health care system in Hawaii. The ten populations studied will include: Japanese; Chinese; Filipino, Hawaiians; Samoans; mixed Asian+Caucasian; mixed Asian+Hawaiian; mixed Hawaiian and Caucasian; and mixed Asian+Hawaiian+Caucasian. A Caucasian-only group will also be included for purposes of comparison. The study will focus on a series of variables known to be important influences in diabetes prevalence and outcomes in each of three broad domains: individual factors; treatment factors; and environmental factors. The specific aims of the study are to: 1. Describe differences in diabetes prevalence, intermediate clinical outcomes and complications among these Asian and Pacific Islander populations; and 2. Identify the most important contributing factors to observed differences among these populations within a series of individual, treatment and environmental factors. The results of this study will provide important information about the underlying causes of disparities among a rapidly growing segment of the US population, with findings potentially relevant to other minority populations, and have practical utility in the strategic design of targeted interventions to achieve optimal outcomes for diabetes among Asian and Pacific Islander populations.

Project Number:	5R01DK099639-02	**Contact PI / Project Leader:**	WALL, STEPHEN P
Title:	COMMUNITY BASED RESEARCH TO IMPROVE ORGAN DONOR REGISTRATION AMONG BLACK MEN	**Awardee Organization:**	NEW YORK UNIVERSITY SCHOOL OF MEDICINE

Abstract Text:

DESCRIPTION (provided by applicant): The U.S. organ donation system is in a perpetual state of crisis. Over 115,000 patients are waiting for transplants while the waitlist increases by several thousand annually despite over 6,500 dying and 3,500 becoming too sick to receive a transplant. Black men are disproportionally affected by this crisis, due to higher prevalence of poorly controlled hypertension and diabetes and inadequate access to treatment, leading to the highest prevalence of end-stage renal disease and a greater need for kidney transplantation. While Blacks comprise only 13 percent of the total U.S. population, they comprise 34 percent of the 93,000 patients waiting for kidney transplants. Black men comprise 19 percent of the waitlist compared to black women comprising 15 percent, indicating a gender disparity as well. Federally supported interventions have increased the number of black donors such that rates are now proportional to their population percentages, but they remain well below the disproportionate need since organs best match when donors and recipients are of similar race. In this application, we will investigate means for improving organ donor registration among black men using educational video programming produced and distributed in partnership with our network of black owned barbershops in NYC. We will use entertainment education videos and determine how content produced for different audiences (generic multicultural, targeted for black men in our barbershops, and tailored for single viewers based on their prior organ donation beliefs) influences organ donor registration. Our application is a 3-phase qualitative and quantitative research design that includes an intervention development phase using digital video interviewing to both derive and provide culturally specific content for the videos (Aim 1); a 3 arm randomized controlled trial phase, in which customers will be randomized to receive the generic, targeted, or tailored video programming delivered with iPads, after which an immediate organ donation opportunity will be offered through registration online or with a mailed in application (Aim 2); and a failure analysis whereby we will interview some of the participants from the randomized trial who registered and failed to register one month after their educational session to ascertain the influence of the programming (Aim 3). Future studies will involve modifying this video programming based on findings from this research to promote organ donation in black owned barbershops through passive messaging with generic or targeted videos shown on large screen TVs, or with tailored programs using interactive kiosks. Through this work, we hope to reduce organ transplantation disparities through increased registration among black men who comprise a group having a disproportionally greater need for kidney transplants.

Project Number:	5R01DK091250-03	**Contact PI / Project Leader:**	WALLS, MELISSA L
Title:	STRESS AND TYPE 2 DIABETES AMONG INDIGENOUS ADULTS	**Awardee Organization:**	UNIVERSITY OF MINNESOTA

Abstract Text:

