NUTRITION OBESITY RESEARCH CENTER

SEPTEMBER 2014

PENNINGTON BIOMEDICAL RESEARCH CENTER LSU

TRAINING UPDATE

Phil Brantley, PhD

The NIH continues to support two T32 Postdoctoral Training Grants at Pennington Biomedical. One supported by NIDDK entitled "Obesity: Genes to Man" encourages researchers to train in multiple areas of obesity research (molecular and genetics, behavioral and body composition); this program has an immediate opening. We are awaiting a council funding decision on the renewal of our NCCAM funded T32 which promotes research into botanical approaches for combating metabolic syndrome. We anticipate seven new fellowship positions as early as January 1, 2015 and are accepting applications. NIH T32 fellowships are open to US citizens and individuals with resident alien status. These programs provide up to three years of training in skills to reach research independence. Find out more about these postdoctoral fellowship opportunities at www.pbrc.edu/training-and-education/.

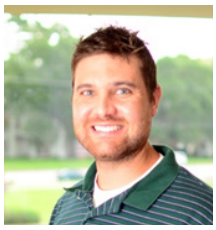
IN THIS ISSUE

NEW AWARDS FOR PILOT AND 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 updates from our 3 P&F winners.

1. EFFECTS OF VARIED MACRONUTRIENT COMPOSITION ON WEIGHT LOSS IN OBESE ADOLESCENTS

John W. Apolzan, PhD



Currently one third of adolescents are overweight or obese, a rate that has tripled over the past 30 years. The prevailing belief is that homeostatic systems are in place to maintain energy homeostasis. However, weight gain and subsequent obesity reflects a long-term positive energy imbalance, and evidence based treatments are needed to reduce long-term weight gain in children and adolescents.

Current optimal dietary treatments for adolescent obesity are unknown. One possible treatment is to consume a greater amount of protein, the most satiating macronutrient, which would also provide beneficial effects by reducing dietary carbohydrate intake. During the ongoing 12-week pilot study, we are testing the effect of two isocaloric energy restricted diets that vary in dietary protein on weight loss, subjective ratings of appetite, and glycosylation in overweight and obese adolescents.

Adolescents 12-17 years old receive an intervention that relies on nutrition education, nutritional counseling, social cognitive therapy, behavioral strategies, self-monitoring, portion size reduction, and increased physical activity. These techniques and treatment strategies have proven beneficial for multilevel and nutritionally complete interventions in adolescents. Participants meet for an individual session then group sessions occur every other week for the remaining 12 weeks. They are (in no order so participants may drop into the rotation): 1) dairy 2) fruits 3) vegetables 4) grains 5) oils and beverages 6) physical activity. Energy restriction and protein intake are discussed

Continued, page 2

Effects of varied macronutrient composition on weight loss in obese adolescents, continued

with each theme. Participants get an individualized dietary meal plan. Dietary counseling is based on the USDA MyPlate guidelines with extra attention and focus on appropriate protein food choice.

Specifically, the meal plan is designed to meet 75% of energy requirements and the protein, carbohydrate, and fat percentages for the participants' assigned group(s). Thus, the lower protein group is instructed to consume 15% of energy as protein, with 25% and 60% of energy from fat and carbohydrate, respectively. The higher protein group is instructed to consume 30% of energy as protein, with 25% and 45% of energy from fat and carbohydrate, respectively.

We are utilizing the NORC Human Phenotyping Core by including psychological questionnaires (Eating Inventory and Food Craving Inventory), ratings of subjective states with VAS (e.g. hunger), and utilizing the remote food photography method to capture energy and nutrient intake.

In summary, adolescent overweight and obesity is a national concern. Besides excess weight, many adolescents have comorbidities or are at an increased risk for these comorbidities in the future. This pilot and feasibility study will allow us to submit future grants to determine the optimal dietary intervention for weight loss in adolescents.

2. BREASTFEEDING DURATION & PRO-INFLAMMATORY BIOMARKERS OBESITY

Henry Nuss, PhD

Although behaviors such as diet and exercise contribute greatly to pediatric health outcomes, biological mechanisms which contribute to obesity should also be considered. Breastfeeding has been associated with improved health outcomes for both mother and child.

