University of Pittsburgh Obesity and Nutrition Research Center (ONRC)
Start Date: 1992
Status: Ongoing
Funding Agency: NIDDK
Website: www.onrc.pitt.edu

Organization and Goals

The University of Pittsburgh Obesity and Nutrition Research Center (ONRC) seeks to facilitate and promote collaborative, interdisciplinary, and translational research to develop effective interventions for the prevention and treatment of obesity, and to gain a more complete understanding of the causes and complications of obesity. Efforts such as the ONRC to promote research related to obesity and body weight regulation have significant public health importance as more than 65% of adults in the United States are classified as overweight and/or obese, and the prevalence of obesity in children and adolescents is approaching 20%. The link between obesity and numerous chronic conditions, and the resulting profound impact on health care costs, further supports the mission of the University of Pittsburgh ONRC.

The Pittsburgh ONRC focuses on patient-oriented research, with particular strengths in health-related behavior change and interventions, and metabolic processes related to obesity and body weight regulation. The Pittsburgh ONRC has a substantial research base that includes work to develop and implement:

1. Innovative intervention strategies for prevention and treatment of obesity in a variety of populations across the lifespan (children to older adults).
2. State-of-the-art technologies and procedures to assess the impact of current treatments of obesity, and understand the physiological, metabolic, and genetic factors that contribute to body weight regulation.

Based on these strengths, the ONRC leadership and investigators focus their resources on supporting interdisciplinary research in the following areas:

1. Weight loss maintenance, prevention of weight regain, and primary prevention of weight gain.
2. Weight regulation in special populations (e.g., pediatric obesity, mental health patients, ethnically diverse populations).
3. Weight regulation in severe obesity (Class II and III obesity) and the enhanced study of bariatric surgery.

These scientific areas of focus are complemented by a common theme of physical activity, a scientific strength of the ONRC leadership that is integrated into each of the ONRC Cores.

Core Laboratories

Over the past year, the Pittsburgh ONRC has been in a no-cost extension, but has maintained functions within each of its Cores to support obesity-related research. The Pittsburgh ONRC is organized into five Cores: 1) Administrative with a Biostatistics and Data Management Sub-Core; 2) Behavior; 3) Metabolism; 4) Epidemiology; and 5) Laboratory.

Administrative Core. The Administrative Core promotes awareness of the resources and facilities of the ONRC. It sets criteria for the use of the Cores and provides fiscal management of the grant. The Administrative Core prepares reports for the University and National Institutes of Health/National Institute of Diabetes and Digestive and Kidney

Diseases (NIH/NIDDK), and organizes related activities, such as the meeting of the External Advisors. Two other key roles for the Administrative Core are management of the program for Pilot and Feasibility grants and organization of the enrichment program. In addition, within the Administrative Core is a Biostatistics and Data Management Sub-Core, which supports the biostatistical and data management needs of obesity-related researchers at the University of Pittsburgh. The Director of the Administrative Core is John M. Jakicic, Ph.D., and the Associate Director is Marsha Marcus, Ph.D. The Director of the Biostatistics and Data Management Sub-Core is Steven Belle, Ph.D.

Behavior Core. Since its inception, the Pittsburgh ONRC has strongly emphasized behavioral interventions for prevention and treatment of obesity. The Behavior Core provides facilities, staff, services, and collaborative expertise in studies of eating behavior and physical activity behavior. Specifically, there is expertise in eating disorders, physical activity interventions, dietary analysis, and development of intervention materials to support ongoing clinical trials related to obesity and body weight regulation. The Director of the Behavior Core is Marsha Marcus, Ph.D. Co-Directors are John Jakicic, Ph.D., and Elizabeth Venditti, Ph.D.

Metabolism Core. The Metabolism Core provides expertise and services for determinations of body composition, energy balance, *in vivo* substrate metabolism and insulin sensitivity, and exercise physiology. The Metabolism Core supports a number of services related to these goals. It is designed to leverage the resources of the ONRC through close interaction with the University of Pittsburgh Clinical Translational Research Center (CTRC), especially for studies of *in vivo* substrate metabolism. It has similar interactions with the Department of Radiology for bio-imaging of body composition, with the Magnetic Resonance Research Center (MRRC) for MRI and magnetic resonance spectroscopy, and with the Positron Emission Tomography Center (PET) for bio-imaging of metabolism. The Director of the Metabolism Core is Bret Goodpaster, Ph.D., and the Associate Director is Robert O'Doherty, Ph.D.

Epidemiology Core. The Epidemiology Core provides expertise in the design and execution of large clinical trials and population-based studies of obesity and nutrition. This epidemiological expertise includes assistance with the collection of clinical outcome data, recruitment of research volunteers, and evaluation of research participants, especially with regard to cardiovascular risk factors. A component of the Epidemiology Core is non-invasive vascular imaging, which helps to enable the study of the relation between obesity and cardiovascular disease in clinical trials. This Core is also the fulcrum for the ONRC effort in bariatric surgery. The Director of the Epidemiology Core is Lewis Kuller, M.D., Dr.PH. The Co-Directors are Andrea Kriska, Ph.D., and Kim Sutton-Tyrrell, Dr.PH.

Laboratory Core. The ONRC Laboratory Core consists of three components in support of obesity and nutrition research. Together, they offer expertise and laboratory facilities for biochemical, hormonal, genetic, and stable isotope mass spectroscopy assays. Two of the three laboratory components are the Heinz Nutrition Laboratory and the Human Genetics Laboratory. The ONRC is affiliated with both laboratories, providing partial support to facilitate their efforts in areas relevant to the mission of the ONRC. The third component of the ONRC Laboratory Core is the Mass Spectroscopy Laboratory, formed to provide analyses necessary for the use of stable isotopes to measure substrate flux, substrate oxidation, and energy expenditure. The Director of the Laboratory Core is Rhobert Evans, Ph.D. The Co-Directors are Robert Ferrell, Ph.D., and James DeLany, Ph.D.

External Advisors Panel. The panel of External Advisors assists in the review of ONRC Cores, provides guidance on direction of the ONRC, and serves as an external reviewer of the ONRC Pilot and Feasibility (P/F) Grant Program. The members of the External Advisors Panel who served during this most recent funding period are listed in the following table.

Advisor	Institution	Primary Assignment for Review
Penney Kris-Etherton, Ph.D.	Penn State University	Epidemiology Core
Eric Ravussin, Ph.D.	Pennington Research Center	Metabolism Core
Satish Kalhan, M.D.	Case Western Reserve University	Laboratory Core
Delia Smith, Ph.D.	University of Arkansas	Behavior Core

Pilot and Feasibility Studies

Current/Ongoing Pilot and Feasibility Studies

Because the Pittsburgh ONRC was in a no-cost extension period over the past year, there was no funding to support new Pilot and Feasibility Studies. Thus, this period was used to complete funded Pilot and Feasibility Studies, and there is currently one that remains open to finalize data analysis.

The Effect of an Exercise Buddy Kiosk on Physical Activity and Cardiorespiratory Fitness in School-Age Children. Amy Otto, Ph.D., R.D., L.D.N., Department of Health and Physical Activity. The goal of the study is to examine the effect of an intervention that integrates behavioral constructs of self-monitoring, goal-setting, and feedback using an Exercise Buddy Kiosk on physical activity levels, cardiorespiratory fitness, and body mass index (BMI) in school-age children compared to a no treatment control group of children.

Recently Completed Pilot and Feasibility Studies

Comparison of Self-Monitoring Techniques for Tracking Eating and Exercise Behaviors. Diane Helsel, Ph.D., Department of Sports Medicine and Nutrition. The study compares low detail, high detail transitioning to low detail, and technology-based self-monitoring techniques to a standard high detail self-monitoring control group, to determine the effect each technique has on completion of eating and exercise behaviors.

Acceptability of Postpartum Behavioral Weight Management. Michele Levine, Ph.D., Department of Psychiatry. The study aims to collect data on obese women's perceptions about a postpartum behavioral weight control intervention. It involves conducting a series of focus groups and obtaining paper and pencil response to questions about the acceptability of a postpartum weight control intervention among obese women with and without a history of gestational diabetes mellitus.

Nitro-Fatty Acid Modulation in Type II Diabetes. Marsha Cole, Ph.D., Department of Pharmacology. This study will examine pharmacokinetics of exogenously administered nitrated

fatty acids (NO2-FA) in a health murine model, and the therapeutic actions in a clinically-relevant murine model of diabetes.

