Pennington Biomedical
Nutrition Obesity
Research Center

Pennington / Louisiana Nutrition Obesity Research Center

Spring 2021 Newsletter

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News from the NORC Director

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The last year of the third 5-year cycle of our Pennington/Louisiana NORC has been a very busy and productive year.

Competitive Renewal Application. In the midst of the COVID-19 pandemic crisis, we submitted our 4th cycle renewal application on June 2, 2020. This novel application was reviewed in October and received an excellent score. The last week of April 2021, we received our notice of award and we can all feel proud that our NORC will be funded until at least April 2026.

The physical resources at Pennington Biomedical are outstanding and increasingly rare at a national level. Our excellent core facilities provide intellectual and experimental resources for state-of-the-art human and animal studies. To maintain our strong foundation and the continued growth of nutrition and obesity research in Louisiana, we are pursuing the following **4 Specific Aims:**

Aim 1. Stimulate and support new and innovative research in nutrition and obesity while attracting new investigators in Louisiana.
The NORC will continue to foster interactions between basic, clinical, and population science investigators by serving as a platform for communication. Importantly, the NORC will work in close collaboration with Pennington Biomedical and its other NIH-funded Center Grant Programs to optimize collaborations not only within the institution but with the best academic institutions in Louisiana. Thanks to the infrastructure and connectivity provided by LA CaTS and our newly identified "NORC champions" (Wayne Backes at LSU-HSC and Lu Qi at Tulane University), NORC has now efficient access to investigators on the main LSU A&M campus as well as at the LSU-HSC, Tulane University, Xavier University and Children's Hospital all in New Orleans. Furthermore, we will continue to grow our own members but also recruit new talents in nutrition and obesity research.

Aim 2. Provide state-of-the-art and cost-effective Scientific Cores including a Human Phenotyping Core, Molecular Mechanism Core and an Animal Model/Phenotyping Core.
Over the past 15 years our NORC leadership has worked to establish state-of-the-art core facilities in tight collaboration with the administration and the other NIH-funded Centers at Pennington Biomedical. These cores provide quality data and cost-efficient services not only to Pennington NORC members but have been instrumental to recruit new PIs and members in Baton Rouge and New Orleans. In the future, the synergism between these Centers can only provide even higher quality core services to investigators in the field of nutrition and obesity. According to the implementation but also cessation of procedures, we continue to update SOPs and Quality Control/Improvement procedures as well as pricing and method descriptions to use in grant

applications (all available on our NORC website at http://norc.pbrc.edu/.

Aim 3. Enhance the translation of discoveries in basic, clinical and population science by incentivizing cross talk and research collaborations among disciplines and institutions within Louisiana.
As fully described in our grant, we have developed at least three targeted research focus areas and created Translational Research Teams, all of which will continue our focus on translational research with initiatives to incentivize PIs to work together and focus on common projects.

Aim 4. Pursue the following new NORC initiatives:
a) Establish an annual course on "**Nutrition and Obesity Research Methodology**". On September 8-10, 2019, we hosted the inaugural Pennington/Louisiana NORC Training in Obesity and Nutrition methods course. Open to postdocs and junior faculty at all 12 NORC's, 27 enthusiastic participants from 11 NORCs around the country visited Pennington Biomedical for this didactic and hands-on training course. The feedback of the attendees was outstanding and by far the most sought-after aspect were the practical labs that were conducted by the Pennington Postdocs and Junior Faculty. We now plan to hold this course on an annual basis resuming in April 2022.
b) **Expand and maintain a data and bio-specimen repository** available to all NORCs. The Human Phenotyping Core was central in developing a data and biospecimen repository. The use of and contribution to the biorepository will now be facilitated by: a) Educating NORC members about the presence of the biorepository, how to access it, and how to contribute samples (blood, muscle, adipose, urine); b) Work with our IAB and EAB to publicize the biorepository and promote its use in P&F grants across NORCs and c) Work with investigators who receive P&F grants to develop their pilot data into larger grant applications that rely on the biorepository or contribute samples to it.
c) **Develop an integrated system of functional genomics and molecular bioimaging to detect changes in gene expression occurring with obesity related phenotypes**. The Molecular Mechanisms Core will develop a functional genomics approach in which high-resolution microscopy bioimaging will be overlaid with gene expression changes, thus providing an integrated functional view of biological processes. The advent of single cell RNA sequencing and 3D imaging now allows such approach of functional and localized genomics. This expanded set of tools to assess gene expression will allow us to ask questions such as which genes change expression, in which cells do the changes occur, where are these cells located in a tissue, and what is their relationship to other cells. With such an integrated approach, we can begin to construct novel perspectives on tissue function in health and disease.
d) Develop **surgical expertise** to support needs for glucose clamps and bariatric surgery in basic and translational laboratory investigations. The Animal Models and Phenotyping Core is expanding services in providing direct technical and surgical support to investigators. We will develop a core suite of surgical capabilities to assist investigators in surgical interventions such as catherization (insulin clamp, etc.), brain cannulation or microinjection, bariatric surgery, or telemetry instrumentation.

