Clinical Nutrition Research Unit of Maryland
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Status: New
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Website: medschool.umaryland.edu/cnru/index.asp

Organization and Goals

The Clinical Nutrition Research Unit (CNRU) of Maryland was funded in October, 2005. Our CNRU brings together resources and expertise in genetic epidemiology, statistical genetics, functional genomics, basic adipose cell biology and clinical investigation that can address basic mechanisms that determine individual responses to energy imbalance and to specific nutrients. Furthermore, our team has the expertise in applied physiology and clinical interventions to carry out clinical and translational research that extend basic research findings. By providing infrastructure that can facilitate the work of our already highly collaborative members, the CNRU of Maryland will foster progress toward the goal of establishing nutritional guidelines that minimize chronic disease risk and address health disparities in our population. Our research base brings together 44 NIH funded investigators working on nutrition-related research at three institutions (University of Maryland, Johns Hopkins University, and U.S. Department of Agriculture, Beltsville), with multidisciplinary expertise and a strong track record of collaboration and NIH funding.

The goals of the CNRU of Maryland are to:

1. Foster inter- and multidisciplinary efforts to identify genes and nutrient-gene interactions that influence nutrient metabolism and the risk of chronic diseases during aging (particularly type 2 diabetes, CVD, and osteoporosis).
2. Understand the mechanisms by which weight loss through caloric restriction and exercise improve risk factors for type 2 diabetes and cardiovascular disease (e.g. hypertension, dyslipidemia, insulin resistance).
3. Test the effectiveness of lifestyle intervention strategies (diet and/or exercise) to:
    a. prevent and treat obesity and its co-morbidities in at risk groups (middle aged/older individuals, urban minorities, and youth) and
    b. prevent and treat sarcopenia and osteopenia associated with deconditioning and suboptimal nutrition in the elderly, as well as improving rehabilitation after hip fracture.
4. Establish 3 core laboratories (1- Clinical Research, 2- Genetics, Genomics and Genetic Epidemiology, 3- Adipose Biology and Basic Mechanisms) to provide state-of-the-art and cost-effective services to expand and enhance nutrition and obesity research in Maryland.
5. Attract young investigators from different fields of biomedicine to apply innovative methods that address important questions in the field of nutrition through the pilot and feasibility grant mechanism.
6. Increase awareness of researchers and practicing health professionals in Maryland about the important role of nutrition in human health by:
    a. administering the newly-created Baltimore Distinguished Lecture Series in Nutrition that will promote academic and research collaborations and
    b. enriching and promoting nutrition education for medical, graduate, and allied health professional students, housestaff, and primary care physicians.

Core Laboratories

Administrative Core: Susan K. Fried, Ph.D., Director; Alan R. Shuldiner, M.D., Associate Director; Andrew P. Goldberg, M.D., Pilot and Feasibility Grant Program; Nanette Steinle, M.D., Enrichment Director; Allison Pledgie, Ph.D., Program Manager

Executive Committee
Susan K. Fried, Ph.D., Alan R. Shuldiner, M.D., Andrew P. Goldberg, M.D., Benjamin Cabellero, M.D., Ph.D.

External Advisory Committee: To be named

Internal Advisory Committee: To be named

Biostatistics Subcore (BSC): J. Sorkin, Director

The BSC will be a service center for CNRU researchers and will provide biostatistical consultation to other investigators who are doing research in the fields of obesity and nutrition at University of Maryland and the Baltimore VA Medical Center. Additionally, the Core will develop new methods for the collection of data from older subjects. The specific aims of BSC are to:

- Provide CNRU researchers with a centralized, user-friendly information system for the acquisition, storage, review, and analysis of data.
- Insure confidentiality, physical security, and logical integrity of all CNRU data.
- Assist the Safety Monitoring Board review the safety of CNRU studies.
- Produce reports that can be used to review data for accuracy, validity, and completeness.
- Analyze CNRU data that are to be presented in papers, reports, and at scientific meetings.
- Assist researchers in the design, implementation, and analysis of CNRU projects.
- Provide didactic training in statistical methods to CNRU faculty, trainees, and staff.
- Develop new methods for data collection in older people.
- Act as a statistical and informatics resource for non-CNRU (e.g. NIH funded) researchers.
- Work with the Genetics, Genomics, and Genetic Epidemiology Core (GGG) on the analysis of Genetic data.