Hydroxychloroquine Use and Metabolic Comorbidities in Rheumatoid Arthritis. Mary Chester Wasko, M.D., M.Sc., Department of Medicine. The study will determine the relationship between hydroxychloroquine use, inflammation, and measures of glucose and lipid metabolism in non-diabetic patients with rheumatoid arthritis.

Physical Activity, Regional Adiposity and Use of Hormone Therapy In Menopausal Women. Molly Conroy, M.D., M.P.H., Department of Medicine. The goal of the study is to gain a better understanding of the relationship of physical activity, regional adiposity, and muscle strength and quality in postmenopausal women, with additional analyses to understand how such relationships may be modified by hormone therapy use.

Genetic Architecture of Inflammatory Markers and their Relationship to Body Composition in Afro-Caribbean Families. Susan Moffett, Ph.D., Department of Epidemiology. The study will examine the association between levels of circulating cytokines, IL-6 and TNF alpha, and body composition in a family linkage study. The analysis will focus on these cytokines and the potential genetic linkages to body composition in 439 members of multigenerational families of African descent living in Tobago.

Influence of Genes, Diet, and Physical Activity in a Healthy Bi-racial Community Sample. Indrani Halder, Ph.D., Department of Psychiatry. The study will test three polymorphisms within three genes—PPARy, PPARa, and PGC1a—for associations with measures of body composition, BMI, metabolic functions, and energy expenditure in healthy, non-patient samples comprised of 832 Caucasian and 191 African-American subjects.

Mitochondria-Hexokinase Interactions in Obesity and Type II Diabetes. Elizaveta Menchikova, Ph.D., Department of Medicine. The study aims to estimate the role of hexokinase in mechanisms of insulin resistance and impairment of glucose utilization in skeletal muscle that is an essential feature of obesity and T2DM.

The Impact of Energy Expenditure and Depressive Symptoms on Weight Gain in the Course of Bipolar Disorder. Isabella Soreca, M.D., Department of Psychiatry. We will study the impact of subsydromal depressive symptomatology on energy expenditure and weight gain in the course of Bipolar Disorder.

Mechanisms of Beta Cell Compensation. Laura Alonso, M.D., Department of Medicine. This project proposed to determine whether lipid infusion induces mouse beta cell replication *in vivo*, and to determine the impact of the lipid infusion on glucose-induced mouse beta cell replication.

Study of Human C-reactive Protein (CRP) Induced Leptin Resistance. Fanghong Li, M.D., Department of Cellular Biology and Physiology. The purpose of this project was to examine the hypothesis that the human plasma CRP attenuates the physiological function of human leptin by directly blocking the actions of human leptin in the central nervous system and/or impeding the access of human leptin to the central nervous system. The studies were conducted in *ob/ob* mice.

The Effect of Vitamin D on Adverse Birth Outcomes in Black and White Women. Lisa Bodnar, Ph.D., M.P.H., R.D., Department of Epidemiology. The objective of this study was to generate pilot data on the vitamin D status of African-American and Caucasian pregnant women

in Pittsburgh, with normal and complicated pregnancies, in order to assess in a future R01 grant the contribution of vitamin D-deficiency to racial and ethnic disparities in birth outcomes.

Mechanism of Metformin-Mediated Regulation of LKBI-AMPK Association. Martin Schmidt, Ph.D., Department of Molecular Genetics and Biochemistry. The goal of this project was to develop assays for measuring the association of AMPK-LKB1 and ultimately to understand the mechanism by which metformin activates AMPK. Specific aims were to express epitope-tagged LKB1 in HeLa cells and demonstrate increased association with AMPK in response to metformin treatment by co-immunoprecipitation, and apply the bimolecular fluorescence complementation system for assaying AMPK-LKB1 association.

The Effect of BMI and Age on the Yield and Multi-Potency of Adipose-derived Stem Cells. Kacey Marra, Ph.D., Department of Surgery. This proposal sought to further understand the variability in behavior of adipose-derived stem cells (ASCs) from patients with different body mass indices, specifically pre- and post-gastric bypass patients. The goal was to begin to understand the effect of weight loss on the yield of stem cells, the proliferation rate of stem cells, the adipogenic differentiation potential of the cells, the sensitivity to apoptosis, nuclear architecture, and chromatin mobility.

Regulation of Glucagon-Like Peptide 1 Receptor. Allessandro Bisello, Ph.D., Department of Medicine. This project proposed to address the hypothesis that the interaction between GLP-1R and caveolin-1 is a fundamental mechanism by which β cells control both the insulinotropic and the proliferative actions of GLP-1.

Genetics of Obesity and Metabolic Phenotypes in Large Multigenerational African Families. Iva Miljkovic-Gacic, Ph.D.**,** Department of Epidemiology. This study attempted to detect, map, and characterize genes influencing variation in obesity-related traits in a unique collection of Afro-Caribbean families. The investigator tried to determine the extent to which genes (heredity) and environmental covariates contribute to obesity-related phenotypes within extended, multigenerational families of African ancestry.

The Role of Leptin in Hepatic Lipid Partitioning. Wan Huang, Ph.D., Department of Medicine. This study aimed to investigate the acute and chronic effects of leptin on hepatic triglyceride metabolism in two situations of elevated hepatic lipogenesis: high sucrose feeding and hyperinsulinemia.

Enteral Feeding and Pancreatic Rest. Neeraj Kaushik, M.D., Department of Medicine. The hypothesis of this investigation was that acute pancreatitis outcome would be improved further if enteral feeding could be given without pancreatic stimulation. Comparisons were made between enteral feeding infused at the level of the duodenum, mid jejunum, and distal jejunum, to assess pancreatic response and amino acid utilization for enzyme and mucosal protein synthesis in healthy human volunteers.

Effects of Social Comparison Feedback and Self-Affirmation on Dietary Change. William Klein, Ph.D., Department of Psychology. The goal of this study was to combine social comparison information and self-affirmation into a tailored feedback intervention with the goal of increasing risk perceptions and changes in diet.

Alterations in Hepatic Lipid Metabolism Mediated by Rapamycin: A New Role for the mTOR Pathway in Regulation of Lipid Metabolism. German Perdomo-Hernandez, Ph.D., Department of Medicine. The goal of this study was to determine the mechanism(s) by which

rapamycin increases mitochondrial fatty acid oxidation and decreases FA esterification/*de novo* FA synthesis in hepatocytes. The investigator attempted to establish the mechanism of these effects by determining how the drug influences flux through specific lipid metabolic pathways and the activity of critical enzymes that regulate those pathways.

Insulin Secretion and Insulin Action in Youth with Type 2 Diabetes Mellitus. Neslihan Gungor, M.D., Department of Endocrinology, Children's Hospital of Pittsburgh. This study aimed to assess the relative roles of insulin deficiency and insulin resistance in the pathogensis of type 2 diabetes of youth and the role that race might play. The investigator compared differences in insulin sensitivity and secretion between African American and Caucasian youth with type 2 diabetes mellitus, and longitudinally evaluated the changes in insulin sensitivity and secretion at diagnosis and after 6 months, in youth with type 2 diabetes mellitus.