Poised for the next phase of success.
To assure the future success of the Pennington/Louisiana NORC, the Center leadership in close collaboration with the leadership of the participating institutions will take all the necessary steps to guarantee the NORC proceeds at the cutting edge of technology and concepts necessary to conduct state-of-the-art nutrition and obesity research. We will continue to seek feedback from our members through REDCap surveys addressing the quality and pricing of the services provided by the three biomedical cores. When necessary, we will take action to make sure the biomedical research core needs are evolving adequately to provide the necessary services to our NORC members. We of course need your help and suggestions to implement any necessary change in the services provided to our members, our Pilot & Feasibility grant recipients and to our trainees. Over the past 15 years the Pennington/Louisiana NORC has demonstrated success in facilitating multidisciplinary translational research in nutrition and obesity. With a very strong and vibrant research base including 146 members, 63 being Regular Members contributing $44.6 million annual direct funds, we are poised to grow even further by leveraging our innovative NORC's cores, P&F awards

which both guarantee the training of the next generation of nutrition/obesity researchers. Our cores and programs are connecting basic, clinical and population scientists to train translational researchers in this important field of research since obesity and its associated chronic diseases of aging are the major threats to public health in the 21st century. With exceptional research facilities and outstanding institutional support, we are ideally positioned to lead the advancement of nutrition and obesity science at a regional, national, and even international level. We are presently establishing Translational Research Teams to address big research questions from the basic science level to clinical investigation and finally to the population around the theme of "**Nutrition, Obesity and Metabolic Health through the Lifespan**".

New Awards For Pilot & Feasibility Studies

The objective of the NORC P&F program is to encourage young investigators by providing research support to test innovative hypotheses involving nutritional programming-related research and other pilot studies related to the function of NORC. Below are the most recent P&F winners.

The effects of dietary protein restriction on inflammatory associated cellular senescence.

Cristal Hill, Ph.D.
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Neurosignaling Laboratory,
Pennington Biomedical Research Center

Obesity and aging are common risk factors that induce senescent cells in adipose tissue which further declines metabolic health. Although senescent cells no longer proliferate, their presence creates a continuous burden that induces an inflammatory environment known as the senescent-associated secretory phenotype (SASP).This inflammatory profile in adipose tissue can be identified by (a) flattened morphology and a higher activity of β-galactosidase, (b) markers of cell cycle arrest including the activation of the p53 tumor suppressor and/or the cyclin-dependent kinase inhibitor p16, (c) and increased cytokines, chemokines, and growth factors. Both calorie and nutrient restriction are associated with improvements in health, especially metabolic health. Although the specific contribution of protein is less clear, so are the immunological responses through which dietary protein restriction might alter.

This NORC P&F study will examine the impact of dietary protein restriction on profiles of senescence that likely alter glucose metabolism and insulin signaling in adipose tissue. Towards the development of this project, Dr. Hill is under the advisement of a multidisciplinary team including and Drs. Jacqueline Stephens, Prachi Singh, and Christopher D. Morrison (PBRC) and Dr. James L Kirkland (Mayo Clinic). Overall, this project will investigate if protein restriction protects against the detrimental effects of senescent cells during obesity and older age. Animals will be grouped housed and fed special diets, weekly body weights will be measured, body composition by NMR and a glucose tolerance test will be measured at the final week of feeding phase of the study. After four months of diet, animals will be euthanized, blood and tissues will be collected for further analysis. The results of this study may for the first time identify that the beneficial adaptive responses to protein restriction also combat inflammation and cellular senescence aiding to prevent age and obesity-related illness.