Obesogenic pro-inflammatory biomarkers, such as tumor necrosis factor alpha (TNF-α), and regulatory hormones (leptin, adiponectin, resistin, ghrelin), are known to be transferred to offspring via breast milk. However, other pro-inflammatory cytokines, such as interleukin 1-beta (IL-1ß) have not been explored fully in this context. Moreover, the quality of breast milk is highly influenced by maternal behaviors, such as smoking, alcohol and dietary intake, e.g., macronutrient content, under- or over-nutrition.

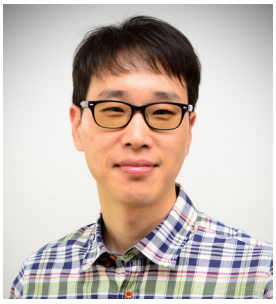
Omega-3 (n-3) fatty acids are known anti-inflammatory agents. Conversely, omega-6 (n-6) fatty acids are thought to have pro-inflammatory effects. While there is evidence that overweight and obese women have different serum lipid profiles than normal weight women during pregnancy, the effects of high levels of n-6 or low levels of n-3 long-chain polyunsaturated fatty acids (LC-PUFA) in maternal blood on breast milk concentrations and subsequent effects on the development of obesity in offspring are unknown. As such, maternal macronutrient intake exerts a strong influence on the risk of obesity in children.

Our goal is to evaluate the relationship between inflammatory biomarkers/hormones in maternal serum and breast milk in normal weight versus overweight and obese mothers. Findings will provide clues to the role of nutrition and inflammation in fetal programming and subsequent childhood outcomes, such as obesity. We will conduct a prospective cross-sectional analysis of two groups of pregnant women—normal weight women and overweight/obese women. We will measure levels of LC-PUFAS (n-3, n-6), pro-inflammatory biomarkers, and regulatory hormones (resistin, ghrelin) in serum (35, 0-36, and 6 weeks gestation and 4, 0-7, and 6 weeks postpartum) and breast milk (4, 0-7, and 6 weeks postpartum) in normal weight (n=20) and overweight and obese (n=20) mothers. Blood serum and plasma and breast milk levels of these measures will be compared from pregnancy to postpartum within and between normal weight and overweight and obese women.

Additional maternal procedures including questionnaires, anthropometrics, body composition measurements, energy intake measurement, and physical activity measurement will be investigated at 35, 0-36, and 6 weeks gestation and 4, 0-7, and 6 weeks postpartum. Infant procedures including anthropometrics, body composition measurements, and energy intake measurement will be investigated at 0 and 6 weeks.

3. GENE PROFILING OF NEURONS ACTIVATED BY TEMPERATURE CHANGES

Sangho Yu, PhD



The hypothalamus is a central regulator of thermogenesis and thus overall energy expenditure. Recent discoveries of functional brown adipose tissue (BAT), a specialized fat tissue for heat production in adult humans, raised tremendous interest in BAT activation as a means to treat obesity. Even though previous studies have identified important brain regions involved in the regulation of BAT thermogenesis, their cell types and exact functions are largely unknown. The proposed research investigates the gene expression profile of neurons in the hypothalamus that are activated by acute ambient temperature change, a major stimulus for BAT thermogenesis. This will be accomplished by phosphorylated ribosome capture, a recent innovation of purifying mRNAs selectively from activated neurons. This technique takes advantage of the fact that the phosphorylation of ribosomal protein S6 can serve as a neuronal activation marker. In other words, immunoprecipitating phospho-S6 co-precipitates ribosome/mRNA complexes from activated neurons, facilitating identification of mRNAs uniquely expressed in activated neurons. Phosphorylated ribosome capture enables the unbiased systematic identification of genes and cell types that are responsive to a stimulus, providing numerous possibilities to study how certain behavior or physiology is controlled by specific populations of neurons. Identified genes can serve as cell type-specific markers to create tools that enable the labeling and recording of neurons using fluorescent proteins, and in vivo manipulations of neuronal activities using optogenetics or pharmacogenetics.

In summary, identification of genes uniquely expressed in activated neurons by temperature change can provide new insights into the mechanism of central thermoregulation including BAT thermogenesis. These newly discovered genes or cell types also could be potential drug targets to increase energy expenditure or to prevent diet-induced decrease in energy expenditure in obesity treatment.