Funding Derived From Previous Pilot and Feasibility Studies

Vitamin D: a Link to Racial Disparities in Birth Outcomes. Lisa Bodnar, Ph.D., MPH, R.D. Funding: NIH/Eunice Shriver National Institute of Child Health and Human Development (NICHD), R01 HD056999, 9/08–7/13

Healthy Bodies, Healthy Hearts after Menopause. Molly Conroy, M.D. Funding: NIH/National Heart, Lung, and Blood Institute (NHLBI), K23HL085405, 9/07–5/11

Association of Pericardial Fat and Coronary Heart Disease Across the Female Lifespan. Molly Conroy, M.D. Funding: NIH/NHLBI. *PENDING*

Enhanced Behavioral Intervention to Improve Long-Term Weight Loss in Young Adults. Diane Helsel, Ph.D. submitted in response to RFA-HL-08-007: "Targeted Approaches to Weight Control for Young Adults." The primary aim of this pending grant submission will be to examine whether an enhanced weight loss intervention (EWLI) that includes technology components results in improved weight loss in young adults (18 to 35 years of age) compared to a standard behavioral weight loss intervention (SBWP) over a period of 24 months. *PENDING*

Glucagon-like Peptide 1 Receptor in Beta Cells. Alessandro Bisello, Ph.D. Funding: NIH/NIDDK, R01 DK082391-01A1. *PENDING*

Injectable Engineered Tissue for Cancer Reconstruction. Kacey Marra, Ph.D. Funding: NIH/National Cancer Institute (NCI), R01 CA114246, 2/06–1/09

Genetics of Lipoproteins in Afro-Caribbean Families. Iva Milijkovic-Gacic, M.D. Funding: National Research Service Award/NHLBI, F32 HL083641, 5/06–4/08

Nutritional Evaluation of Methadone-Exposed Mother-Infant Dyads. Debra Bogen, M.D., F.A.A.P. Funding: Gerber Foundation

The Relationship Between Breast-Feeding Duration on Obesity in Low-Income Preschool Children. Debra Bogen, M.D., F.A.A.P. Funding: Building Interdisciplinary Research Careers in Women's Health award (local funding)

Insulin Secretion and Insulin Action in Youth with Type 2 Diabetes Mellitus (T2DM). Neslihan Gungor, M.D. Funding: Thrasher Research Fund

Enhancing Adherence to the Peritoneal Dialysis Dietary Regimen. Mary Ann Sevick, Sc.D., R.N. Funding: NIH/NIDDK, R21 DK067181, 2006–Present

Impact of a PDA-Based Dietary Adherence, Intervention on Interdialytic Weight Gain and Blood Pressure. Mary Ann Sevick, Sc.D., R.N. Funding: Paul Teschan Award, 2/06–1/09

Acceptance of Colorectal Cancer Risk Factor Feedback. William Klein, Ph.D. Funding: NIH/NCI, 1R03 CA101529-01A2, 4/05–3/07

Hepatic Fatty Acid Metabolism and Insulin Resistance. Nick Brown, Ph.D. (Primary Mentor), Maja Stefanov-Racic, M.D. (Principal Investigator). Funding: NIH/NIDDK, K08 Mentored Clinical Scientist Development Award, 4/01/04–3/31/09

Muscle Lipid and Insulin Resistance in Aging. Bret Goodpaster, Ph.D. Funding: NIH/National Institute on Aging (NIA), R01 AG20128-01, 07/04–06/08

Skeletal Muscle Lipid and Insulin Resistance: Effects of Physical Activity and Weight Loss. Bret Goodpaster, Ph.D. Funding: American Diabetes Association, Clinical Research Award, 1/15/04–1/14/07

Ciliary Neutrophic Factor (CNTF) Receptor Alpha (CNTFRa) Genotype and its Relation to Obesity. Stephen Roth, Ph.D. Funding: NIH/NIA, R01, 3/03–2/06

Ciliary Neutrophic Factor Receptor Alpha (CNTFRa) Genotype and its Relation to Obesity. Stephen Roth, Ph.D. Funding: NIH/National Institute of Neurological Disorders and Stroke, R21 NS046021, 3/03–2/05

Carnitine Palmitoyltransferase, Fatty Acids and Diabetes. Nick Brown, Ph.D. Funding: American Diabetes Association, Junior Faculty Award, 1/01/03–12/31/05

Can the Dexefenfluramine Challenge Test Predict the Weight Loss Response to Dexefenfluramine? Katherine Williams, M.D., M.P.H. Funding: NIH/NIDDK, K23 DK02647, 1999–2004; NIH/NIDDK, R03 DK064171, 2003–2005

Psychological Insights and Outcome Following Gastric Bypass Surgery. Melissa Kalarchian, Ph.D. Funding: NIH/NIDDK, K23 DK62291, 8/1/02–7/31/07

Personal and Familial Risk for Eating Pathology in Ballet Dancers. Kelly Klump, Ph.D. Funding: NIH/National Institute of Mental Health, R03, 4/02–3/04; R03 MH065447, 5/02–4/04

Behavioral Strategies for Reducing Calorie and Fat Intake: Comparison of Three Approaches. Lora Burke, Ph.D., M.P.H., R.N. Funding: NIH/NIDDK, R01 DK58631, 5/01–4/06

The Relationship Among Weight Change, Sex Hormones, and Bone Mineral Density in Older Men.
Nancy Glynn, Ph.D. Funding: NIH/NHLBI, R01 HL66070, 2001–2006

Physical Appearance and Health-Related Motivations for Weight Loss: Can Enhancement of Motivations Improve Treatment Outcome? Cheryl Smith, Ph.D. Funding: NIH/NIDDK R01 DK53924, project period not available; NIH/NIDDK R01 DK58387, 9/00–8/05

Gender Differences in Stress-Induced Eating. Catherine Greeno, Ph.D. Funding: NIH/National Institute of Mental Health, K01 MH001898, 6/1/00–5/31/05

Mechanisms of Hyperleptinemia-Induced Improvements in Skeletal Muscle Insulin Resistance in Diet-Induced Obesity. Robert O'Doherty, Ph.D. Funding: NIH/NIDDK, R01 DK58855, 2000–2005

Behavioral Weight Control for Obese African American Adolescent Women. Linda Ewing, Ph.D., R.N. Funding: National Center on Minority Health and Health Disparities, R01 HD38425, 2000–2004

Developing a Genetic Model with Peripheral Leptin Resistance. Allan Zhao, Ph.D. Funding: American Diabetes Association, 2000–2004

Prevention of Weight Gain in Young Women. Mary Lou Klem, Ph.D. Funding: NIH/NIDDK, R01 DK53942, 3/99–2/05

The Effect of Intrauterine Growth Retardation Upon Insulin Resistance and Mitochondrial Function and Gene Expression in the Rat. Robert Lane, M.D. Funding: National Center on Minority Health and Health Disparities, K08 HD01225, 1/99–12/03; National Center on Minority Health and Health Disparities, K08 HD01225, 1/99–12/03; American Diabetes Association Research Award, 1/99–12/01

Obesity, Liver, and Cardiovascular Risk. Monica Yamamoto, Dr.P.H., R.D., F.A.D.A. Funding: NIH/NIDDK, U01-DK57002, 1999–2004

The Influence of Obesity on Endogenous Substrate Utilization During Exercise. Bret Goodpaster, Ph.D. Funding: NIH/NIA, K01 AG00851, 9/98–8/03

Visceral Adipose Tissue in Polyp Prevention Trial. Robert E. Schoen, M.D. Funding: NIH/NCI, K07 CA72561, 12/97–11/02

Physician-Based Intervention for Obesity and Exercise Promotion. Laurie Simkin-Silverman, Ph.D.
Funding: NIH/NIDDK, R01-DK52050, 9/97–9/02

Effects of Cereal Feeding on Body Composition and Cholesterol Metabolism in Infants. Carol H. Gilmour, M.D., M.P.H. Funding: NIH, HD30367, 12/1/96–11/30/99

Perinatal Imprinting Effect on Hypothalamic Mechanisms Influencing Obesity. Sherin U. Devaskar, M.D. Funding: National Center for Minority Health and Health Disparities, HD25024, 7/1/96–6/30/01

Exercise Adherence in a Behavioral Weight Loss Program. John M. Jakicic, Ph.D., Funding: NIIH/NHLBI, HL56127, 5/96–4/00

Effect of Obesity on Glucose Transport and Phosphorylation by Skeletal Muscle as Measured by Positron Emission Tomography. Mark A. Mintun, M.D. Funding: American Diabetes Association Feasibility and Development Grant, 1/96–12/97

Dietary Modulation of Tumor Suppressor Gene Activity. Richard A. Steinman, Ph.D. Funding: American Institute for Cancer Research, 7/95–6/97

Effects of Obesity in Muscle Free Fatty Acid Metabolism. David E. Kelley, M.D. Funding: NIH/NIDDK DK49200, 1/1/95–12/31/97

Changes in Substance Use Following Weight Loss/Food Restriction. Kenneth A. Perkins, Ph.D. Funding: NIH, DA04174, 9/94–8/98

Ontogeny of Obesity Protein Receptors (OB-R) in Fetal and Neonatal Rats and its Modulation by Prenatal Administration of Steroids. Saroj Parida, M.D. Funding: Local funding agency

Specific Accomplishments

A brief synopsis of the significant accomplishments of the University of Pittsburgh ONRC follows.