DESCRIPTION (provided by applicant): This revised RO1 application is in response to the Health Disparities in NIDDK Diseases Program Announcement (PA-09-262). It focuses on American Indians (AI) whose rates of type 2 diabetes (T2D) are the highest in the world. This population also copes with disproportionate stressors including economic disadvantage, unemployment, community violence, discrimination, and the long- term effects of historical cultural traumas and losses. Yet, paradoxically, AI people tend to score lower on some self-report measures of stress and have lower prevalence rates of stress-related mental disorders such as major depressive episode and anxiety disorders. The goals of the proposed research are to advance measurement of stress processes among AI people through comparisons of stress biomarkers and self-report measures; and to use multiple indicators of stress including stress biomarkers to investigate the interactions between stress processes T2D disease progression and treatment compliance among AI adults. This community based participatory research is based on partnerships with five Ojibwe reservations in Minnesota and Wisconsin who invited the research team to work with their clinics. The first specific aim is to couple our existing preliminary data on community salient stressors with new qualitative feedback on existing measures to adapt and subsequently examine via pilot surveys the psychometric properties of stress measures for this population. The second specific aim is to investigate the relationship between stress biomarkers and self-reported psychosocial stressors, symptoms of distress, and diagnostic measures of anxiety, depression, and trauma to ascertain the degree to which self report measures are indicative of actual physiological stress levels among a cohort of 200 AI adults who have been recently diagnosed with T2D. The third specific aim is to follow a cohort of 200 recently diagnosed T2D AI adults for two years to investigate an innovative conceptual model (Figure 1) of multiple measures of stress processes, treatment compliance, mental health, and risk factors for disease complications

Project Number:	5R01DK097340-02	**Contact PI / Project Leader:**	WANG, DAVID H
Title:	HEDGEHOG SIGNALING IN THE DEVELOPMENT OF BARRETT'S ESOPHAGUS	**Awardee Organization:**	UT SOUTHWESTERN MEDICAL CENTER

Abstract Text:

DESCRIPTION (provided by applicant): Barrett's esophagus, the metaplastic change of the distal esophageal epithelium from squamous to columnar, significantly increases the risk of esophageal adenocarcinoma, the prevalent form of esophageal cancer in this country. Understanding the molecular mechanism underlying esophageal epithelial columnar metaplasia is critical to designing molecularly targeted chemopreventative or therapeutic strategies for both Barrett's esophagus and esophageal adenocarcinoma. We propose that reactivation of latent developmental signaling a pathway within the esophagus is a fundamental requirement for Barrett's metaplasia. This project will expand on our previous work that identified Hedgehog (Hh) pathway activation in Barrett's esophagus and demonstrated that forced Hh expression and subsequent downstream Bone morphogenetic protein (BMP) 4 signaling induces columnar changes in esophageal epithelium. We previously identified SOX9, a transcription factor expressed in the embryonic esophagus, as a Hh-BMP4 target gene that is upregulated in Barrett's esophagus and induces expression of columnar genes. We have now identified a second Hh-BMP4 target gene and embryonic esophageal transcription factor, FOXA2, to be expressed in Barrett's esophagus but not in normal adult esophageal epithelium. Our hypothesis is that expression of these two embryonic transcription factors, activated by Hh and BMP4 signaling induced by gastroesophageal reflux disease (GERD) is required for the development of columnar metaplasia. We will attempt to further define the role of Hh and BMP4 signaling in Barrett's esophagus through three specific aims: Aim 1) To delineate how BMP4 upregulates SOX9 and FOXA2 expression in human esophageal epithelial cells; Aim 2) To determine if sequential and combinatorial stable expression of SOX9, FOXA2, and CDX2 in esophageal squamous epithelial cells results in phenotypic features of Barrett's metaplasia; and Aim 3) To determine in vivo expression levels of Hh and BMP4 pathway proteins and their downstream targets (SOX9, FOXA2) and CDX2 in biopsy samples of esophageal squamous epithelium from GERD patients with and without Barrett's esophagus. Through these studies, we expect to define the role Hh-BMP4 signaling plays in establishing columnar metaplasia and determine if there are differences in Hh-BMP4 signaling between GERD patients with and without Barrett's esophagus. These findings would contribute towards our objectives of 1) identifying specific molecular markers that can be used to predict which GERD patients would benefit from aggressive anti-reflux therapies to prevent Barrett's esophagus; 2) designing a molecularly targeted chemopreventative or therapeutic strategy for Barrett's esophagus and esophageal adenocarcinoma; and 3) validating our innovative approach of applying developmental biology to the understanding of Barrett's metaplasia.