THE OBESITY SOCIETY EARLY-CAREER RESEARCH GRANT

Courtney Peterson, Ph.D., MSC

Dr. Courtney Peterson is currently an assistant professor whose research focuses on dietary approaches to combat obesity and diabetes. Dr. Peterson recently received a prestigous Early-Career Research Grant from The Obesity Society (TOS). She was chosen as one of two recipients out of 156 applicants for the award. Her grant entitled “Does Meal Timing Affect Energy Expenditure” will explore whether when we eat affects how many calories we burn.

Recent studies suggests that meal timing may affect weight loss, and that eating early in the day may have the most benefits. A 2013 study published in the journal *Obesity* found that women on a 1400-calorie diet lost 2.4 times more weight when they consumed half of those calories at breakfast, rather than at dinner. Similarly, a study in 420 overweight men and women found that dieters who ate their largest meal before 3 p.m. lost 29% more weight than those who ate their main meal after 3 p.m., despite similar calories eaten and exercise. Conversely, one study showed that when people snack at night, it disrupts fat burning.

But what is unknown is whether eating early in the day facilitates weight loss by curbing appetite, so that people eat less food, or by causing people to burn more calories; this is the big unanswered question. In a handful of studies in mice and rats, eating earlier in the day did cause the rodents to burn more energy. Dr. Peterson’s study will test whether eating early in the day also increases the number of calories people burn using Pennington Biomedical’s state-of-the-art metabolic chambers.

The study will also look at how meal timing affects blood sugar levels, heart rate, physical activity, and circadian rhythms. If Dr. Peterson’s hypothesis that meal timing can affect calorie- and fat-burning is correct, this would be an important finding and would overturn the idea that grazing is best for health. Dr. Peterson’s study will start in fall 2014 and will finish by fall 2015.

THE REGULATION AND METABOLIC EFFECTS OF gp130 CYTOKINES IN HUMAN WHITE ADIPOSE TISSUE DEPOSITS

Ursula A. White, PhD

White adipose tissue (AT) is a dynamic organ that impacts whole body energy homeostasis. While obesity, or overall excessive adiposity, is associated with serious co-morbidities such as Type 2 Diabetes Mellitus (T2DM), the distribution of adipose tissue (AT) may be a stronger predictor of metabolic health risks. Upper-body adiposity, especially visceral (VAT) but also subcutaneous abdominal (scABD) depots, is associated with metabolic complications of obesity, while lower-body adiposity (subcutaneous gluteal and femoral [scFEM] depots) may be protective against adverse health effects.

Current research is focused on identifying the factors and mechanisms that regulate the distribution, expansion, and function of distinct AT depots and influence metabolic health.

Adipose tissue secretes adipokines that influence both AT and systemic metabolism. The gp130 cytokines are a group of structurally related proteins that modulate many biological processes. Though circulating levels of these cytokines have been observed in humans, most obesity-related research has focused on interleukin (IL)-6 and ciliary neurotrophic factor (CNTF) as potential therapeutic targets. Studies have shown that other gp130 cytokines, namely cardiotrophin (CT)-1 and oncostatin M (OSM), are expressed in rodent AT and can modulate glucose and fat metabolism in mice. Limited data highlight CT-1 as a positive effector of energy metabolism in rodents, as CT-1 null mice develop obesity, dyslipidemia, hyperglycemia, and insulin resistance, mimicking the Metabolic Syndrome. OSM has well-characterized actions in liver development and may influence hepatic insulin resistance & steatosis.

Our novel preliminary findings in eight subjects reveal that CT-1 and OSM are differentially expressed in metabolically distinct AT depots of humans. Additional preliminary data indicate that OSM expression is elevated with increasing body mass index (BMI) and highly correlates with whole-body insulin resistance. Overall, the modulation of CT-1 and OSM in human AT and whole-body metabolism has not been fully elucidated. Hence, the proposed experiments are necessary to assess CT-1 and OSM in human metabolism using a large sample analysis.

The objective of this K01 grant is to examine the novel regulation (expression and secretion) of specific gp130 cytokines (CT-1 and OSM) in distinct AT depots of obese and non-obese humans. Notably, VAT, scABD, and scFEM depots, which have different metabolic properties, will be assessed.

