

## **Boston Nutrition Obesity Research Center**

**Start Date: 1992**

**Status: Ongoing**

**Source of NIH Support: NIDDK**

**Website: <http://www.bonrc.org>**

### **Organization and Goals**

The Boston Nutrition Obesity Research Center (NORC), based at the Boston Medical Center since October 1998, represents a collaborative effort of five major Boston institutions that represent all three medical schools in the city. These include the Tufts University School of Medicine (Tufts University), Massachusetts General Hospital (Harvard University), Beth Israel Deaconess Medical Center (Harvard University), Boston Medical Center (Boston University), and the Harvard School of Public Health (Harvard University). Boston NORC goals are to:

- Foster ongoing collaborative relationships among healthcare professionals and scientists interested in the study of obesity and nutrition.
- Produce the major advances necessary to resolve the questions surrounding the development of obesity and the regulation of energy metabolism.
- Promote interactions among scientists and institutions and make resources available through support of pilot and feasibility studies, an enrichment program, and the core laboratories.

### **Core Laboratories**

#### **Administrative Core (Boston Medical Center):**

Susan K. Fried, Ph.D. (Boston University School of Medicine), Director

George L. Blackburn, M.D., Ph.D. (Beth Israel Deaconess Medical Center), Associate Director for Clinical Education

Lee M. Kaplan, M.D., Ph.D. (Massachusetts General Hospital), Associate Director for the Pilot and Feasibility Program

#### **External Advisory Group Members:**

Lars Berglund, M.D., Ph.D., University of California Davis Health System (03/10–02/13)

Terry T-K Huang, Ph.D., University of Nebraska Medical Center (05/10–04/13)

Barry Popkin, Ph.D., UNC Carolina Population Center (09/08–08/11)

Steven R. Smith, M.D., Florida Hospital/Sanford-Burnham Institute (09/08–08/11)

Richard Bergman, Ph.D., University of Southern California (10/07–09/09)

Jack Yanovski, M.D., Ph.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development (05/07–04/10)

#### **Adipocyte Core (Boston Medical Center):**

Susan K. Fried, Ph.D., Director

**Clinical and Community Research Core (Tufts University School of Medicine):**

Aviva Must, Ph.D., Director

**Epidemiology and Genetics Core (Harvard School of Public Health):**

Frank B. Hu, M.D., M.P.H., Ph.D., Director

**Transgenic Core (Beth Israel Deaconess Medical Center):**

Bradford Lowell, M.D., Ph.D., Director

<b>Pilot and Feasibility Studies</b>
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**Ongoing Projects**

**Characterizing murine and human brown adipose tissue via PET/CT (positron emission tomography/computerized tomography).** Aaron Cypess, M.D., Ph.D., Joslin Diabetes Center (09/08–03/31/11). The first set of studies (Aim 1) will validate <sup>18</sup>F-FDG PET/CT ([<sup>18</sup>F]-2-fluoro-D-2-deoxy-D-glucose positron emission tomography/computerized tomography) as a methodology to quantify whole-body brown adipose tissue (BAT) mass and activity and establish a gene expression profile of BAT and white adipose tissue depots in mice and humans. The second phase (Aim 2) will assess how known pharmacological and nutritional activators of BAT modify its function as measured by PET/CT and indirect calorimetry. Finally, the human studies (Aim 3) will further characterize human BAT in terms of its anatomic distribution and the anthropometric and metabolic parameters affecting its mass and activity.

**Potential regulation of FGF-21 by fasting and diet-induced ketosis in healthy adults.** Jody Dushay, M.D., Beth Israel Deaconess Medical Center (04/07–09/10). This project will test the hypothesis that FGF-21 levels in healthy adults will change in response to fasting and diet-induced ketosis.

**The role of adipose tissue carbohydrate response element binding protein (ChREBP) in adipose tissue glucose metabolism and glucose homeostasis.** Mark Herman, M.D., Beth Israel Deaconess Medical Center (04/09–03/11). The objective of this proposal is to determine the role of adipose tissue ChREBP in adipocyte glucose sensing and to determine the role of adipose tissue ChREBP in regulating adipocyte glucose utilization, whole-body glucose homeostasis, and energy balance.