Support for Selected Major Clinical Trials

Action for Health and Diabetes (LookAHEAD). The NIH-NIDDK funded LookAHEAD Trial is designed to examine the effect of long-term weight loss and physical activity on reductions in cardiovascular mortality and events in more than 5,000 individuals with type 2 diabetes. Pittsburgh is one of 18 clinical sites for this study. The 4-year outcome assessments have been completed and manuscript preparation is currently underway. Moreover, the 84 month assessment window has recently opened for those subjects who have entered that phase of the study. The ONRC, through the contribution of Dr. John M. Jakicic and Dr. Amy Otto and other support staff, has played and continues to play a significant role in the development of the intervention protocol. Moreover, Dr. Jakicic has been instrumental in the development and implementation of the fitness testing and accelerometry protocols. Other investigators are also participating in numerous ancillary studies (e.g., body composition, sleep apnea, etc.). The ONRC provides support for the Pittsburgh LookAHEAD clinical site by providing intervention space and consultation, and by assisting with assessment space, equipment, and personnel. Recently the ONRC assisted in an ancillary grant to the NIA that has received a fundable priority score and will start in July 2009. This ancillary study will focus on assessing physical and cognitive function in the LookAHEAD population.

Longitudinal Assessment of Bariatric Surgery (LABS). One of the projects that the ONRC has been deeply involved with is the NIH-NIDDK funded, multi-center bariatric surgery research consortium termed LABS. This is an example of how the Pittsburgh ONRC collaborates across its Cores and other ONRCs (New York) to address important questions within a thematic area of our center. This project seeks to evaluate the risks and benefits of bariatric surgery by following a cohort of men and women who have elected to undergo one of several types of bariatric surgery. There are six clinical sites, including the University of Pittsburgh. Dr. Anita Courcoulas is the principal investigator (PI) of the Pittsburgh clinical site and Dr. Marsha Marcus is a co-investigator. The University of Pittsburgh also serves as the Data Management Center for LABS, and the PI for this component is Dr. Steven Belle. ONRC investigators also play significant roles in sub-studies and ancillary studies for this trial. For example, Drs. Marsha Marcus and Melissa Kalarachian are co-investigators in a behavior sub-study examining eating disorders and detailed parameters on quality of life in this cohort, Dr. Bret Goodpaster is the PI on an ancillary study examining body composition changes in the cohort.

Studies to Treat or Prevent Type II Diabetes (STOPP-T2D). Consistent with the theme to study childhood obesity and related chronic diseases, the ONRC provided support for two NIDDK-supported multi-site investigations within the STOPP-T2D Trial, which included the TODAY Study and the HEALTHY Study. Through these initiatives, the ONRC has become well-represented in the pediatric investigation of obesity and type 2 diabetes.

Dr. Silva Arslanian, pediatric endocrine investigator at Children's Hospital, is the principal investigator and Dr. Marsha Marcus and Dr. Andrea Kriska are co-investigators for the TODAY Study (grant # DK61254). The goal of this multi-site investigation is to develop and evaluate treatments for pediatric type 2 diabetes. Dr. Arslanian has been instrumental in development of the overall protocol, and Drs. Marcus and Kriska helped to develop the lifestyle intervention utilized in the study. Results of TODAY will yield critically important data to guide the management of type 2 diabetes in children and adolescents.

Dr. Marsha Marcus is the principal investigator and Drs. John M. Jakicic and Elizabeth Venditti are co-investigators for the HEALTHY study, which focuses on prevention of obesity and diabetes. After three years of pilot studies, the HEALTHY intervention was launched in six Pittsburgh schools in September 2006. Almost 700 children enrolled in the study and participated in a health screening (a participation rate of more than 70% of eligible sixth-grade children), and the intervention phase began in January 2007, and it was recently completed in December 2008. Results from the seven-site HEALTHY study will provide critically important information on the utility of school-based obesity prevention programs.

Interdisciplinary Research

Enhanced Behavioral Intervention to Improve Long-Term Weight Loss in Young Adults (U01 HL096770-01): The ONRC assisted in the development of an interdisciplinary application in response to RFA-HL-08-007 "Targeted Approaches to Weight Control for Young Adults." The focus of this study is to examine innovative intervention strategies to improve long-term weight loss in young adults. The resources of the ONRC were significantly involved in the development of this application and the approach that is being taken within the intervention that has been proposed. For example, the ONRC has been involved with the development of technologies that can be used within interventions such as text messaging, wearable technologies that provide feedback of behavioral goals, and web-based initiatives. All of these components were built into the intervention that was proposed. Moreover, Dr. Belle and the resources within the Biostatistical Sub-Core of the ONRC developed the required Research Coordinating Unit (RCU) application that accompanied the parent grant. This has also included resources from the Behavior Core (Drs. Marcus, Jakicic, and Otto) along with the involvement of investigators from other disciplines (Dr. Diane Helsel, Clinical Dietetics and Nutrition; Dr. Kavitha Bhat-Schelbert, Department of Family Medicine; Dr. Kathleen Spadaro, Nursing).

Center of Excellence for Research on Obesity (CERO). The ONRC was instrumental in the conceptualization and development of a successful grant application to the Pennsylvania Department of Health, with funding awarded in June 2006 ($4.2 million, total costs) for a 4-year period. This was in response to a Request for Applications (RFA) that was funded through monies allocated from the Tobacco Settlement process. The ONRC leadership was requested by the Vice-Chancellor of the Health Sciences and Dean of the School of Medicine Dr. Arthur Levine to take a leadership role in the development of an application in response to this RFA. The ONRC Administrative Core played a strong role in this process, reflecting our collaborative, interdisciplinary, and translational capabilities. The Pittsburgh ONRC used this as an opportunity

to bring together all of its Cores to address important scientific questions related to severe obesity, and the contribution of physical activity to the treatment of Class II and III obesity. Consistent with the RFA, this resulted in a "single project" (rather than a program project format) being developed. At least half of the funding is being used for clinical research and clinical translation research; the project has a prominent community outreach component and will address issues of health disparity, and there is an emphasis on identification of novel biomarkers and the study of novel aspects of the pathogenesis of obesity. The title of this project is "Preventing Adverse Effects of Class II and Class III Obesity."

Physical Activity

An increasing area of strength of the Pittsburgh ONRC is the role of physical activity in body weight regulation. This is an interest of current Director Dr. John M. Jakicic. During the current funding cycle, physical activity has been strategically integrated across the ONRC Cores (Behavior, Metabolism, Epidemiology, and Laboratory Cores). The ability to integrate physical activity across the Cores has allowed for an interdisciplinary approach to the study of physical activity in the regulation of body weight and related diseases. The Behavior Core (Dr. Jakicic) allows for the study of interventions to modify physical activity behavior, to test the dose-response of physical activity on weight control, and to refine technologies that are used for assessment of physical activity that can also serve as an intervention tool in clinical studies of obesity. This is facilitated by the Physical Activity and Weight Management Research Center, which has supported intervention research along with the application of portable wearable technology for the monitoring of free-living physical activity (see "Enhanced Technology to Support Obesity-Related Research" below for further description). Recently the focus has been expanded to include children with severe pediatric obesity. A pilot intervention study is currently underway to examine strategies to improve physical activity in this population and to determine if this improves body weight regulation. This facility also provides sites for supervised on-site cardiovascular exercise. The Metabolism Core (Dr. Bret Goodpaster) allows for the study of how physical activity affects energy balance and metabolic parameters that may contribute to weight control and related diseases. The Epidemiology Core (Dr. Andrea Kriska) allows for the study of physical activity in large population-based and community-based interventions. The Laboratory Core, primarily the Mass Spectroscopy Laboratory (Dr. James DeLany), allows for the study of physical activity to the contribution of total energy expenditure and energy balance using stable isotope techniques.

The focus and strength of the Pittsburgh ONRC in the area of physical activity is also supporting studies conducted at other institutions throughout the United States. For example, ONRC resources are being used to support research efforts in physical activity assessment or interventions at Brown University and The Miriam Hospital (Dr. Rena Wing and Dr. Dale Bond), University of Pennsylvania (Dr. Thomas Wadden), University of Colorado Health Science Center (Dr. James Hill), University of North Carolina (Dr. Deborah Tate), and the University of Florida (Dr. Anne Matthews).