In addition, this project will evaluate how the production of CT-1 and OSM is modulated by insulin sensitivity in humans and assess the direct effects of these cytokines on insulin action. Testing of the specific aims involves the collection and analysis of human samples and physiological data from 3 completed and on-going clinical studies [“Cellular Dynamics of Fat Distribution” (R01-DK090607); “Fat Cell Size and Overfeeding“(R01-DK060412); and “Effect of Bariatric Surgery and Weight Loss on Energy Metabolism and Insulin Sensitivity” (Ethicon Endo-Surgery, Inc. Grant #25404)- all PI: Ravussin, E)]. We hypothesize that CT-1 and OSM production and secretion are modulated by depot and adiposity and highly correlate with systemic insulin resistance. In addition, we propose that CT-1 and OSM can directly affect insulin sensitivity in human adipocytes.

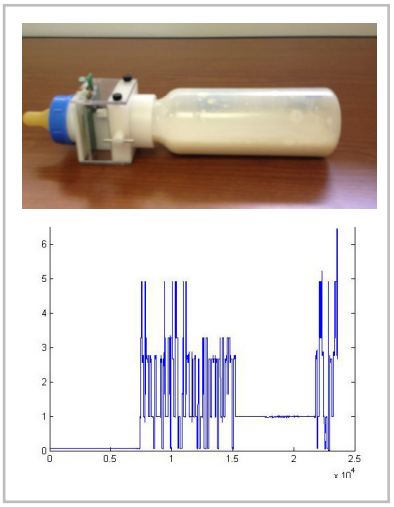
These studies will fill a critical void in the literature by providing novel information about gp130 cytokine regulation in human AT metabolism.

MATERNAL AND INFANT PHENOTYPING CORE

Leanne Redman, PhD

The NORC is excited to announce the establishment of the Maternal and Infant Phenotyping Laboratory. Directed by Dr. Leanne Redman the MIP laboratory exemplifies the purpose of the NORC being on nutrition programming by focusing on the collection of outcome assessments in infants and their mothers in both the pregnant and postpartum states.

The MIP laboratory houses an infant scale and infant lengthboard, two Neonur feeding bottle apparatuses, an infant EchoMRI, a PEAPOD, and an infant metabolic chamber. The lab has the necessary equipment and laboratory space to conduct studies focusing on maternal and infant areas of interest. They have dedicated expertise. In addition to Dr. Redman, Ms. Abby Duhé M.S. oversees the daily operation of the laboratory, developed the standard operating procedures, maintains quality control and conducts outcome assessments.



Current standard operating procedures include: assessment of infant anthropometrics including length, weight, head, and abdominal circumferences, infant body composition by skinfold thickness, PEAPOD and EchoMRI, energy metabolism by infant metabolic chamber, nutritive sucking behavior by Neonur feeding testing, breast milk collection and processing, and placental biospecimen collection and processing.

We would like to highlight two resources unique to the Maternal and Infant Phenotyping Laboratory: the Neonur infant feeding bottles and the infant metabolic chamber. The Neonur infant feeding bottle includes a bottle attachment that fits with a commercially available bottle and nipple which can be filled with infant formula or expressed breast milk. The bottle attachment contains a pressure sensor with a circuit board that can measure and store 5 sucking variables: total intake of formula/milk (g), total number of sucks, overall sucking rate (sucks/s), maximum sucking pressure (mmHg), and suck rate within sucking bursts (sucks/s). The total number of sucks measured (an indicator of energy intake) in 3 month old infants has been shown to be a significant predictor of body weight in children aged 1 and 2 years.

Our newest addition to the Maternal and Infant Phenotyping Laboratory is the infant metabolic chamber that can be used to measure energy expenditure, activity and energy requirements in infants. Energy expenditure components including total energy expenditure, pre-prandial basal metabolic rate, standard metabolic rate, and the index of physical activity can be measured up to 4 hours in infants ≤ 1 year of age by indirect calorimetry using the infant metabolic chamber. The chamber holds a small plexiglass enclosure which has four arm holes allowing for infant interaction and care. A parent or staff member can place arms through the holes for various activities including feeding or changing diapers throughout measurement. The enclosure includes a comfortable mattress, and infants can be placed on the mattress with clothing, diapers, and blankets. Parents and study staff can monitor activity and comfort of the infant during the infant's stay in the infant metabolic chamber. The infant metabolic chamber includes a computer system for data collection and storage for infant supplies.

