



August 2020

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NEWS FROM THE NORC DIRECTOR



Eric Ravussin, PhD
*Boyd Professor
AED of Clinical Science
Pennington Biomedical
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So far, 2020 has been a busy and productive year for our Pennington / Louisiana NORC.

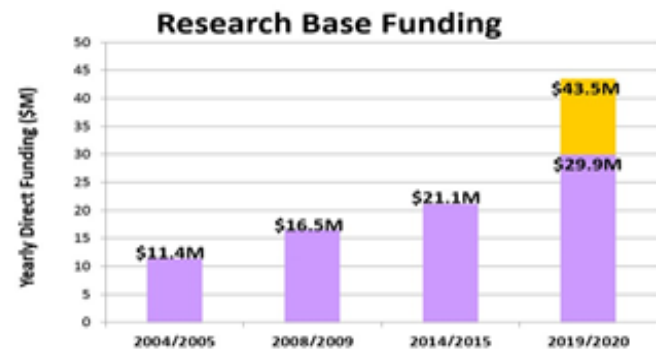
Obesity Day. The first annual Obesity Day was held on January 24, 2020 in New Orleans. See page 4 for details.

2020 NORC P&F applications were due on May 29, 2020 and two awards were issued on July 7, 2020. See page 2 and 3 for descriptions.

- Prachi Singh “Metabolic effects of metformin therapy in obstructive sleep apnea” (\$68,531).
- Yanlin He “Asprosin activates AgRP neurons through SK3 ion channel via sigma-1 receptor” (\$40,000).

Competitive Renewal Application. In the midst of COVID-19 pandemic crisis, we submitted our 4th cycle renewal application on June 2, 2020. This competitive application will be reviewed in October. Our current funding ends on April 31, 2021 and hopefully, despite a sharp competition, we will be renewed for May 2021. The highlights of the competitive renewal are:

- The growth of our NORC in terms of yearly nutrition/obesity direct funding and the number of NORC members since its inception in 2005 until this year is illustrated below. We have increased our research base direct cost to almost \$30M only at Pennington (purple) and up to >\$43M with our new members in New Orleans (yellow). We now have 56 NORC full members contributing to this research funding.



- NORC members will continue to have access to three state-of-the-art biomedical cores to



conduct their research with the highest rigor standards.

- **Human Phenotyping Core**
- **Molecular Mechanism Core**
- **Animal Model and Phenotyping Core**
- 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”**.
- After 15 years of operation, the Pennington/Louisiana NORC has never been as well-positioned to advance the science of nutrition and obesity on so many fronts and to foster the next generation of leaders in these fields.

P&F funding for research advances in obesity and Alzheimer’s disease and related disorders (ADRD). An application was submitted on March 5, 2020 to NIH for P&F funding for research advances in obesity and Alzheimer’s disease and related disorders (ADRD). We were awarded \$240k supplemental funding on June 26, 2020 and an RFA was immediately issued. We received five LOIs and three are presently continuing in the full application process due August 31, 2020.

Supplemental Grants. In July 2020, our NORC was successful in securing two supplemental grants.

- The first was a **Minority P&F** awarded to Dr. Cristal Hill (\$90,273). See P&F section for project description. The goal of Dr. Hill’s NORC proposal is to determine if remodeling of adipose tissue by dietary protein restriction reduces senescent cells in the adipose tissue, therefore reducing the senescence-associated secretory phenotype leading to impaired metabolic health. This pilot and feasibility grant will test the central hypothesis that dietary protein restriction protects against the detrimental effects of senescent cells during obesity.
- The second was for a **Trans-NORC Training Course** that will take place at Pennington Biomedical in April 2021. This course will provide

lectures and hands-on lab work related to nutrition and obesity research to Early Stage Investigators from the 12 NORCs. Importantly, it will facilitate future collaborations between the NORCs. Stay tune for more information.

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.

Metabolic effects of metformin therapy in obstructive sleep apnea



Prachi Singh, PhD,
Associate Professor,
Sleep and Cardiometabolic
Health Laboratory,
Pennington Biomedical
Research Center

Obstructive sleep apnea (OSA) is an established independent risk factor for diabetes and cardiovascular disease. Standard OSA treatment with positive airway pressure (PAP) is efficient in eliminating pathological intermittent hypoxia but shows inconsistent reduction in insulin resistance and metabolic risk factors. This underscores the need for development of therapeutic augmentation strategies aimed at improving insulin sensitivity and metabolic profile in OSA.

The modest effects of PAP therapy in OSA patients partly result from poor compliance but also suggest presence of underlying mechanisms which do not resolve with elimination of intermittent hypoxia. Chronic intermittent hypoxia mediated increased cellular senescence presents as a convincing underlying mechanism for persisting metabolic risk



in PAP treated OSA patients. Cellular senescence entails irreversible growth arrest and secretome changes through which senescent cells can cause tissue dysfunction and promote senescence in neighboring cells as well. Notably, increased cellular senescence is a recognized mechanism for development of metabolic disorders such as obesity and diabetes. We propose that adjunct metformin therapy will reduce the persisting cellular senescence in PAP treated OSA patients to improve tissue insulin sensitivity and metabolism.

In this NORC P&F study, we will examine the efficacy of metformin to improve whole-body, skeletal muscle, and adipose tissue insulin-sensitivity along with longitudinal assessment of tissue senescence burden and glucose metabolism. Towards this goal, we have brought together a multidisciplinary team including Drs. Noland and Gadde. We will conduct a 3-month double-blind, placebo-controlled, randomized clinical trial in non-diabetic OSA subjects using PAP therapy. We will also examine other recognized metabolic risk factors including body composition, lipid profile, and blood pressure. Our findings will provide a strong framework for a future clinical trial to evaluate the ability of metformin based adjunct therapy to restore metabolism in OSA patients. We seek to shift the clinical practice paradigm in OSA from preventing intermittent hypoxia to resolving underlying mechanisms which may contribute to detrimental metabolic consequences of OSA.