Enhanced Technology to Support Obesity-Related Research

Rapid advancements in technology may provide opportunities to improve the treatment and study of obesity and related diseases. The Pittsburgh ONRC has been at the forefront of the development of technologies to support these clinical research initiatives. For example, the ONRC has developed applications that use technologies for bio-imaging, body composition, and the understanding of physiological processes that may influence body weight regulation.

Moreover, the ONRC has invested in refining techniques for the assessment of physical activity and energy expenditure.

An example of this is the collaboration of the ONRC with industry to develop portable technologies for the assessment of energy expenditure. Drs. John M. Jakicic, Bret Goodpaster, and James DeLany have been working closely with BodyMedia, Inc. (Pittsburgh, PA) to refine the validity and reliability of the SenseWear Pro Armband™. This resulted in Dr. Jakicic publishing the first validation manuscript on this device in 2004, with additional research currently being prepared as a manuscript for peer review. This has lead to numerous grant submissions, and Dr. Jakicic currently has NIH grants that are under review to further study this technology. Dr. Jakicic and his colleagues published the results of an intervention trial in *Obesity* that showed the effect of this system on weight loss when used in the context of a behavior intervention, and the ONRC is currently supporting a longer-term study to further evaluate the use of this technology system within the context of a weight loss intervention. Dr. Jakicic has also completed a study funded by NIDDK to collaborate with LifeChek, LLC (Pittsburgh, PA) to conduct validation testing of another portable system that uses heat flux technology. The manuscript is currently in the submission and review process.

Additional research using technologies to monitor dietary intake are being conducted by Laura Burke, Ph.D. and Mary Ann Sevick, Ph.D. Moreover, recent enhancements to the ONRC website include portals that allow interventionists and intervention participants to have access to web-based tools to support weight loss initiatives such as self-monitoring, chat, e-mail, and posting intervention materials. Recently this web-based tool has undergone additional refinement and will be used in a study that is slated to begin in June 2009. Moreover, Kathleen McTigue, M.D. has developed an Internet-based weight-loss program based on the Diabetes Prevention Program that is currently being tested in the Department of Medicine, and Dr. Marsha Marcus is examining the use of a similar technology for the treatment of anorexia nervosa. Dr. Jakicic has implemented a web-based initiative to disseminate a weight-loss program to the community (http://aom2.americaonthemove.org/Communities/Pennsylvania/home.aspx and www.getmovingpittsburgh.org). This builds on the collaborative work that Dr. Jakicic is pursuing with Dr. Bess Marcus (Brown University and The Miriam Hospital, Providence, RI) to study tailored Internet interventions to modify physical activity behaviors.

Studies of Hunger and Satiety Related to Obesity

Dr. Kirk Erickson has recently joined the faculty at the University of Pittsburgh in the Department of Psychology. His expertise is in the area of physical activity and brain function in the elderly. Dr. Erickson has vast experience in the use of computed tomography (CT) for this purpose. Recently, the ONRC has initiated a collaboration with Dr. Erickson to apply his knowledge to the understanding of brain function related to physical activity and eating behavior, primarily hunger and satiety, within the context of obesity and body weight regulation. ONRC resources are being provided to develop this collaboration with a small study planned for summer/fall 2009 to pilot test the research paradigms that are being developed. In addition, a study to examine the acute effects of exercise on biomarkers of hunger and satiety (GLP-1 and Acylated Ghrelin) is currently being supported by the ONRC, and this study is being conducted by a doctoral student (Jessica Unick) under the supervision of Dr. Jakicic. It is anticipated that this will expand the research in this area of study at the University of Pittsburgh and within the ONRC. *NOTE: The training provided in part by the ONRC of Jessica Unick has allowed her to secure a post-doctoral fellowship for Fall 2009 at Brown University under the supervision of Dr. Rena Wing.*

Enhanced Mass Spectroscopy Capabilities

The ONRC and the Department of Medicine recruited Dr. James DeLany to establish and direct this laboratory in July 2005. Dr. DeLany is a recognized expert in the stable isotope doubly-labeled water (DLW) method for measurement of free living energy expenditure, and has been working with this technique since 1987. This very rapidly led to enhanced collaborations among investigators. For example, Dr. Stephen O'Keefe, who is engaged in amino acid research using stable isotopes, relocated the Gas Chromatography-Mass Spectroscopy that was in his lab to the ONRC Mass Spectroscopy Laboratory, which expanded the capabilities of the Mass Spectroscopy Laboratory by providing the capability of an ionization technique known as chemical ionization. The Mass Spectroscopy Laboratory was also instrumental in the successful Center for Excellence in Obesity Research (CERO) application described above, and has allowed for the inclusion of DLW to be used in this study to measure energy expenditure. There is also an ongoing collaboration with Dr. Juan Ochoa in the Department of Surgery and Critical Care Medicine to use stable isotopes in a citrulline project, and Dr. DeLany and the Mass Spectroscopy Laboratory have collaborated on grant applications with three University of Pittsburgh investigators: 1) Dr. Stephen Thomas, Center for Minority Health; 2) Dr. John M. Jakicic, Department of Health and Physical Activity; and 3) Dr. Mingui Sun, Department of Surgery. The Mass Spectroscopy Laboratory also worked closely with two external investigators on recent grant submissions: 1) Dr. Carol Boushey at Purdue; and 2) Dr. Kiri Ness at St. Jude Children's Research Hospital.

Enhanced Imaging Techniques for Body Composition and Metabolic Research

Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS). An exciting development during this past funding cycle with regard to Nuclear Magnetic Resonance Imaging at the University of Pittsburgh has been the installation of four new research-dedicated whole body MR scanners in the Magnetic Resonance Research Center (MRRC), three new 3.0T Siemens scanners, and a 7T Siemens scanner, one of the only 7T human scanners currently in the United States. This allows the Metabolism Core to continue to advance the implementation of noninvasive *in vivo* NMR methodologies in the clinical investigation of obesity and related disorders of metabolism.

MRI and Computed Tomography (CT) Analysis of Regional Body Composition. The ONRC has advanced the use of imaging techniques to study body composition through the use of both Computed Tomography and Magnetic Resonance Imaging. This has been extremely useful in reliable assessments of longitudinal changes in body composition for current studies.

Whole Body MRI Protocol. The ONRC has worked in close collaboration with the New York ONRC to use a "whole-body" MRI protocol for body composition assessment.

Bio-Imaging with Positron Emission Tomography (PET). The technologies of PET imaging pioneered by Pittsburgh ONRC investigators have provided a unique opportunity to carry out studies *in vivo* in human skeletal muscle to examine the kinetics of glucose transport and phosphorylation. Dynamic PET imaging can be a highly sensitive method for the study of insulin action in skeletal muscle in health and insulin resistance.

Enhanced Metabolic Research

Regional Fat Distribution. One of the primary themes for the Metabolism Core has been the examination of regional fat content and its distribution, in association with insulin resistance of

obesity, type 2 diabetes, and also with age-related sarcopenia. The areas that have been addressed are abdominal adiposity, skeletal muscle lipid content and adipose tissue distribution, and hepatic fat content.

Fat Oxidation. The Pittsburgh ONRC is known for research involving methods of assessing fat oxidation. Current studies are ongoing in the context of a "controlled" exercise protocol that emphasizes moderate-intensity exercise with determination of O_2 and CO_2 from breath samples and an aliquot for isotope enrichment, along with blood sampling to measure fatty acid flux. In collaboration with Dr. Gerald Vockley at Children's Hospital of Pittsburgh, an approach is being developed to explore use of acylcarnitine profiling measured by tandem mass spectroscopy to examine for "build-up" of short- to medium-chain acyl-carnitines in plasma that could be indicative of impaired fat oxidation.

Nutrient Partitioning. ONRC investigators have been highly productive in addressing the role of nutrient partitioning in the pathogenesis of insulin resistance in obesity and type 2 diabetes. This has resulted in a body of experimental evidence that reveals *impaired fasting rates of fat oxidation in skeletal muscle in obesity and type 2 diabetes occurs in conjunction with insulin-resistant glucose metabolism*, which has been articulated as the concept of 'metabolic inflexibility.' Integral to the concept of impaired fatty acid metabolism and insulin resistance of obesity and type 2 diabetes is the concept of non-adipose tissue (ectopic) lipid accumulation.

Muscle Mitochondria. The ONRC Metabolism Core has supported several studies centered on metabolic outcomes related to muscle mitochondria. A panel of assessments developed mostly by Dr. Vladimir Ritov and Dr. Elizaveta Menchikova have allowed for the study of electron transport chain activity, Kreb cycle enzymes, and mitochondrial morphology.