Project Number:	5R01DK097165-02	**Contact PI / Project Leader:**	WANG, VIRGINIA
Title:	CASCADING IMPACTS OF BUNDLED PAYMENT ON PERITONEAL DIALYSIS PROVISION & OUTCOMES	**Awardee Organization:**	DUKE UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Despite the appeal of peritoneal dialysis (PD) to patients, physicians, and providers, there is limited understanding of the mechanisms behind PD's low and diminishing utilization in the US. Patient and physician determinants of PD utilization have not adequately explained its declining trends, suggesting that nonmedical factors in the healthcare delivery system have contributed to PD's limited use. The availability of PD treatment services at dialysis facilities plays an important role in patient decision-making and is a necessary pre-condition of PD utilization. A declining proportion of facilities offer PD services, which may be due to financial incentives that favor the use of hemodialysis (HD) over PD. In 2011, Medicare implemented an end-stage renal disease (ESRD) bundled payment that modifies the financial incentive of dialysis treatments to induce greater supply and utilization of PD at dialysis facilities. Through a systematic program of research, the goal of this study is to evaluate the cascading effects of ESRD UU bundled payment on 1) dialysis facility practice patterns, 2) patient utilization, and 3) patient outcomes of PD. This will be accomplished by merging several years of administrative databases from the US Renal Data System and Medicare to assess changes in organizational and patient outcomes impacted by payment reform in the years preceding and immediately following implementation of ESRD bundled payment. This project has three specific aims. Aim 1 of this study will examine changes in dialysis facility UU provision of PD services and identify factors associated with changes in dialysis facility PD availability and program size. Building from this work, Aim 2 will assess the extent of and factors associated with changes in utilization of PD among incident dialysis patients, modality switches and changes in PD patient characteristics after ESRD bundled payment. Building from the work of the previous aims, Aim 3 will evaluate the comparative effectiveness of bundled payment and changes in HD and PD utilization on patient hospitalization and mortality. Results from the proposed work will inform CMS, dialysis providers, and ESRD patients on the organizational and clinical impacts of payment reform. Our approach is innovative because it examines a range of organizational as well as patient outcomes impacted by ESRD bundled payment, involves the use of several merged administrative databases to improve the quality of existing standalone data on dialysis facility practices, and employs relatively unused analytic methods to inform gaps in the evidence base and future refinements to dialysis practices and Medicare policy. The proposed research is significant because Medicare payment reform is a natural experiment that should be rigorously evaluated to determine its effectiveness in achieving Medicare's goals of aligning patient preferences and clinical appropriateness for PD, reducing costs, and improving care for a growing population of patients with ESRD.

Project Number:	5R01DK088711-05	**Contact PI / Project Leader:**	WATERMAN, AMY DOGGETTE
Title:	TAILORED COMPUTER EDUCATION TO INCREASE LIVING DONATION IN AFRICAN-AMERICANS	**Awardee Organization:**	UNIVERSITY OF CALIFORNIA LOS ANGELES

Abstract Text:

DESCRIPTION (provided by applicant): Kidney transplantation offers patients in end-stage renal disease (ESRD) 3 to 17 additional years of life and improved quality-of-life compared to remaining on dialysis. Because of the deceased donor organ shortage, more kidney patients are choosing to receive kidneys from family and friends, a process called living donor kidney transplantation (LDKT). Although African-Americans are 3.7 times more likely to develop ESRD, they are less likely to receive LDKTs. Therefore, this project will assess whether racial disparities in transplant knowledge, readiness to pursue LDKT, completion of transplant medical evaluation, and receipt of LDKTs can be reduced when ESRD patients receive access to personalized coaching and individually-tailored feedback using an Explore Transplant computerized Expert System. This multilevel study will also examine how other known patient, family, and healthcare system barriers to LDKT impact the Expert System's effectiveness. ESRD patients presenting for transplant medical evaluation at Barnes-Jewish Transplant Center in St. Louis, Missouri (465 African-Americans, 465 Whites) will be stratified by race and randomized to one of two education conditions (Explore Transplant Expert System vs. Standard Education Control). As they complete transplant medical evaluation, patients in the Expert System condition will receive individually tailored feedback reports and personalized coaching addressing variables important to behavior change and associated with LDKT health disparities. Control patients will only receive standard-of-care education provided by the transplant center. Changes in key outcomes will be assessed at four time points (2-months before in-hospital evaluation day (IHED) (baseline), 2- and 6-months post-IHED, and 18-months post-baseline). The grant has four aims: Aim 1 (Primary): Compared to the Control Group, to determine whether African-American and White patients receiving the Expert System increase in their LDKT readiness and transplant knowledge 6-months post-IHED. Aim 2: Compared to the Control group, to determine whether African-American and White patients receiving the Expert System are more likely to complete transplant medical evaluation and pursue LDKT 18- months post-baseline. Aim 3: To examine whether the Expert System's effectiveness in changing LDKT decision-making and behavior is equivalent between African-Americans and Whites. Aim 4: To examine how known patient, family, and healthcare system barriers to LDKT act alone and in combination with the Expert System to affect African-Americans' decision-making and behavior. At the conclusion of the study, we will have developed an innovative and cost-effective Explore Transplant Expert System that could be utilized by providers in 5,000 dialysis and 250 transplant centers to tailor LDKT discussion and education based on the needs of individual patients of different races.