**The role of circulating monocytes in the development of obesity-induced inflammation and insulin resistance.** Jongsoo Lee, Ph.D., Joslin Diabetes Center (01/09–03/11). The proposed studies will determine the role of circulating monocytes in the development of obesity-induced insulin resistance.

**The role of stress in insulin resistance following bariatric surgery. Sherry Pagoto, Ph.D., University of Massachusetts Medical School, Worcester (04/07–09/10).** This study will explore whether two groups (one group with Perceived Stress Scale scores  $\geq 30$  and the other group with scores  $< 26$ ) of bariatric surgery candidates with insulin resistance, experiencing chronic stress, have a higher degree of inflammation and HPA axis dysfunction than those with

low stress at baseline. Second, the study will compare the two groups on the degree of change in insulin sensitivity, weight, inflammation, and HPA axis dysfunction 6 months following surgery. Finally, the study will test whether the relationship between chronic stress and change in insulin sensitivity in 6 months is mediated by HPA axis dysfunction and heightened inflammation.

**Genome-wide association based scan for abdominal obesity genes in humans.** Lu Qi, M.D., Ph.D., Harvard School of Public Health (12/07–03/11). The specific aims of the project include: 1) to combine the Nurses' Health Study (NHS) genome-wide association (GWA) scan with existing GWA scans on abdominal obesity and generate a ranked list for GWA signals associated with waist circumference. The analyses will be adjusted for BMI, age, and disease status; and 2) to replicate the top 48 single nucleotide polymorphisms with the highest significant levels from Aim 1 in an independent random sample of 2,000 healthy women from the Nurses' Health Study.

**Effects of profilin-1 in diet-induced obesity and adipose inflammation correlation with vascular outcomes.** Giulio Romeo, M.D., Joslin Diabetes Center (09/08–03/11). The primary goal of this project is to characterize the effect of the actin-binding protein profilin-1 (pfn) in high-fat diet-induced metabolic abnormalities and inflammation.

**Interrelationship of circulating levels of vitamin D, adiposity, and risk of developing type 2 diabetes in postmenopausal women.** Yiqing Song, M.D., Sc.D., Brigham & Women's Hospital (04/09–03/11). The objective of this project is to investigate the role of vitamin D in predicting future risk of type 2 diabetes, as well as understand the modulating role of adiposity on these relationships in a prospective case-control study within a well-characterized cohort, the Women's Health Study.

**Effects of Roux-En-Y gastric bypass on diet induced thermogenesis in mice.** Nicholas Stylopoulos, M.D., Massachusetts General Hospital (11/08–3/11). The research hypothesis of this project is that the enhanced energy expenditure observed after Roux-en-Y Gastric Bypass (RYGB) is an important contributor to RYGB-induced weight loss.

**Obesity, physical activity, and successful aging.** Qi Sun, M.D., Sc.D., Harvard School of Public Health (01/09–03/11). Data from the Nurses' Health Study will be used to examine the following primary specific aims: 1) to examine midlife overall obesity, as measured by body mass index, and central obesity, as measured by waist circumference and waist-to-hip ratio, in relation to successful aging in women; and 2) to examine associations between midlife physical activities, including both moderate and vigorous activities, and successful survival in women.

**Identification of novel secretory proteins from subcutaneous fat that improve metabolism.** Thien Tran, Ph.D., Joslin Diabetes Center (01/09–03/11). The goal of this proposal is to identify and characterize novel secretory proteins from subcutaneous fat that can improve metabolism. The results of this research will lead to targets for the prevention and/or treatment of obesity and its related diseases.