Subclinical Measures of Cardiovascular Disease and Atherosclerosis

We continue to have an interest in subclinical measures of atherosclerosis, and Dr. Kim Sutton-Tyrrell was added to the Epidemiology Core to bring her expertise in this area to the ONRC. Dr. Sutton-Tyrrell is a leading scientist in the use of carotid intima-media thickness (IMT) to study subclinical atherosclerosis, and this has been integrated into numerous trials over the past 5 years. Most notably, this technique was added to the Center for Excellence for Research on Obesity (CERO) Study to provide an enriched understanding of the health effects of obesity on cardiovascular disease. Dr. Lewis Kuller and his colleagues in the Epidemiology Core have also brought expertise in the use of coronary and aortic calcium to investigate atherosclerosis, subclinical cardiovascular disease, and subsequent risk of cardiovascular disease. Again, these measures have been included in the CERO Study and other ongoing clinical studies. Because of the expertise in this area, the Pittsburgh ONRC will be positioned to continue to adapt new techniques as these become available and apply these to the study of obesity, lipoprotein metabolism, insulin resistance, and diabetes.

Special Populations

Pediatric Obesity. The Pittsburgh ONRC has increased its study of pediatric obesity. This led to the involvement of the ONRC in both the TODAY and HEALTHY multi-center trials. The leadership for these efforts comes from collaborations between colleagues in Children's Hospital of Pittsburgh (Silva Arslanian, M.D.), Western Psychiatric Institute and Clinic (Dr. Marsha Marcus, Dr. Elizabeth Venditti), the Department of Health and Physical Activity (Dr. John M. Jakicic), and the Department of Epidemiology (Dr. Andrea Kriska). This has led to additional research in the study of severe pediatric obesity. Drs. Marcus, Kalarchian, and Arslanian are

examining a family-based intervention for the treatment of severe pediatric obesity. Drs. Marcus, Arslanian, and Jakicic recently submitted a grant to the NIH to further understand behavior change strategies for severe pediatric obesity. Moreover, Drs. Marcus and Jakicic completed a recent ONRC supported pilot study to better understand "enjoyment" as a mediator of physical activity participation in severe pediatric obesity patients ($\geq 97^{th}$ BMI percentile), and this has led to an ONRC supported intervention study that is being piloted to determine if additional strategies added to an intervention can improve physical activity and result in improved body weight regulation in this population.

Severe Obesity and Bariatric Surgery. In response to the increasing prevalence of severe obesity (BMI $\geq$35 kg/m^2), the Pittsburgh ONRC has strengthened its research in this area. This is demonstrated by the involvement of the ONRC in the CERO study ("Preventing Adverse Effects of Class II and Class III Obesity") funded by the Pennsylvania Department of Health. Moreover, the ONRC has been involved in the studies of bariatric surgery (LABS and related ancillary studies) being conducted by Drs. Anita Courcoulas, Marsha Marcus, Melissa Kalarachian, and Bret Goodpaster. Dr. Kalarchian has two NIH grants to conduct studies in the area of bariatric surgery, and Drs. Goodpaster and Jakicic have received a NIDDK-funded grant to examine the role of physical activity in patients who have undergone bariatric surgery. This builds on the work being conducted by a graduate student (Deborah Josbeno) being mentored by Dr. Jakicic, who recently published the results of a study examining patterns of physical activity and physical function in patients prior to and following bariatric surgery, and who is currently completing a study to examine physical activity and physical function in individuals at $\geq$3 years post-bariatric surgery.

This expanded focus on bariatric surgery has resulted in the ONRC supporting two Challenge Grants under ARRA. A collaborative grant has been developed to conduct a feasibility study to compare two forms of bariatric surgery (gastric bypass and lap band) to an intensive lifestyle weight loss intervention in patients with type 2 diabetes. This will involve a 12 month intervention period with outcomes assessed at 0, 6, and 12 months. The ONRC has committed resources to add measures of physical activity, body composition, and fitness to this study, and has also committed resources to the development of the lifestyle intervention, should it receive a favorable priority score for funding. Primary collaborators included Drs. Courcoulas, Jakicic, Goodpaster, and Belle. A second application has been submitted by Dr. Kalarchian to expand the long-term follow-up of bariatric surgery patients and to implement a lifestyle intervention to prevent weight gain following bariatric surgery. Primary collaborators include Drs. Kalarchian, Marcus, Venditti, and Jakicic.

Eating Disorders. During the current funding cycle, initiatives to further study eating disorders, primarily anorexia nervosa and bulimia nervosa, were pursued. These efforts were led by Dr. Marsha Marcus and her colleagues Drs. Jennifer Wildes and Cynthia Bulik. This resulted in the submission of three pending applications that focus on intervention strategies for these disorders, the study of the effect of mood and anxiety on eating disorders, and the use of technology as a dissemination tool in the treatment of bulimia nervosa. This research is a critical next step in developing the evidence base for the treatment of eating disorders, enhancing the understanding of the etiology of eating disorders that may contribute to the identification of novel treatment targets, and potentially offering cost-effective strategies for improving dissemination of evidence-based treatment for eating disorders.

Bipolar Disorder. A recent focus has been growing research on bipolar disorder. This is of interest to obesity researchers because of the concomitant medical burden found in these psychiatrically ill patients, with particular interest in obesity that appears to be present as a

consequence of medication. The ONRC Behavior Core and Metabolic Core have assisted Dr. David Kupfer in the development of a pending application to adapt a behavioral weight-management intervention program for individuals with bipolar disorder. Dr. Marcus is a co-investigator on this project. This is consistent with the interest in this area as shown by the funding provide to Dr. Isabella Sorecca through the ongoing Pilot and Feasibility program (titled "The Impact of Energy Expenditure and Depressive Symptoms on Weight Gain in the Course of Bipolar Disorder"). Moreover, Drs. Bret Goodpaster, John M. Jakicic, David Kupfer, Amy Otto, and Andrea Fagiolini assisted Dr. Sarah Fleet with her study titled "Obesity, Body Composition and Insulin Resistance in Women with and without Bipolar Disorder," with results of this study recently published in the *Journal of Consulting and Clinical Psychology*. Dr. Jakicic is also assisting Ms. Carol Janney, a graduate student, who is working with Drs. Ellen Frank, Kupfer, Marsha Marcus, and Isabella Sorecca, on a pilot physical activity intervention for patients with stable bipolar disorder. These initiatives highlight the growing interest and support of the ONRC for this area of study.

Diverse Population Groups: The ONRC provides opportunities for researchers to examine obesity- and nutrition-related diseases in diverse population groups. Access to large populations comes mostly from the involvement of the Epidemiology Core, which has access to large national and international populations. For example, the Epidemiology Core participated in studies of heterogeneous populations in Japan, Japanese in Hawaii, African-American and Caucasian persons in the United States, Native Americans, older and younger men and women, children, etc. Moreover, investigators in the Epidemiology Core have been working with the Trinidad and Tobago government to develop a community-based prevention-of-obesity study in Tobago. This provides unique opportunities for rapidly applying techniques available through the ONRC to understand factors associated with body weight regulation and related diseases in a variety of human populations.

Substance Abuse, Obesity, and Physical Activity: The ONRC Behavioral Core assisted with the submission of a grant application in response to DA-09-013 Interactions Between Physical Activity and Drug Abuse. The title of this application submitted in response to this RFA is "Impact of the Addition of Physical Activity Intervention on Drug Abuse Outcomes (R01 DA-027453)," and Dr. Daley (Department of Psychiatry) and Dr. Jakicic are serving as Co-PIs on this application. The focus of this application is on adding physical activity to a substance abuse treatment program to examine the effect of abstinence along with other health-related outcomes such as body weight and a variety of CVD markers such as lipids, inflammatory markers, etc. This application is currently under review.