In addition, an instrument rack houses the oxygen and carbon dioxide analyzers, flow meter, barometric pressure, temperature and humidity sensors, and the electronic eye controller which are all continually measured for consistency, measurement, and safety.

We look forward to working with NORC members to develop innovative research ideas using the infant metabolic chamber system, various methods for infant body composition analysis and infant feeding behavior with the Neonur.

PENNINGTON BIOMEDICAL'S NORC TO HOST DECEMBER SCIENTIFIC SYMPOSIUM – "NUTRITIONAL PROGRAMMING AND OBESITY: STATE-OF-THE-SCIENCE, INNOVATION AND FUTURE DIRECTIONS"

The NIDDK-funded Nutrition Obesity Research Center (NORC) in conjunction with Pennington Biomedical Research Center will host a scientific symposium December 7-9, 2014 in Baton Rouge.

The symposium "Nutritional Programming and Obesity: State-of-the-Science, Innovation and Future Directions," will be co-chaired by Drs. Eric Ravussin, Moshe Szyf and Leanne Redman, with the goal of supporting the mission of Pennington Biomedical's NORC: "to facilitate and promote collaborative and multi-disciplinary interactions that will foster new research ideas and enhance the translation of basic nutritional research findings into the clinical arena and ultimately into practical application."

A select group of invited scientists will provide updates on the current scientific knowledge on the role of environmental factors with an emphasis on nutrition in utero and postnatal and its impact on chronic diseases, which may lead to novel interventional strategies to slow down the increase in the prevalence of obesity and its comorbidities.

Other goals are to review key mechanisms to developmental and nutritional programming of obesity and related chronic disease such as Type 2 diabetes and hypertension; to review and discuss the likelihood that epigenetic-based changes contribute to the early establishment of a predisposition to later in life disease; to increase participant knowledge of nutritional programming of obesity, chronic diseases and aging; to increase the knowledge of study designs and analytical approaches to conduct epigenetic-based research studies contributing to the programming of obesity and chronic disease; to understand the role of epigenetics in personalized approaches to disease management; and to produce a peer-reviewed publication to enhance the knowledge of epigenetic mechanisms contributing to the programming of obesity and related chronic diseases.

PENNINGTON BIOMEDICAL RESEARCH CENTER
in conjunction with the Nutrition Obesity Research Center (NIDDK) present:

SCIENTIFIC SYMPOSIUM
Nutritional Programming and Obesity
State-of-the-Science, Innovation and Future Directions December 7-9, 2014

SUNDAY, DECEMBER 7

6:00-9:00 PM — Pennington Biomedical Research Center Tour, Jazz Reception & Dinner

MONDAY, DECEMBER 8

All symposium meetings 12/8 and 12/9 will be held in the Abell Board Room of the Lod Cook Conference Center, LSU Main Campus, 3838 W. Lakeshore Drive, directly across from the Lod Cook Hotel

6:00-9:00 PM — **Welcome and Overview**
Leanne Redman, Ph.D.
Associate Professor, Reproductive Endocrinology & Women's Health Research

8:40-9:20 AM — **Early life exposures setting up life-long trajectories, implications for obesity**
Moshe Szyf, Ph.D.
Full Professor, Department of Phyarmacology and Therapeutics, McGill University Montreal, Quebec, Canada

SESSION I: EPIDEMIOLOGY AND MECHANISMS

9:20-10:00 AM — **Epidemiology of nutritional programming**
Suzanne Ozanne, Ph.D.
Reader in Developmental Endocrinology, University of Cambridge, UK

10:00-10:15 AM — **BREAK**

10:15-10:55 AM — **Mechanistic insights from animal models**
Rebecca Simmons, M.D.
Professor of Pediatrics, Perelman School of Medicine, Philadelphia, PA