Asprosin activates AgRP neurons through SK3 ion channel via sigma-1 receptor



Yanlin He, Ph.D.
Assistant Professor,
Brain Glycemic and
Metabolism Control,
Pennington Biomedical
Research Center

Normal feeding behavior is essential for survival and homeostatic control of

energy balance. Aberrant feeding is associated with obesity and eating disorders (e.g. anorexia nervosa and binge eating disorder). These medical conditions constitute a major health issue to western societies. Hypothalamic agouti-related peptide (AgRP) neurons are essential for normal feeding behavior, and thus there is substantial interest in defining their functional regulation.

My earlier data demonstrated that AgRP neurons express high levels of the small conductance calcium-activated potassium channel 3 (SK3) and that SK3-channels inhibit neural firing. We also observed that food deprivation reduced SK3 expression in AgRP/NPY neurons and that this decrease in SK3 activity contributed to fasting-induced increases in AgRP neuron activity. Therefore, we have identified a novel mechanism that controls the activity of this important neural population. Importantly, our *Nature Medicine* paper reported that the newly discovered hunger hormone asprosin regulated food intake by directly activating AgRP neurons. Since obese humans and animals have high asprosin in circulation, these data suggest that AgRP neurons may contribute to asprosin-dependent changes in food intake. However, the mechanism through which asprosin activates AgRP neurons is unclear.

In this NORC Pilot and Feasibility study, we hypothesize that asprosin acts via the sigma-1 receptor and SK3 channel to activate AgRP neurons, resulting in increased food intake. This proposal will seek to directly test this overarching hypothesis. I will first generate mice with conditional deletion of SK3 in AgRP neurons and use them to test if SK3 is required for normal AgRP neuron activity, feeding behavior, and asprosin responsiveness. I will also test if blocking sigma-1 receptors blocks asprosin's effect on food intake in WT but not SK3 KO mice. Importantly, these studies will combine *in vitro* electrophysiological analysis of the mechanisms underlying neural activity with functional *in vivo* measures of mouse feeding behavior. Ultimately, this project focuses on a fundamentally novel mechanism to explain the

mechanism mediating the effects of the new feeding-related hormone asprosin, while also testing a novel mechanism regulating AgRP neuron activity.

NEWS ON ENRICHMENT AND TRAINING

Pennington Biomedical's NIDDK supported T32 on Training in Obesity Research began its third consecutive 5-year funding cycle in July of 2019. In the past year, two trainees successfully graduated from the program. **Nicole Fearnbach** was promoted to an Assistant Professor – Research position at PBRC. **Kara Marlatt** has also been promoted to an Assistant Professor position at PBRC and has been awarded a LA CaTS Roadmap Scholarship. During this time, the program has recruited and appointed three new trainees so that all five positions are filled. The bios below highlight our newest T32 trainees.



Melissa Linden received her PhD in Exercise Physiology from the University of Missouri. In November of 2019, Dr. Linden was appointed to the T32 and she will pursue research with mentors, Robert Noland, PhD and Krisztian Stadler, PhD.



Melissa Erickson received her PhD in Exercise Physiology from the University of Georgia. She was appointed to the T32 in December of 2019 to pursue her research with her mentors John Kirwan, PhD and Gangarou Davuluri, PhD.



Redin Spann received his PhD in Neuroscience from the University of Mississippi Medical Center. Dr. Spann was appointed to the T32 program in August of 2020 and will be perusing research with Dr. Chris Morrison in the Neurosignaling laboratory.

FIRST ANNUAL OBESITY DAY

January 24th, 2020 marked the inaugural NORC Obesity Day held at the LSU Health Sciences Center (HSC) in New Orleans. There were 53 attendees from Pennington Biomedical, LSU HSC and Tulane and thus this event offered a conduit for scientific exchange between members of the NORC community. This half-day event featured a welcome from Eric Ravussin, NORC Director, presentations from each Core Director, 17 “blitz” presentations on NORC member research and an overall discussion. This event will become an annual Enrichment Core activity with plans for future expansion to other institutions within the state either with a similar in-person event or a virtual event via webinar.



Molecular Mechanisms Core at Obesity Day 2020.



Owen Carmichael, PhD presents at Obesity Day.



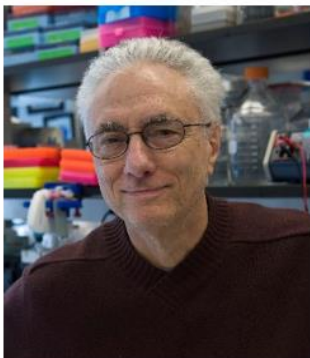
SAVE THE DATE – LAUNCH OF THE PENNINGTON/LOUISIANA NORC BIOREPOSITORY

The Pennington/Louisiana NORC was awarded a supplemental grant from NIH to develop a biorepository. The goal of the repository is to provide nutrition and obesity researchers access to data and biospecimens collected in clinical research studies performed at Pennington Biomedical. In the newly completed Phase 1, the online portal allows NORC members to independently search the availability of clinical data from over 13,000 participants in more than 200 studies. Via the portal members can submit requests for data. The repository will allow new and exciting hypotheses to be studied and for investigators to obtain preliminary data in support of grant applications.

Join us for a virtual tour of the on Thursday August 27th at 11:00am CST via a [Microsoft Teams Meeting](#).

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 operation and strategic planning of the center



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