Women's Health

The Pittsburgh ONRC has been actively involved in the study of Women's Health issues. For example, Dr. Kathleen McTigue, in collaboration with Dr. Lewis Kuller and colleagues, completed a longitudinal evaluation of approximately 8 years of follow-up among 91,000 participants in the Observational Study of the Women's Health Initiative (WHI) in order to evaluate morbidity and mortality in relationship especially to class II and III obesity among postmenopausal African-American and Caucasian women. This study includes one of the largest samples of women with Class III obesity (a total of 3,234) ever studied. This includes 2,322 Caucasian women (3.2% of all Caucasian women) and 750 African-American women (9.6% of all African-American women) who had a BMI >40. All-cause mortality for Caucasian women increased from 68/100000 with BMI 18.5-24.9 to 116/100000 with BMI >40 and for African-American women, 86/100000 to 110/100000. Much of this risk was attributable to the effect of obesity on risk factors of diabetes and hypertension, as well as effects of cigarette smoking and

use of lipid-lowering drugs. Waist circumference but not hip circumference was strongly related to mortality within each BMI category. These results show that risk factors such as hypertension, diabetes, and elevated lipids account for much of the excess mortality associated with obesity, and that waist circumference is a powerful predictor within BMI categories, at least up to class III BMI.

Another important clinical trial related to obesity was initiated in recent years. The study of the Reduction of Triglycerides in Women (Women On the Move through Activity and Nutrition [WOMAN] study) has been funded by the NHLBI and was recently approved for renewal. This trial is evaluating the effects of weight loss and specific dietary changes on sub-clinical atherosclerosis in women who were currently or previously on hormone therapy (HT). It is the first major trial in women to utilize sub-clinical measurements (i.e., coronary artery calcium and carotid studies) to evaluate the changes in relationship to weight loss, exercise, and specific dietary changes in a large sample over a long period of time. The ONRC has been actively involved in this trial, providing a Pilot and Feasibility award to Dr. Molly Conroy, assistant professor of medicine and epidemiology, to study, in collaboration with Dr. Bret Goodpaster of the Metabolism Core, the effects of the intervention on body composition, specifically changes in muscle and visceral fat. This 5-year-trial will evaluate behavioral and biochemical determinants of weight regain in the intervention arm as well as the effects on sub-clinical outcomes. The WOMAN study has given us the opportunity to study, in a large sample (around 500 women), the effects of very substantial weight loss in a group of women who were only moderately obese (BMI = 31 kg/m^2) with excellent initial weight loss results. Unfortunately, there was subsequent weight regain over the 5 years of follow-up. This study will be one of the first to examine the effects of weight loss on changes in many cardiovascular risk factors and on sub-clinical measurements of atherosclerosis across different patterns of weight change.

We also received a small foundation grant to study women who are predominantly very thin, healthy, and who had breast augmentation surgery many years ago. This group is unique in having relatively low body weight mostly from young adult life onward, being very healthy, and being relatively low-risk for many diseases. The WHI is unique in having detailed weight histories on most of the participants, large sample sizes in different racial and ethnic groups, and good follow-up information. We are also working with Dr. Simin Liu at the University of California School of Public Health on NIH-funded studies of biochemical risk factors and genetic factors within the WHI in relation to risk of type 2 diabetes.

Minority Health

As highlighted above, the ONRC was instrumental in the conceptualization and development of a successful grant application to the Pennsylvania Department of Health, with funding awarded in June 2006 ($4.2 million, total costs) for a 4-year period. This was in response to a Request for Applications that was funded through monies allocated from the Tobacco Settlement process, with a theme of these applications to address health disparities related to obesity prevention and treatment. The ONRC Administrative Core played a strong role in this process and reflects the true collaborative, interdisciplinary, and translational capabilities of the Pittsburgh ONRC through the integration of all the ONRC Cores. The project has a prominent community outreach component and addresses issues of health disparity, and we have recently established collaborations with organizations in minority-based communities in Pittsburgh (The Hill House Association) to implement the weight-loss components of this project in these communities. This was made possible through our collaborations with the Department of Family Medicine and the Center for Minority Health at the University of Pittsburgh, both of which have a strong focus on health disparities. This has also resulted in ONRC investigators collaborating with faculty at

Cheyney University of Pennsylvania, a Historically Black College, by training faculty at Cheyney to conduct obesity research through the implementation of a pilot study of body weight regulation in college students.

Dr. Rachel Mackey and Dr. Lewis Kuller have a grant to evaluate adipokines, ghrelin, and lipoproteins, and also will evaluate inflammatory markers in both African-American and Caucasian women in the WHI who are predominantly obese (BMI >40 kg/m^2) as well as in a sample of women with relatively low-body-weight through women with Class II obesity. The study focuses on better phenotyping of obesity, including weight history, waist circumference, degree of obesity, and adipokines, lipoproteins, and with other data in the WHI on inflammatory markers. Data will subsequently be used for genomic analysis. We published data recently in *JAMA* from the WHI on the association of severe obesity and risk of cardiovascular disease and mortality among both African-American and Caucasian women.

In the WHI, a minority fellow in the Department of Medicine, working with Drs. Kuller, Kriska, and others, has been evaluating the relationship of obesity to disability, especially among African-American and Caucasian women. Similarly, Dr. Kathleen McTigue has a K-award to study the development of obesity among high-risk African-American and Caucasian children and adolescents in Pittsburgh. Dr. Kuller serves as Dr. McTigue's mentor. The Pittsburgh Girls Study is being conducted in collaboration with Dr. Rolf Loeber to study 2,450 urban girls aged 10 to 13. This study focuses on a very-high-risk population of urban girls and may provide an understanding of the etiology of obesity. Fifty-two percent of the sample are African American and are over-sampled in poorer neighborhoods. The project will focus on three aims that include the following: 1) to understand factors relate to mental health which include how symptoms of emotional, behavioral, and mental disorders influence repeat measures of body weight development in a population of high-risk adolescent girls of two racial and ethnic backgrounds; 2) to examine how overweight influences the onset of emotional, behavioral and mental health problems that alter adolescent physical health; and 3) to determine in sub-samples of subjects in this study how the risk of late-life adolescent health are consequences of general obesity. The study will utilize the ONRC Metabolic Core for measures of body composition. Researchers will collaborate with the Behavioral Core and the Physical Activity Sub-Core in conducting measurements of physical activity and in evaluating a variety of behavioral attributes.

Plans are also underway to develop grant applications to expand our understanding of potential ethnic-racial differences related to body weight regulation. This will include an expanded focus on metabolic and behavioral factors that can contribute to body weight regulation and energy balance. The ONRC is supporting this collaboration and Dr. DeLany is taking the lead on developing a grant application in this area.

AIDS

The ONRC continues to support AIDS research, primarily in the area of body composition. Dr. Sharon Riddler of the Division of Infectious Disease is examining effects of anti-HIV therapy upon body composition and uses the ONRC dual-energy x-ray absorptiometry equipment as part of this project. The multi-center AIDS Cohort Study is a study which involves groups from Johns Hopkins University, Northwestern University, the University of California (Los Angeles), and the University of Pittsburgh. This study analyzed lipids in homosexual and bisexual men infected with the HIV virus before and after seroconversion and after treatment with highly-active antiretroviral therapy (HAART). Results indicate that HIV infection causes substantial decreases in serum TC, HDLc, and LDLc levels, whereas subsequent HAART elevates TC.

Health Promotion and Disease Prevention

In the Behavior Core, Dr. John M. Jakicic's research examined the ability of obese participants to adopt and maintain various doses and intensities of physical activity over a 24-month intervention. Dr. Jakicic also demonstrated that approximately 250-to-300 minutes per week of moderate-intensity physical activity is an important component of a comprehensive weight-loss program, and these findings have recently been accepted for publication in *Archives of Internal Medicine*. Moreover, Dr. Jakicic led support for a recently completed clinical trial examining the role and dose of physical activity to prevent weight gain and the development of obesity in adults. These results were prominent in recent recommendations by leading health-related organizations to promote these levels of physical activity for long-term weight loss maintenance. Moreover, this has resulted in Dr. Jakicic serving as a consultant to the Centers for Disease Control and Prevention, which is developing national public health guidelines for physical activity.

The ONRC also developed a weight-loss intervention manual to assist with the implementation and dissemination of weight-control initiatives within clinical settings. Over the past year these materials have been adopted by a local health insurer (University of Pittsburgh Medical Center [UPMC] Health Plan) to be implemented in clinical efforts related to weight control. In addition, the ONRC has assisted this health insurer in training staff to effectively deliver these weight control interventions in-person and by telephone.