Effect of sleep restriction on adipose tissue and skeletal muscle insulin sensitivity

Kara Marlatt, PhD, MPH
Assistant Professor-Research,
Healthy Aging & Metabolism Lab,
Pennington Biomedical Research Center

Inadequate sleep is an independent risk factor for metabolic abnormalities, including obesity, insulin resistance, and hyperglycemia. Women report the most sleep disruption during the menopause transition (perimenopause) and into the postmenopausal years. In fact, sleep disruption is one of the primary reasons why midlife women seek medical care, with up to 60% reporting significant sleep disturbances (e.g., trouble falling asleep, early morning waking). Despite most women experiencing sleep disruption in midlife, most sleep manipulation trials have been conducted in

healthy men (not women). Furthermore, no study has investigated the molecular mechanisms linking sleep disruption and the changes in metabolism that coincide with menopause. Understanding these molecular mechanisms is the first step to the development of feasible treatment modalities that target sleep optimization and circadian function in midlife women.

In this ongoing NORC P&F study, we are conducting a randomized, crossover trial investigating the effect of sleep restriction compared to habitual sleep on adipose tissue and skeletal muscle insulin sensitivity in vivo and ex vivo. Notably, our study leverages the expertise of several key Pennington investigators, including Dr. Prachi Singh (sleep), Dr. Jacqueline Stephens (adipose tissue), Dr. Robert Noland (skeletal muscle), and myself (midlife women's health and metabolism). To accomplish our goals, we are randomizing up to 10 healthy, postmenopausal women with ≥7 hours of self-reported habitual nightly sleep to 4 consecutive nights of sleep restriction and habitual sleep. At the end of each sleep treatment, we are administering a two-step hyperinsulinemic-euglycemic clamp and are collecting skeletal muscle and adipose tissue biopsies. The overarching hypothesis is that sleep restriction will reduce adipose tissue and skeletal muscle insulin sensitivity compared to habitual sleep. Importantly, our findings will provide a strong framework for future clinical trials that investigate the effect of sleep disturbances on midlife women and allow us to define customized treatment strategies that target sleep optimization with the goal of improving metabolic health in these women.

Food Intake and Intra-Nasal Insulin for African American Adults

Katy Gwizdala, Ph.D.
Postdoctoral Fellow
Physical Activity & Ethnic Minority Health,
Pennington Biomedical Research Center

Over 5 million Americans have Alzheimer's Disease (AD) with the total projected to reach 14 million by 2060. Because diabetes and obesity are major risk factors for AD, and cerebral glucose hypometabolism is an AD hallmark, central insulin dysregulation as a driver of AD pathological pathways is under intense scrutiny. Besides AD pathology, central insulin dysregulation disrupts neural signals underlying feelings of fullness, hunger, and satiety, thus contributing to overeating.

Increasing central insulin availability via an intranasal exogenous insulin spray is hypothesized to correct central insulin dysregulation. Such sprays have been shown to preserve cognitive function among individuals diagnosed with, or at risk of, AD with minimal effects on peripheral insulin status. However, the metabolic and ingestive behavior effects of intranasal insulin sprays among AD patients or at-risk groups are not well understood. This is especially true among African Americans who are underrepresented in research and face disparities in metabolic diseases and AD.

This NORC P&F study will measure the effects of intranasal insulin on acute food intake and ingestive behavior psychological constructs among African American adults. We will utilize a double-blind, placebo-controlled, randomized crossover design to compare a single acute dose of intranasal insulin to saline placebo. Additionally, family history of AD, APOE genotyping, and adiposity (i.e., DXA) will be collected to assess how these factors influence intranasal insulin effects on caloric intake and ingestive behavior constructs. This could be the first step towards larger-scale studies of brain insulin effects on metabolism and AD in under-served populations. Importantly, it leverages the unique metabolism resources of the NORC and establishes a new research method at PBRC that could enhance the research environment.

The Effect of Altered Nitric Oxide Bioavailability on the Interaction of Obesity and Alzheimer's Disease

Tim Allerton, Ph.D.
Postdoctoral Fellow
Adipocyte Biology,
Pennington Biomedical Research Center

Both obesity and Alzheimer's Disease (AD) are associated with significant cardiometabolic complications that reduce the length and quality of life. The metabolic dysfunction that occurs during obesity, such as type 2 diabetes, increases the

risk of developing AD by as much as 50%. Hence, understanding the mechanistic link between obesity and AD is essential to develop novel therapeutic strategies for the prevention and treatment of AD. Among the shared pathologies between obesity and AD is reduced endothelial function that occurs because of reduced nitric oxide (NO) bioavailability. The loss of NO function in obesity causes reduced microvascular blood flow to peripheral tissue and the brain. Likewise, in AD, there is reduced cerebrovascular blood flow that likely has several negative effects including the enhanced deposition of β-amyloid (Aβ) and eventual cognitive decline.