Project Number:	5R01DK098744-03	**Contact PI / Project Leader:**	WENG, FRANCIS L
Title:	INCREASING LIVE DONOR KIDNEY TRANSPLANT AMONG BLACKS ON THE TRANSPLANT WAITLIST	**Awardee Organization:**	ST. BARNABAS MEDICAL CENTER

Abstract Text:

DESCRIPTION (provided by applicant): The best treatment for severe chronic kidney disease (CKD) is usually a live donor kidney transplant (LDKT), but large racial disparities persist in receipt of LDKTs. In 2009, Blacks, who comprised 36.9% of the dialysis population, received 32.4% of deceased donor kidney transplants (DDKTs) but just 13.7% of LDKTs. A multi- component intervention that addresses the many barriers that impede LDKT (e.g. transplant candidates' lack of knowledge about LDKT; fears regarding donor's future health; guilt; and discomfort with discussing LDKT) could plausibly increase LDKT among Blacks. Our main objective is to test an educational and behavioral intervention that is designed to increase receipt of LDKT among newly-listed transplant candidates who are Black. We hypothesize that a multi-component intervention will increase both readiness to pursue LDKT and actual receipt of LDKTs among Blacks. We propose a parallel group, two-arm randomized trial among 500 Black kidney transplant candidates. After Blacks are placed on the waiting list for a DDKT, we will randomly assign them to either: (1) a control group that will receive Usual Care, or (2) an Intervention group that will receive a culturally sensitive, group-based intervention. Participants randomized to the Intervention will be asked to attend a 60-90 minute small group seminar (family and friends strongly encouraged to attend) that will feature brief talks regarding: basic facts about CKD, transplant, and the waiting list; basic facts about live kidney donation; the experience of receiving a transplant and LDKT; the experience of serving as a live kidney donor; and skill-building regarding how to ask for a live donor. These talks will directly address the barriers that impede LDKT. Physicians and Black LDKT recipients and live donors will lead these talks, supplemented by educational videos. In our preparatory aim, we will develop the Intervention and train the speakers. Our primary aim will compare LDKT readiness and LDKT receipt in the Intervention vs. Usual Care groups of our randomized clinical trial; our primary outcome is change in readiness to pursue LDKT, and our main secondary outcome is actual receipt of LDKT, after 18 months of follow-up. Our secondary aims will determine (a) the social and behavioral variables that modify the effect of the Intervention upon LDKT readiness and receipt; and (b) whether changes in social and behavioral factors mediate the effect of the Intervention upon LDKT readiness and receipt. This clinical trial will occur at two neighboring transplant centers that share the same policies, procedures, and personnel. In an average year, these two centers combine to place over 200 Blacks on the DDKT waiting list and perform over 135 LDKTs (including ~29 among Blacks). By intervening upon patients "distal" in the transplant process, at two centers that perform many LDKTs, we have excellent power to detect a beneficial effect of the Intervention upon LDKT readiness and receipt. At the end of this study, we will have developed and tested a culturally sensitive educational and behavioral Intervention that has the potential to increase receipt of LDKT among Blacks and decrease the striking racial disparities in receipt of LDKT.

Project Number:	5R01DK095828-02	**Contact PI / Project Leader:**	WU, CHAODONG
Title:	METABOLIC REGULATION OF ADIPOCYTE-MACROPHAGE CROSSTALK IN OBESITY	**Awardee Organization:**	TEXAS A&M AGRILIFE RESEARCH

Abstract Text:

DESCRIPTION (provided by applicant): Metabolic regulation of adipocyte-macrophage crosstalk in obesity Summary Obesity-associated adipose tissue inflammation critically contributes to the development of insulin resistance and type 2 diabetes. While much evidence demonstrates the importance of both adipocytes and macrophages in initiating adipose tissue inflammation, little is known about precisely how nutrient metabolism is linked to inflammatory responses in both adipocytes and macrophages. It is also unknown about the mechanisms underlying metabolic regulation of the crosstalk between adipocytes and macrophages. The long-term goal of this research is to dissect adipocyte-macrophage crosstalk so that novel evidence-based approaches can be developed for preventing and/or treating insulin resistance. As an adipose tissue-abundant gene, PFKFB3 encodes for a regulatory enzyme whose product stimulates glycolysis. For this project, the central hypothesis is that PFKFB3 orchestrates appropriate metabolic regulation of adipocyte-macrophage crosstalk to suppress macrophage proinflammatory (M1) activation, stimulate macrophage alternative (M2) activation, and improve adipocyte functions, thereby protecting against obesity-associated adipose tissue inflammation and systemic insulin resistance. This hypothesis is based on the following novel findings: 1) PFKFB3 stimulates adipocyte production of palmitoleate (a mono-unsaturated fatty acid), which in turn blunts macrophage M1 activation; 2) PFKFB3 is involved in PPARgamma stimulation of macrophage M2 activation; and 3) Myeloid cell-specific PFKFB3 disruption exacerbates diet-induced adipose tissue dysfunctions. Thus, the goal of this project is to define the novel role of PFKFB3 in regulating adipocyte-macrophage crosstalk. Accordingly, mice with selective PFKFB3 disruption in adipocytes and/or myeloid cells are generated. For Specific Aim 1, experiments have been designed to test the hypothesis that adipocyte factors generated in response to PFKFB3 action, in particular palmitoleate, suppress macrophage M1 activation and/or stimulate macrophage M2 activation. Moreover, the in vivo effects of adipocyte PFKFB3 disruption on adipose tissue macrophage polarization, adipose tissue inflammation, and systemic insulin sensitivity will be examined. For Specific Aim 2, experiments have been designed to test the hypothesis that PFKFB3 links nutrient metabolism and macrophage polarization. Also, the in vivo effects of PFKFB3 disruption in myeloid cells on adipose tissue inflammation and systemic insulin sensitivity will be examined. For Specific Aim 3, experiments have been designed to test the hypothesis that the PFKFB3 in adipocytes and/or macrophages is needed for actions of PPARgamma activation. Accordingly, the involvement of the PFKFB3 in adipocytes versus macrophages in PPARgamma regulation of adipocyte-macrophage crosstalk, adipose tissue inflammation, and systemic insulin sensitivity will be examined. Together, the proposed research will illustrate a new paradigm on metabolic regulation of adipocyte-macrophage crosstalk, and provide the experimental basis for insulin sensitization by means of selective PFKFB3 activation.

Project Number:	5R01DK093623-04	**Contact PI / Project Leader:**	YANG, FAJUN
Title:	FINE-TUNING LIPID METABOLISM BY LSD1	**Awardee Organization:**	ALBERT EINSTEIN COLLEGE OF MEDICINE

Abstract Text:

DESCRIPTION (provided by applicant): Sterol regulatory element-binding protein-1c (SREBP-1c) is a key transcription activator of lipogenic genes. Given the close association between dysregulation of lipid homeostasis and major human diseases, such as type 2 diabetes, understanding the regulation of SREBP-1c-dependent transcription will provide not only novel insights into the molecular control of the development of fatty liver and dyslipidemia but also potential therapeutic opportunities for fighting these diseases. At present, the pathways that regulate nuclear SREBP-1c activation and inactivation are poorly defined. Recent studies have demonstrated the NAD-dependent protein deacetylase SIRT1 as a negative regulator of SREBP-1c, suggesting that modulation of SIRT1 expression or enzymatic activity can affect lipid metabolism. The preliminary data have shown that the lysine-specific demethylase-1 (LSD1) is a critical regulator of SIRT1 and controls the expression of lipogenic genes. Surprisingly, a frequently used small molecule, which has known functions on lipid metabolism, displayed a novel function of inhibiting LSD1 activity. Thus, the central hypothesis of this proposal is that LSD1 activates SREBP-1c-mediated transcription and lipogenesis by repressing SIRT1. The following three Specific Aims are proposed to test this hypothesis: 1) Determine the role of LSD1 in regulating lipid metabolism in primary hepatocytes and mouse livers in vivo; 2) Elucidate the molecular mechanisms of LSD1 regulation on SIRT1 in relevance to de novo lipogenesis; and 3) Target LSD1 for modulating SREBP-1c activity/level and de novo lipogenesis. A series of in vitro and in vivo experiments are proposed to determine the regulatory mechanisms and significance of the LSD1/SREBP pathway in lipid metabolism. The long-term objectives of this proposal are to determine the role of LSD1 in nutritional regulation of SREBP-1c function and in controlling lipid homeostasis in conditions of metabolic disorder. This application is not only significantly relevant to public health, but also highly innovative and will have major impacts to the field of lipid metabolism. Together, the proposed studies will address the molecular link between LSD1 and SREBP-1c in regulating lipid homeostasis and its potential role in the development of diseases with dysregulated lipid homeostasis, such as obesity, type 2 diabetes and cardiovascular diseases.