Genetics, Genomics, Genetic Epidemiology Core (GGG): Alan Shuldiner, M.D., Director; Braxton Mitchell, Ph.D. and Dai-Wei Gong, Ph.D., M.D., Co-Directors

The GGG Core will support a major goal of our center: to discover genes and gene-nutrient interactions associated with risk of obesity, diabetes, hypertension, atherogenesis, and longevity as well as to understand their molecular, cellular and physiological roles in the etiology of obesity, diabetes, and associated metabolic abnormalities. Thus, this Core will provide investigators with access to large genotyped population databases and assist investigators with access to gene chip technology, unique Expressed Sequence Tags (EST) libraries, and bioinformatic tools. Importantly, the Core will facilitate studies of the genetic underpinnings in phenotypic responses to nutrition interventions such as weight loss or specific dietary components.

The objectives of the GGG Core are to provide the following services and support for CNRU investigators:

Molecular Genetics:

- DNA sequence analysis
- High throughput short tandem repeat (STR) analysis
- High throughput single nucleotide polymorphism (SNP) analysis
- Mutation detection by denaturing high performance liquid chromatography (dHPLC)
- DNA extraction and quantitation
- Other general molecular biology and genetics methods (PCR, primer design, site directed mutagenesis, cDNA, and genomic cloning)

Genetic Epidemiology:

- Data entry and management
- Study design and power calculations
- Association and linkage analysis
- Haplotype construction and analysis
- Access to Banked DNA, Serum, and Plasma

Functional Genomics:

- cDNA microarray analysis (probe labeling, hybridization, washing, scanning)
- Bioinformatics and microarray data analysis
- Real time RT-PCR

Clinical Research Core (CRC): A. Goldberg, M.D., Director; Alice Ryan, Ph.D., Co-Director; Heidi Ortmeyer, Ph.D., Lab Manager

The CRC will serve as the central CNRU resource to facilitate clinical nutrition research. The CRC multidisciplinary team of experts in nutrition, exercise physiology, body composition, metabolism, and behavioral therapy will assist and train CNRU investigators in the skills necessary to conduct clinical nutrition research. It will also provide comprehensive quality-controlled phenotyping of research subjects with respect to the following basic nutrition and physical activity assessments:

- Medical evaluation and screening
- Body composition and regional fat distribution
- Exercise capacity and ambulatory function
- Dietary intake and nutritional status
- Energy expenditure
- Glucose metabolism, hormones, and metabolites

The objectives of the CRC are to:

- Obtain baseline medical evaluations and standardized, quality-controlled measures of: a) body composition, including total body fat, lean mass, visceral fat, intramuscular fat, and bone density, b) physical activity habits and VO_2 max, c) lipids and glucose tolerance, and d) dietary assessment, eating, and activity habits to characterize (phenotype) subjects for enrollment in clinical research protocols;
- Perform selected clinical nutrition laboratory tests (bone-mineral metabolism, liver and renal function, minerals, and nitrogen containing compounds) and measures of insulin sensitivity, cytokines, hormones, and metabolites for clinical research studies;

- Conduct clinical trials in nutritional sciences, metabolism, and the modification of CVD and osteoporosis-related hip fracture risk in patients by providing specialized resources such as a metabolic kitchen, nutrient assessment services, exercise testing and training facilities, and core laboratory services for the conduct of intervention studies;
- Serve as an educational/consultation resource for investigators, junior faculty, fellows, and students in developing hypothesis-driven experimental designs, performing and interpreting specialized research laboratory tests, and implementing clinical research studies in nutrition and obesity; and
- Initiate new research that relates to CRC service functions by developing a CNRU Metabolism/Genetics Patient Registry to enhance recruitment, permit cross-sectional and interventional studies, and maintain longitudinal follow-up of participants. This registry will foster collaborations among CNRU investigators by providing a database that integrates metabolism with measures of phenotypic and genetic traits to permit the investigation of gene-environment-metabolism interactions.