Hypothalamic mitochondrial dysfunction has been also shown to be involved in the early stages of Aβ plaque formation and is considered the primary site of metabolic dysfunction in animal models of AD. Mitochondrial biogenesis can be increased in a NO-dependent manner. Whereas other data show overproduction of NO, as a result of chronic inflammation, can inhibit mitochondrial function. The functional role of NO in AD and obesity remains a major knowledge gap in the metabolic/vascular contributions to AD-related cognitive decline.

In this NORC Obesity and Alzheimer's Disease and Related Disorders (ADRD) Pilot and Feasibility study, we will examine the effects of increased versus decreased NO bioavailability in an obese mouse model of AD - APPswe/PS1dE9 (APP/PS1) mice. We will include the amino acid L-citrulline or Nγ-nitro-L-arginine methyl ester (competitive inhibitor) in the drinking water to increase or decrease NO bioavailability, respectively. We will assess cerebrovascular blood flow using a non-invasive near-infrared spectroscopy approach. Behavioral assessments will be performed throughout our 6-month study using a delayed matched-to-position task. Finally, we will perform high-resolution respirometry on hypothalamic homogenates to assess mitochondrial function. Drs. Paul Soto (behavioral psychology) and Brian Irving (mitochondria function) will contribute their respective expertise to the completion of the study aims. Dr. Jacqueline Stephen will serve as the primary mentor on this project. The results of this study will offer insight into the nature of NO function in obesity and its impact on AD-related mitochondrial dysfunction.

Enrichment Core Update

The Enrichment Core is excited to serve the NORC once again in its 3rd renewal. Our staff includes the Enrichment Program Director, Dr. Leanne Redman and Dr. Casie Lindsly Coordinator of Education and Training. Over the next five years our goal is to continue to offer a focused framework of outreach activities that:

- Foster multidisciplinary scientific approaches to nutrition/obesity research.

2021 Pilot and Feasibility Grants Request for Applications

The Pennington / Louisiana NORC invites applications for the 2021 Pilot and Feasibility (P&F) awards. The NORC will give **highest priority to translational research related to nutrition/obesity throughout the lifespan**. The hope for a P&F award is that it will generate enough preliminary data for the investigator to obtain extramural research funding from the NIH (e.g., R01).

We **encourage investigators** to approach problems relevant to our understanding of metabolism and function while increasing our understanding of the basic and clinical aspects of nutrition in the etiology, pathophysiology, therapy, and prevention of diseases.

Who is Eligible: Full-time Associate or Assistant Professors, and senior post-doctoral fellows at Pennington Biomedical Research Center and/or full-time faculty at another institution that is part of the NORC. See other criteria here.

Timeline:

- May 31, 2021 Letter of Intent (LOI) due. Detailed instructions can be found here.
- June 17, 2021 Invitations sent to those selected to present LOI.
- July 2, 2021 Full application due from those invited to submit after LOI presentations.

- Attract new investigators and investigators with relevant complementary expertise to nutrition/obesity research.
- Train the next generation of scientists in nutrition/obesity research.
- Provide a conduit between researchers and the lay community.

To achieve these goals, we strive to ensure our enrichment program caters to five unique groups: NORC members, the participating institutions' faculty, postdocs and students, and the lay community.

Stay tuned for updates on the upcoming Enrichment Core Events:

NORC Training Course on
Nutrition & Obesity Research Methods
April 26 - 28, 2022
at Pennington Biomedical Research Center

Fall 2021 NORC Sponsored Visiting Speakers
Thursdays at 11am CT
Invitations will be sent via NORC listserv.

NORC External Advisory Board

The Pennington / Louisiana NORC would like to express our gratitude and acknowledge the contributions of our external advisory board members. Their Advice and feedback are invaluable to the operations and strategic planning of the center.

Rudolph L. Leibel, M.D.
Professor of Medicine
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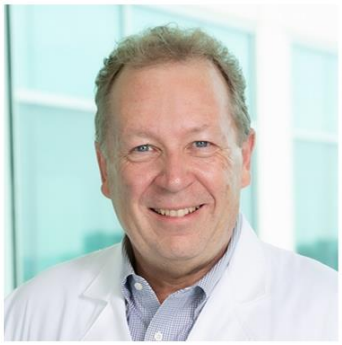

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