**Use of a lipogenic mutant to investigate a novel link between carbohydrate and lipid metabolism.** Raphael Zoeller, Ph.D., Boston University School of Medicine (01/09–03/11). The specific aims of this project are as follows: 1) to investigate the profile of metabolites that could

be altered due to a glucosephosphate isomerase (GPI) deficiency; 2) to initiate a molecular characterization of signaling pathways that may be involved in this relationship; 3) to test the hypothesis that GPI is linked to the localization of lipin 1 $\alpha$  (PAP1) to the nucleus; and 4) to test this GPI/lipin 1 (PAP1) link in other cell types.

### **Newly Funded (American Recovery and Reinvestment Act [ARRA] Funds)**

#### **The effects of a novel GH (growth hormone) releasing factor on mitochondrial function.**

Hideo Makimura, M.D., Ph.D., Massachusetts General Hospital (03/10–02/11). The aim of this proposal is to improve mitochondrial function by improving GH secretion and normalizing altered GH pulsatility in obese subjects using a novel GH releasing factor.

#### **Role of FSP27 (fat specific protein 27) in fat metabolism and insulin sensitivity.**

Vishwajeet Puri, Ph.D., Boston Medical Center (03/10–02/11). This pilot project will generate data toward understanding the role of FSP27 in lipid droplet dynamics in adipocytes, and consequences for the regulation of fatty acid turnover and insulin sensitivity in humans.

#### **A computer-based cue system for motivational interviewing counseling.**

Lisa Quintiliani, Ph.D., R.D., Boston Medical Center (03/10–02/11). This pilot project proposes to develop and test a non-obtrusive web-based computer system for peer counselors to guide motivational interviewing-based counseling for nutrition and physical activity behaviors. The system will have three main practical uses: as an aid in training the peer counselors, guiding the peer counselors through telephone counseling sessions, and facilitating reflective feedback to the peer counselors.

#### **Sleep loss and circadian dysregulation—important risk factors for obesity and diabetes mellitus.**

Vettrivelan Ramalingam, Ph.D., Beth Israel Deaconess Medical Center (03/10–02/11). This project investigates the effects of chronic sleep loss and circadian dysregulation on energy metabolism and glucose homeostasis in mice.

#### **The role of promyelocytic leukemia zinc finger (PLZF) in adipogenesis.**

Zhao Xu, Ph.D., Beth Israel Deaconess Medical Center (03/10–02/11). The long-term goal of this study is to provide insight into the transcriptional regulation of adipocyte biology and to identify novel molecular targets for treating insulin resistance and related metabolic diseases.

### **Funding Derived From Pilot and Feasibility Studies**

*Note: This includes currently funded and previously funded Pilot and Feasibility investigators.*

#### **Causes and impact of minority stress on health and development in youth (S.B. Austin, co-PI).**

S. Bryn Austin, Ph.D., Brigham and Women's Hospital. Funding: National Institutes of Health/Eunice Kennedy Shriver National Institute of Child Health and Human Development (NIH/NICHHD) 1R01HD057368-01A2 (09/15/09–06/30/14)

#### **Neuronal protein tyrosine phosphates in metabolism. Kendra Bence, Ph.D., University of Pennsylvania.**

Funding: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK) 3R01DK082417-01A1 (07/01/09–06/30/14)

**Human brown adipose tissue and its impact on metabolism.** Aaron Cypess, M.D., Ph.D., Joslin Diabetes Center. Funding: NIH/NIDDK 1K23DK081604-01A1 (09/01/09–08/31/14)

**Small RNAs: regulation and regulatory activity in body weight control.** Deborah Good, Ph.D., Virginia Tech University. Funding: NIH/NIDDK 1RC1DK086655-01 (09/20/09–08/31/11)

**Rock1 signaling in glucose metabolism.** Young-Bum Kim, Ph.D., Beth Israel Deaconess Medical Center. Funding: NIH/NIDDK 1R01DK083567-01A1 (03/01/10–02/28/15)

**The role of circulating monocytes in the development of obesity-induced insulin resistance.** Jongsoon Lee, Ph.D., Joslin Diabetes Center. Funding: American Diabetes Center/Basic Science Grant (01/01/10–12/31/12)