Project Number:	5R01DK088210-04	**Contact PI / Project Leader:**	YEN, CHI- LIANG ERIC
Title:	INTESTINAL TRIACYLGLYCEROL METABOLISM AND ENERGY BALANCE	**Awardee Organization:**	UNIVERSITY OF WISCONSIN-MADISON

Abstract Text:

DESCRIPTION (provided by applicant): The intestine plays a pivotal role in lipid metabolism and energy balance. It is the portal for dietary nutrients, the source of apolipoprotein B-containing chylomicra, and an endocrine organ that signals current nutritional status to other tissues to maintain homeostasis and promote metabolic efficiency. However, many molecular mechanisms involved in these processes remain elusive. The long-term goal of our research is to understand how intestinal lipid processing regulates systemic lipid metabolism and energy balance. The overall objective of this proposal is to elucidate the mechanism(s) by which acyl CoA:monoacylglycerol acyltransferase-2 (MGAT2) regulates whole body energy balance. Mice deficient in MGAT2 (Mgat2-/- mice) display a remarkable resistance to obesity and related metabolic disorders induced by high-fat feeding. In contrast to the well- established role of the intestine in regulating food intake and nutrient assimilation, the phenotype of Mgat2-/- mice suggests a previously unrecognized role of the intestine in modulating energy expenditure. Among known MGAT enzymes, MGAT2 is highly expressed in the intestine of human and mouse. MGAT activity is best known for its role in the absorption of dietary fat, because it catalyzes triacylglycerol re-synthesis, a required step for the formation of chylomicra, which deliver dietary fat to peripheral tissues. Despite consuming and absorbing normal amounts of fat, Mgat2-/- mice are protected from excessive weight gain on a high-fat diet. Compared to their control littermates, however, these mice expend significantly more energy. The difference in energy expenditure increases, as dietary fat increases. Although Mgat2-/- mice absorb normal quantities of fat, more of the dietary fat is absorbed from the distal intestine, thereby delaying the entry of dietary fat into the circulation. In addition, their postprandial levels of glucose-dependent insulinotropic peptide (GIP) are lower, whereas glucagon-like peptide1 (GLP1) levels are higher than in controls. Both gut hormones can affect energy balance. Thus, we hypothesize that MGAT2 coordinates the uptake and processing of lipid for chylomicron formation in enterocytes and modulates the secretion of GIP and GLP1 from enteroendocrine cells. As such, intestinal MGAT2 directs the delivery of dietary fat toward storage for efficient assimilation of this calorie-dense nutrient. To test our hypothesis, in Aim 1, we will elucidate the role of MGAT2 in intestinal lipid metabolism, chylomicron formation, and gut hormone release. In Aim 2, we will determine the functional consequences of lacking MGAT2 on the distribution of dietary fat. In Aim 3, we will assess the overall impact of intestinal MGAT2 on systemic energy balance using mice that express MGAT2 only in the intestine and mice that lack MGAT2 in the same intestine-specific manner. By completing these aims, we will advance our understanding of how intestinal lipid metabolism modulates systemic energy balance, which would be important, because it would build a new paradigm for understanding fat assimilation, a fundamental physiological process that is crucial for survival during lean times but may lead to excessive body fat in periods of abundance.