Adipose Tissue Biology and Basic Mechanisms Core (ABC): Susan K. Fried, Ph.D., Director; John McLenithan, Ph.D. and Carole Sztalryd, Ph.D., Core Managers

The ABC facilitates access of investigators to adipose tissue samples from well-characterized subjects and assists investigators with analysis of adipose tissue morphology and metabolism, specialized cell and organ culture methods, and analysis of gene and protein expression. This Core enables investigators to accurately phenotype adipose tissue and adipocyte functions and to assess the functional importance of their gene or protein of interest. The Core will bank tissue and RNA samples from well-characterized human subjects undergoing weight loss and nutrition interventions, as well as tissue and cell samples from relevant cell and organ culture studies. The Core will also provide consultation on the study of adipose tissue in animal models of obesity, diabetes, and caloric restriction to allow members to quickly and efficiently test disease regulation of their gene or protein of interest. An important function of this Core is to facilitate mechanistic cell and molecular studies in tissue samples from clinical researchers who mainly study whole body metabolism, and vice versa, to allow basic researchers to understand the relevance of their findings in cell and animal models to human physiology and pathophysiology.

The objectives of the ABC are to:

- Provide investigators with
  - standardized acquisition of adipose tissue samples,
  - assessment of adipose morphology,
  - adipocyte metabolism (glucose transport, metabolism, lipolysis),
  - qRT-PCR analysis of gene expression,
  - Western analysis of key adipocyte proteins, and
  - easy access to well-characterized cell and organ culture systems and specialized technologies for adipose and other cell types (as needed).
- Provide training to students, fellows, and investigators in specialized methods of adipose biology, including microscopy and gene transfer technologies.
- Develop new technologies as needed by a critical mass of CNRU investigators.

Pilot and Feasibility Studies

First Year Awards.

A Family Based Study of Adiponectin and Lipoprotein Levels as Predictors of Response to Dietary Fat. Toni Pollin, Ph.D., Assistant Professor, Division of Endocrinology, Diabetes and Nutrition, Department of Medicine UMB. The overall goal of this pilot and feasibility project is to elucidate the relationship between adiponectin and lipid metabolism. We will utilize data that is being collected as part of an ongoing family study that includes a rich set of cardiovascular-related phenotypes to address the following aims: 1) to evaluate the correlation of baseline adiponectin and lipoprotein phenotypes with post-fat load triglyceride excursion and endothelial function, and to assess the partitioning of this correlation into genetic and nongenetic components; 2) to evaluate the correlation between adiponectin and a number of specific lipoprotein phenotypes (lipoprotein particle sizes and concentrations, apolipoproteins AI, AII, B, CII, CIII and E) at baseline and to assess the partitioning of this correlation into genetic and nongenetic components; and 3) to identify genetic variants that influence circulating levels of adiponectin and mediate the correlations between these lipid metabolism-related phenotypes.

Mechanisms of Sleep Apnea-Induced Alterations in Lipid Metabolism. Vladimir Savransky, M.D., Ph.D. Research Associate, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine. Metabolic disturbances observed in sleep apnea (SA), particularly insulin resistance and dyslipidemia, contribute to cardiovascular morbidity. SA is associated with hypercholesterolemia independent of obesity. Potentially both IH and SF may affect metabolic function, and the major purpose of the current proposal is to define the pathways and mechanisms through which SA leads to dysregulation of lipid metabolism. We propose that IH, but not SF without hypoxia, leads to hyperlipidemia and up-regulation of lipid metabolism in the liver. We anticipate that IH will increase plasma lipid levels in both lean and obese individuals. We hypothesize that IH acts by up-regulating lipid biosynthesis in the liver via pathways controlled by sterol regulatory element binding protein 1 (SREBP 1). Finally, we predict that IH will attenuate therapeutic effects of lipid lowering therapy. Our approach is to examine the effects of validated models of IH and SF in lean and obese inbred mice, to explore the functional significance of SREBP pathways using specific transgenic mice, and to examine interactions between IH and lipid lowering treatment. Specifically, we propose: 1) to examine plasma lipid levels, lipid levels and biosynthesis in the liver, and expression of the enzymes of lipid biosynthesis in the liver of lean mice during IH of different severity and during non-hypoxic SF; 2) to examine the effects of IH on plasma lipids and lipid biosynthesis in the presence of dietary obesity and genetic obesity (*db/db* and agouti yellow mice); 3) to determine whether the knockout of SREBP pathways alters metabolic responses to IH; and 4) to explore interactions between IH and lipid lowering therapy with weight loss and HMG-CoA reductase inhibitors. The proposal will elucidate causative pathways linking SA and dysregulation of lipid metabolism and identify potential intervention for preventing hyperlipidemia and reducing cardiovascular risk in patients with SA.