**Biomarkers of dietary variables commonly misreported.** Megan McCrory, Ph.D., Purdue University. Funding: NIH/NIDDK 1R01DK075862-01A1 (09/30/09–07/31/11)

**Regulation of JNK signaling by dual specificity phosphates in adipocytes.** Ron Morrison, Ph.D., University of North Carolina Greensboro. Funding: NIH/NIDDK 1R15DK082799-01A1 (03/10–02/13)

**The role of nicotinamide N-methyltransferase in glucose and lipid homeostasis.** Pavlos Pissios, Ph.D., Beth Israel Deaconess Medical Center. Funding: NIH/NIDDK 1R01DK083694-01A1 (05/01/10–04/30/15)

**School worksite weight gain prevention intervention study (L. Pbert, co-PI).** Lori Pbert, Ph.D., University of Massachusetts Medical School Worcester. Funding: National Institutes of Health/National Cancer Institute (NIH/NCI) 5R01CA132941-02 (07/17/09–06/30/11)

**Ghrelin's role in mood.** Jeffrey Zigman, M.D., Ph.D., University of Texas Southwestern Medical Center. Funding: National Institutes of Health/National Institute of Mental Health (NIH/NIMH) 1R01MH085298-01A2 (04/01/10–12/31/14)

## Scientific Advances/Accomplishments

The NORC's progress is reflected in the manuscripts that were published using services of the various Cores. Following are abstracts of some of the publications that were supported by Core facilities during this period.

### Adipocyte Biology, Obesity, and Diabetes (Adipocyte and Transgenic Cores)

**Simard JR, Meshulam T, Pillai BK, Kirber MT, Brunaldi K, Xu S, Pilch PF, Hamilton JA. Caveolins sequester FA on the cytoplasmic leaflet of the plasma membrane, augment triglyceride formation, and protect cells from lipotoxicity. *J Lipid Res.* 2010;May;51(5):914-22. PMID: PMC2853459**

Drs. Paul Pilch and James Hamilton collaborated on studies that show that two important physiological correlates of the ectopic expression of caveolins-1 and -3 are (i) enhanced

triglyceride accumulation and (ii) protection of cells from toxicity at high fatty acid (FA) concentrations. These results, together with in vivo data from caveolin/caveolae-deficient animals, support a physiologically important role for caveolins in modulating cellular FA flux and storage. Caveolins sequester FA on the cytoplasmic leaflet of the plasma membrane, augment triglyceride formation, and protect cells from lipotoxicity.

**Wang T, Si Y, Shirihai OS, Si H, Schultz V, Corkey RF, Hu L, Deeney JT, Guo W, Corkey BE. Respiration in adipocytes is inhibited by reactive oxygen species. *Obesity (Silver Spring)*. 2010;Aug;18(8):1493–502. PMID: PMC20035277**

Dr. Barbara E. Corkey's laboratory published studies that suggest for the first time that adipocyte oxygen (O<sub>2</sub>) consumption may be inhibited by reactive oxygen species (ROS). Pyruvate or the antioxidant N-acetylcysteine stimulated respiration. Therefore ROS inhibition of O<sub>2</sub> consumption may explain the difficulty of identifying effective strategies to increase fat burning in adipocytes.

**Molina AJ, Wikstrom JD, Stiles L, Las G, Mohamed H, Elorza A, Walzer G, Twig G, Katz S, Corkey BE, Shirihai OS. Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. *Diabetes*. 2009;Oct;58(10):2303–15. Epub 2009 Jul 6. PMID: PMC2750232 [Available on 2010/10/1]**

Shirihai and colleagues collaborated on studies that point to a key role of mitochondrial networking in protecting beta cells from nutrient induced apoptosis.

**Chakrabarti P, English T, Shi J, Smas CM, Kandror KV. Mammalian target of rapamycin complex 1 suppresses lipolysis, stimulates lipogenesis, and promotes fat storage. *Diabetes*. 2010;Apr;59(4):775–81. Epub 2010 Jan 12. PMID: 20068142 [PubMed – indexed for MEDLINE] PMID: PMC2844824 [Available on 2011/4/1]**

Studies by the laboratory of Dr. Konstantin Kandror demonstrated that the mammalian target of rapamycin complex 1 promotes fat storage in mammalian cells by suppression of lipolysis and stimulation of de novo lipogenesis.