10:55-11:35 AM — **Prospects for probing epigenetic mechanisms in human studies**
Bas Heijmans, Ph.D.
Associate Professor, Leiden University Medical Center, The Hague Area, Netherlands

SESSION II: INTERVENTION STUDIES

11:35-12:15 PM — **Effects of nutrient supplementation and in utero exposures on newborn epigenetic profiles**
David B. Dunger, M.D.
Professor of Pediatrics, University of Cambridge Metabolic Research Laboratories Cambridge, UK

12:15-1:00 PM — **LUNCH – Lod Cook Alumni Center, Cook Room**

1:00-1:40 PM — **Diet and exercise interventions in adults**
Charlotte Ling, PhD
Associate Professor, Lund University Department of Clinical Sciences Skane University Hospital, Malmo, Switzerland

1:40-2:20 PM — **Weight loss interventions**
J. Alfredo Martinez, Ph.D.
Professor of Food Sciences and Nutrition, University of Navarra, Pamplona, Spain

2:20-2:35 PM — **BREAK**

2:35-3:35 PM — **Panel Discussion – Current insights and potential mechanisms Panelists:**
Speakers 1, 2, 3
Moderator: Szyf

3:35-5:00 PM — **Panel Discussion – Lessons learned from intervention studies: How do we identify people at risk?**
Panelists: Speakers 4, 5, 6, 7
Moderator: Ravussin

5:00-7:00 PM — **Hospitality Suite – Lod Cook Hotel, Room TBD**

7:00-9:00 PM — **Dinner - Lod Cook Alumni Center, Cook Room**

TUESDAY, DECEMBER 9

SESSION III: TRANSLATION

9:00-9:40 AM — **Role of epigenetics in personalized medicine**
Robert Waterland, Ph.D.
Associate Professor of Pediatrics and Molecular & Human Genetics
Baylor College of Medicine

9:40-10:20 AM — **Considerations for intervention designs**
Marie-France Hivert, M.D., MMSc
Assistant Professor, Department of Population Medicine Harvard Pilgrim Health Care Institute, Harvard Medical School

10:20-10:35 AM — **BREAK**

10:35-11:15 AM — **Panel Discussion - What interventions should be done and when?**
Panelists: Speakers 8, 9
Moderator: Redman

SESSION IV: ROUNDTABLE - ALL meeting participants

11:15-12:15 PM — **Consensus Discussion - Putting it together**
Boxed Lunch

INTERNAL ADVISORY BOARD

Featured are the members of our NORC Internal Advisory Board. We would like to express our gratitude to these members and acknowledge their contributions. They advise the Executive Committee in decision making and strategic planning, provide instruction and mentorship for our enrichment programs, and offer peer review support to our pilot and feasibility grant initiatives.

Wayne Backes, Ph.D.
Professor, Pharmacology
LSU HSC

George Bray, M.D. (Chair)
Boyd Professor, Clinical Research,
Pennington Biomedical

Elizabeth Floyd, Ph.D.
Assistant Professor,
Ubiquiton Lab,
Pennington Biomedical

William Johnson, Ph.D.
Professor, Biostatistics,
Pennington Biomedical

Peter Katzmarzyk, Ph.D.
AED for Preventive Medicine and Healthy Aging,
Pennington Biomedical

Jackie Stephens, Ph.D.
AED for Basic Science,
Pennington Biomedical

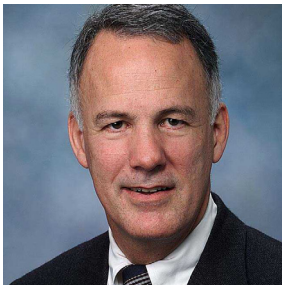
EXTERNAL ADVISORY BOARD

Featured are the members of our NORC External Advisory Board. We would like to express our gratitude to these members and acknowledge their contributions. Their advice and feedback are invaluable to the operation and strategic planning of the NORC.

Brad B. Lowell, M.D., Ph.D.
Associate Professor of Medicine, Division of Endocrinology, Beth Israel Deaconess Medical Center, Harvard Medical School

Daniel P. Kelly, M.D.
Scientific Director,
Professor, Burnham Institute for Medical Research

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



John M. Miles, M.D.
Professor of Medicine,
Endocrinology, Mayo Clinic