Project Number:	5R01DK098662-02	**Contact PI / Project Leader:**	ZHOU, BEIYAN
Title:	MICRORNA REGULATED MACROPHAGE POLARIZATION IN ADIPOSE TISSUE INFLAMMATION	**Awardee Organization:**	TEXAS A&M AGRILIFE RESEARCH

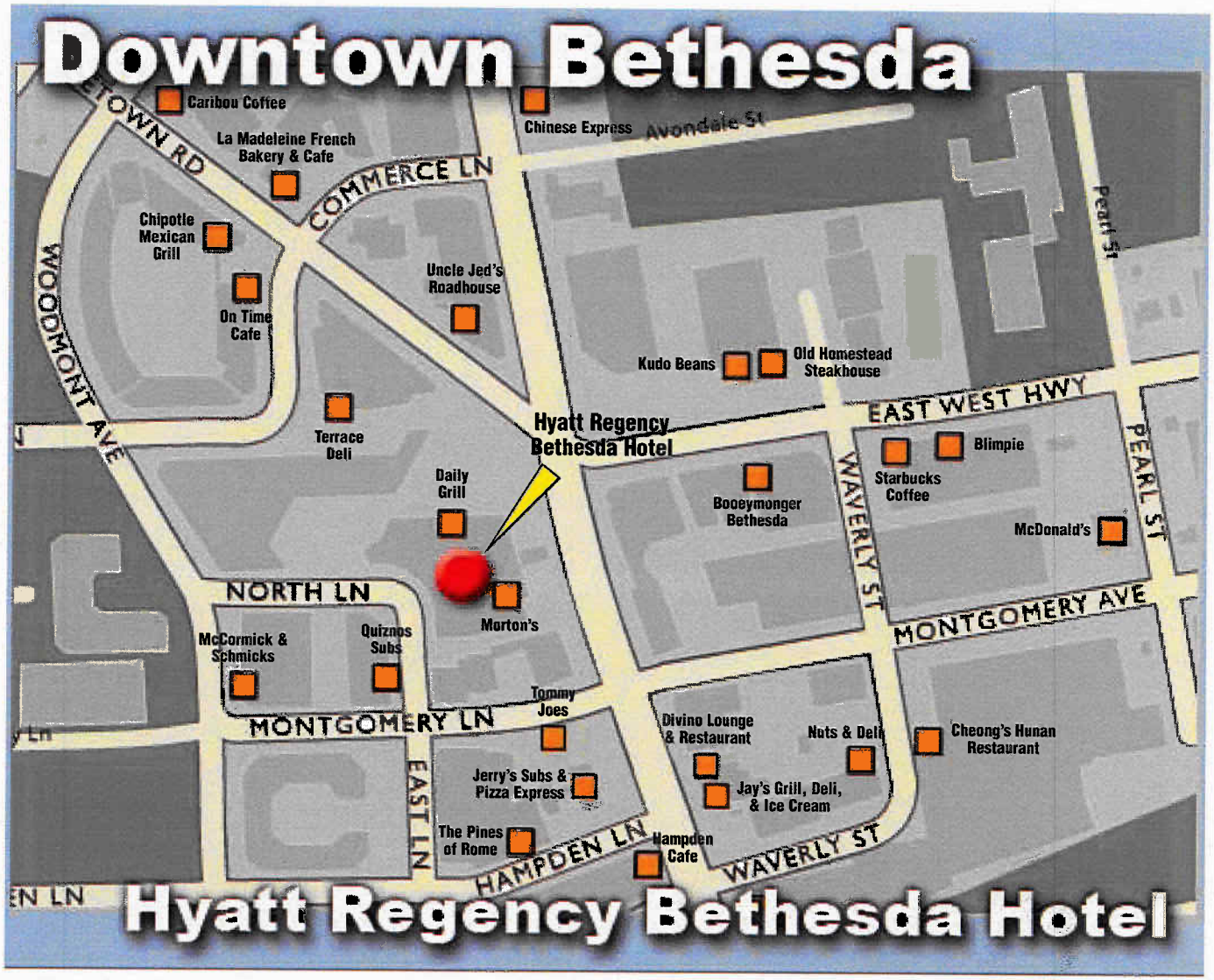
Abstract Text:

DESCRIPTION (provided by applicant): Adipose tissue macrophages (ATMs) regulated adipose tissue inflammation is an important contributor to the pathogenesis of insulin resistance associated disorders, including type 2 diabetes and cardiovascular diseases. Chronic nutrient excess induces ATMs to undergo a distinct phenotypic switch (macrophage polarization) from anti-inflammation (M2) in lean tissues to pro-inflammation activation (M1) in obese tissues. We recently discovered, for the first time, that miR-223 is a potent regulator of diet-induced adipose tissue inflammation, which primarily acts through controlling macrophage polarization. Moreover, miR-223 is dramatically decreased in human diabetes patients, reinforcing the potential function of miR-223 in adipose tissue inflammation. However, to date, it remains unknown how miR-223 exactly regulates macrophage polarization and promote these ATMs toward M1 activation under challenges. Our preliminary studies showed that miR- 223 is markedly increased during M2 activation which can be further enhanced by a PPARgamma agonist; and loss of miR-223 in macrophages results in blunted M2 activation to PPARgamma agonist. Moreover, genomic survey predicted three PPARgamma consensus binding elements upstream of miR-223 precursor. Thus, we hypothesize that miR-223 is a potent macrophage M2 activator and a PPARgamma-miR-223 circuit is an important pathway to control ATM polarization in chronic nutrient excess induced adipose tissue inflammation and systemic insulin resistance. Three specific aims will be carried out to address this hypothesis: Specific Aim 1: Determine the mechanisms of PPARgamma-miR-223 circuit in regulating macrophage polarization. We will employ macrophages with altered miR-223 levels and specific PPARgamma agonist or inhibitor to dissect in detail the functional interactions between PPARgamma and miR-223 during macrophage activation. Specific Aim 2: Determine the role of miR-223 in PPARgamma action against adipose tissue inflammation and insulin resistance. We will use gain- and loss-of miR-223 mouse models with PPARgamma agonists and antagonists to determine the role of miR-223 in protective effects of PPARgamma against excess nutrients induced adipose tissue inflammation and systemic insulin resistance. Specific Aim 3: Identify the target genes of miR-223 that are required for the PPARgamma-miR-223 pathway. To dissect the PPARgamma-miR-223 pathway, we will identify miR-223 target genes and validate their functions in regulating macrophage polarization and adipose tissue inflammation. The overall goal of this project is to determine the molecular mechanism underlying miR-223 mediated regulation of macrophage polarization and adipose tissue inflammation. Completion of this project will provide a novel microRNA-based paradigm with respect to ATM polarization. Moreover, this study will provide crucial insights for developing new therapeutic strategies in mitigating adipose tissue inflammation associated diseases using miR-223 mimetics or antagonists of miR-223 regulated target genes.

Project Number:	5R01DK092412-03	**Contact PI / Project Leader:**	ZINGMAN, LEONID
Title:	SKELETAL MUSCLE KATP CHANNELS DETERMINE BODILY ENERGY BALANCE	**Awardee Organization:**	UNIVERSITY OF IOWA

Abstract Text:

DESCRIPTION (provided by applicant): The modern world has experienced enormous growth in obesity, a disease associated with increased incidence of and mortality from diabetes, cardiovascular disease and cancer. Even moderate weight loss in the range of 5-10% has been shown to prevent the long-term consequences of obesity. Unfortunately, the current treatment options for obesity remain limited in both their application and effect. Our preliminary data indicate that sarcolemmal ATP-sensitive K+ (KATP) channels limit muscle energy expenditure under physiological workload, while KATP channel deficit provokes an extra energy cost of muscle performance. Inefficient fuel metabolism in KATP channel-deficient muscles reduces body fat deposits promoting a lean phenotype. The current proposal builds on this finding to determine the mechanisms by which KATP channel function affects skeletal muscle performance, and adipose tissue mobilization. We hypothesize that membrane potential modulation, due to KATP channel opening in response to a physiological workload, limits calcium and sodium inward currents and thus energy consumption related to ion homeostasis and contraction continuation. Under conditions of surplus calorie intake this promotes weight gain. Conversely, disruption of KATP channel function would result in exaggerated cellular calcium turnover, causing increased energy consumption and activation of calcium/calmodulin dependent protein kinase (Ca2+/CaMKII). We propose, that induction of CaMKII triggers both Akt-dependent production and Ca2+- dependent secretion of a signaling peptide - musclin. This peptide is known for its ability to modulate clearance of atrial natriuretic peptide (ANP) - a potet activator of lipolysis. In this way, musclin signaling could translate increased activity related energy consumption into adipose tissue mobilization. The goal of this project is to directly study the molecular mechanism of KATP channel control of activity- related energy consumption and the mechanism of consequent adipose tissue mobilization and body weight reduction. The proposed investigation will be performed across multiple models - biochemical and electrophysiological studies on cellular and isolated organ levels will be used to verify molecular mechanisms for findings obtained on the whole body level. Understanding these mechanisms will provide novel avenues for targeted management and prevention of obesity and related diseases.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