The ONRC recently became engaged in a community-based initiative to improve physical activity and eating behaviors in the Greater Pittsburgh community. This outreach effort (America On the Move in Pittsburgh and Get Moving Pittsburgh) has both public (City of Pittsburgh Parks and Recreation Department) and private (UPMC Health Plan, HJ Heinz Company, Del Monte Corporation, KDKA-TV) partnerships to provide free health promotion initiatives in the Greater Pittsburgh region. Since its inception in September 2006, approximately 10,000 individuals participated in this ongoing initiative. Very recently (December 2007), this initiative was expanded to involve schools (Schools On the Move) in an effort to promote healthful eating and other healthy behaviors in children and adolescents.

The ONRC continues to support efforts related to prevention and treatment of type 2 diabetes mellitus. These efforts primarily focus on collaborative efforts with the University of Pittsburgh Diabetes Institute. Moreover, the ONRC supports the NIH-funded LookAHEAD multi-center clinical trial of the long-term effects of moderate weight loss and increased physical activity on cardiovascular health and disease prevention in patients with type 2 diabetes mellitus.

Professional/Public Education Efforts

The ONRC's extensive Enrichment Program is coordinated by the Administrative Core. The Enrichment Program is designed to provide intellectual stimulation and opportunities for interaction among current users of the ONRC; attract other investigators to the field of obesity and nutrition research; and update health care professionals on topics related to obesity and nutrition, including those outside the ONRC and outside the University. The objectives of the Enrichment Program are achieved through a number of initiatives that have developed over the 15 years that the Pittsburgh ONRC has been in existence. Below we briefly discuss our initiatives related to the ONRC Enrichment Program.

ONRC Newsletter. To increase awareness of the ONRC and initiatives related to obesity and nutrition, a two-page newsletter is produced on a quarterly basis. This has been an ongoing practice of the ONRC since Fall 2000. The newsletter is distributed to approximately 3,700

faculty and staff at the University of Pittsburgh, who represent more than 25 academic departments and research centers. The central topic of a newsletter is recent activity within one of the 4 scientific Cores, rotating so that each Core (Behavior, Metabolism, Epidemiology, Laboratory) receives coverage annually. A section of the newsletter is also used to highlight new services or changes in services offered by the ONRC. A recent addition is that the newsletter serves as a forum for ONRC investigators to report on newly initiated studies or highlight recent research achievements.

ONRC Website. The ONRC website (*www.onrc.pitt.edu*) was recently upgraded to allow for new features and enhancements. The two portals of interest that tie into the Enrichment Program are the Public Portal and the Researcher Portal. Through these portals we can post our quarterly newsletter and promote the Speaker Series. Moreover, the website allows us to maintain an accurate list of ONRC services available through each of our Cores and the cost, when applicable, for these services. We are also currently posting our Pilot and Feasibility application on this website, and soon will have the capability to have these grant applications submitted electronically by investigators. Current enhancements to this website are underway to expand the capacity of this system to support the initiatives of the Pittsburgh ONRC.

Speaker Series. The Pittsburgh ONRC has a long-standing, prominent, and effective Speaker Series, and we propose to continue this effort. To facilitate these efforts, the ONRC has partnered with other University of Pittsburgh initiatives such as the Endocrinology Research Conference, University-Wide Endocrinology Conference, and the Epidemiology Speaker Series. Moreover, the ONRC partnered with the Pittsburgh Mind-Body Center to organize these opportunities as well. These seminars involved eminent speakers, both from within and outside the University of Pittsburgh, from a variety of disciplines related to obesity and nutrition. The ONRC often assists in supporting the travel and lodging for these speakers. Below are examples of speakers who have recently presented at the University of Pittsburgh on topics related to obesity and nutrition.

External Speakers (Non-University of Pittsburgh)

Topic	Name and Title / Affiliation
Physical Activity Across the Curriculum: A School-Based Program to Improve Health and Academic Performance of Youth	Joseph Donnelly, Ph.D., Professor and Director of the Energy Balance Laboratory, University of Kansas, Director Mercy Children's Hospital, Center for Physical Activity, Nutrition and Weight Management
Intervention Strategies for Long-Term Weight Loss	Rena Wing, Ph.D., Professor, Dept of Psychiatry and Human Behavior, Brown Medical School
Diabetes Update 2009	
• The ACCORD on the ADVANCEs in Diabetes Management	• Mary Korytkowski, M.D.
• Steroid Related Hyperglycemia	• Jodie Reider, M.D.
• Update on the LookAHEAD Study	• John M. Jakicic, Ph.D.
• Bariatric Surgery-Effects on Diabetes	• Anita Courcoulas, M.D.
• Differential Diagnosis and Treatment of Painful Diabetic Neuropathy	• Eva Feldman, M.D., Ph.D.
• Diagnosis and Treatment of Charcot Neuro-Osteoarthropathy	• Diane Wukich, M.D.
• Diabetic Foot Ulcer Treatment	
• Amputation Prevention-A Primary Care Responsibility	• David Steed, M.D. • Jan Ulbrecht, M.D.

The PAT Family of Lipid Droplet Proteins: Bouncers at the Door to the Fat Club	Perry E. Bickel, M.D., Associate Professor and Director, Center for Diabetes and Obesity Research, Brown Foundation Institute of Molecular Medicine, The University of Texas Health Science Center at Houston
Diabetes and Vascular Disease	David L. Steed, M.D., Professor of Surgery, Vascular Director, Wound Healing/Limb Preservation Clinic, University of Pittsburgh Medical Center
The Perks of Insulin Trafficking and Secretion: A Balancing Act Among Glucose Homeostasis, Neonatal Diabetes, and Insulin Resistance	Douglas Cavener, Ph.D., Professor and Head of Biology, Biology Department, Eberly College of Science, Penn State University
Hyperinsulinemic Hypoglycemia: Advances in Infants and Adults	Mark A. Sperling, M.D., Professor of Pediatrics, Division of Endocrinology, Children's Hospital of Pittsburgh
Transdifferentiation Properties of the Adipose Organ	Saverio Cinti, M.D., Professor of Anatomy Director, Institute of Normal Human Morphology and Diagnostic EM Unit of Faculty of Medicine, University of Ancona
Metabolism of Fat Oxidation and Gluconeogenesis in the Liver	Shawn C. Burgess, Ph.D., Assistant Professor, Advanced Imaging Research Center and Department of Pharmacology, University of Texas Southwestern Medical Center

Interactions of Basic Science and Clinical Investigation

There are a number of examples of interactions between basic science and clinical investigators that the ONRC facilitated. For example, as highlighted above, the ONRC was instrumental in the conceptualization and development of a successful grant application to the Pennsylvania Department of Health that was focused on health disparities and body weight regulation. The ONRC played a strong role in this process and reflects the true collaborative, interdisciplinary, and translational capabilities of the Pittsburgh ONRC through the integration of all the ONRC Cores. The Pittsburgh ONRC used this as an opportunity to bring together all of its Cores to address important scientific questions related to severe obesity, and the contribution of physical activity to the treatment of Class II and III obesity. Consistent with the Request for Applications, at least half of the funding is being used for clinical research and preferably, clinical translation research; the project has a prominent community outreach component and addresses issues of health disparity; and there is an emphasis placed upon identification of novel biomarkers and studies of novel aspects of the pathogenesis of obesity.

The ONRC also facilitated additional interactions between basic science and clinical investigations. For example, Dr. Allan Zhao, of the Department of Cell Biology, has found several leptin interacting proteins in serum that appear to confer leptin resistance in obesity. Isolated using leptin-affinity chromatography, mass-spectrometry revealed that one is C-reactive protein (CRP). The project is examining both human samples and basic science animal research components to determine how CRP-leptin interactions inhibit the binding of leptin to its receptors and blocks its ability to signal. Dr. Zhao also has a major role in the ONRC's project within the CERO Study to investigate non-surgical treatment for severe obesity described in another abstract. Dr. Zhao will determine whether or not the novel finding of CRP-induced leptin resistance in vitro and in animal models translates into leptin resistance in human obesity. This is

a clear and excellent example of the translational aspect of our ONRC. Another interaction has been between clinical investigators concerning impaired fat oxidation by skeletal muscle in obesity and basic scientists examining regulation of the β-oxidation pathway of fatty acid catabolism. This work is examining whether as a consequence of a reduced capacity of the electron transport chain to accept electrons generated in the β-oxidation pathway, there is a build up of incomplete products, of chain length longer than 2 carbons, and will examine blood patterns of acylcarnitines.