Magnitude and Variance of Changes in Energy Metabolism in Response to an Exercise Intervention. William Rumpler, Ph.D., Research Physiologist, U.S. Department of Agriculture, Beltsville, MD. The aim of this project is to determine the effect of increasing physical activity level (PAL) by one category (sedentary → light active or light active → moderate active as described in the Dietary Reference Intake) on food intake, daily physical activity, fuel management, physical fitness, and body weight and composition in non-obese, over-weight women and men. The hypotheses to be tested are: 1) increasing physical activity will elicit

negative energy balance and subsequent body weight loss; 2) increasing physical activity will not be compensated for by a decline in spontaneous non-exercise activity; and 3) increasing physical activity will elicit a partial compensation by an increase in food intake over the length of the study.

Transcriptional Regulation of Hepatic Glucose Metabolism. Carles Lerin, Ph.D., Post-doctoral fellow, Dept of Cell Biology, Johns Hopkins University. Glucose homeostasis is highly dysregulated in metabolic diseases such as obesity and diabetes as well as in dietary manipulations such as caloric restriction (CR). It is well established that reduction of dietary energy produces hormonal and metabolic changes similar to fasting conditions, such as the activation of hepatic gluconeogenesis to maintain glucose homeostasis and organismal survival. It has been previously shown that the transcriptional coactivator PGC-1α is a key regulator of glucose production in the liver of fasted and diabetic mouse models by activating the whole hepatic gluconeogenic pathway. PGC-1α is a substrate for the NAD^+-dependent deacetylase SIRT1, a protein implicated in the connection between CR and life span. Moreover, PGC-1α acetylation levels are regulated during the fasting/feeding cycle modulating its transcriptional activity. We have recently identified GCN5 as the acetyl transferase for PGC-1α. We have also found that GCN5 strongly acetylates PGC-1α, repressing its transcriptional activity. Importantly, ectopic expression of GCN5 in the mouse liver blocks the induction of gluconeogenic genes in response to fasting, leading to lower glucose production by the liver in this condition. On the other hand, we have identified a novel protein called Wdr18 in the PGC-1α complex. Wdr18 expression is reduced during fasting as well as in different diabetic mouse models. Our preliminary results show that Wdr18 directly interacts with GCN5 and represses PGC-1α transcriptional activity. Taking these results together, the major goal of this proposal is to test the hypothesis that Wdr18 controls hepatic glucose production through modulating PGC-1α transcriptional activity in response to nutrient and hormonal signals. Our general strategy is to identify how Wdr18 represses PGC-1α activity regulating gene expression to control hepatic glucose production. We have three specific aims: 1) using biochemical analysis, we will characterize the mechanism through which Wdr18 represses PGC-1α transcriptional; 2) we will study whether Wdr18 regulates the expression of gluconeogenic genes and hepatic glucose production in hepatic cells; and 3) we will assay the ability of Wdr18 to modulate glucose homeostasis by expressing this protein in the mouse liver *in vivo*. The findings of this investigation will allow us to identify the molecular mechanisms by which two transcriptional regulators, PGC-1α and Wdr18, control glucose production in mammals. Therefore in the long term, our studies will lead to a better fundamental understanding of hormonal and nutrient regulated molecular events that may be useful for anti-diabetes, anti-obesity or aging drug development.