**Miyoshi H, Souza SC, Endo M, Sawada T, Perfield JW 2nd, Shimizu C, Stancheva Z, Nagai S, Strissel KJ, Yoshioka N, Obin MS, Koike T, Greenberg AS. Perilipin overexpression in mice protects against diet-induced obesity. *J Lipid Res*. 2010;May;51(5):975–82. Epub 2009 Oct 1. PMID: PMC2853465 [Available on 2011/5/1]**

The laboratory of Dr. Andrew Greenberg published a paper demonstrating that perilipin overexpression in mice protects against diet-induced obesity, most likely by influencing the activity of brown adipose tissue (where the construct was overexpressed). The Transgenic Core assisted with the preparation of the transgenic mice.

**Wang XL, Suzuki R, Lee K, Tran T, Gunton JE, Saha AK, Patti ME, Goldfine A, Ruderman NB, Gonzalez FJ, Kahn CR. Ablation of ARNT/HIF1beta in liver alters gluconeogenesis, lipogenic gene expression, and serum ketones. *Cell Metab*. 2009;May;9(5):428–39. Erratum in: *Cell Metab*. 2009 Jun;9(6):565. PMID: PMC2803070**

Studies from the laboratory of C.R. Kahn and his collaborators, including N. Ruderman, used a novel liver-specific knockout of ARNT/HIF1beta action in the liver, coupled with that in beta cells, could contribute to the metabolic phenotype of human type 2 diabetes.

**Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009;Apr 9;360(15):1509–17. PMID: PMC2859951**

One of our Pilot and Feasibility awardees, A. Cypess published a much-cited paper in the *New England Journal of Medicine* indicating that brown adipose tissue exists and is functional in adult humans. Unlike mice, the brown adipocytes were dispersed in white adipose tissue. Intriguingly, the amount of brown adipose tissue is inversely correlated with body-mass index, especially in older people, suggesting a potential role of brown adipose tissue in adult human metabolism.

### **Clinical and Community Research (Clinical and Community Core)**

**Pagoto SL, Curtin C, Lemon SC, Bandini LG, Schneider KL, Bodenlos JS, Ma Y. Association between adult attention deficit/hyperactivity disorder and obesity in the US population. *Obesity (Silver Spring).* 2009;Mar;17(3):539–44. Epub 2009 Jan 8. PMID in process.**

L. Bandini and colleagues addressed the important area of the relationship between neurobehavioral disorders and obesity. In a paper published in *BMC Pediatrics*, they provide data suggesting that adult attention deficit hyperactivity disorder is associated with overweight and obesity.

**Bandini LG, Anderson SE, Curtin C, Cermak S, Evans EW, Scampini R, Maslin M, Must A. Food selectivity in children with autism spectrum disorders and typically developing children. *J Pediatr.* 2010;Mar 31. [Epub ahead of print] PMID in process**

Dr. Aviva Must's group also published a study that suggests that conduct problems in childhood are prospectively associated with overweight and obesity in young adulthood.

**Tovar A, Chasan-Taber L, Bermudez OI, Hyatt RR, Must A. Knowledge, attitudes, and beliefs regarding weight gain during pregnancy among hispanic women. *Matern Child Health J.* 2010;Aug;157(2):259–64. PMID: PMC20362301**

Dr. Must and colleagues examined the effects of gestational weight gain and diet on abnormal glucose tolerance test (AGT) during pregnancy in Hispanic women, as well as attitudes and beliefs about weight gain during pregnancy among Hispanic women. Decreasing levels of saturated fatty acids and energy-dense snack foods and increasing levels of fiber and polyunsaturated:saturated fat ratio were significantly associated with decreased risk of AGT, independent of gestational weight gain. Attitudes toward weight gain recommendations differed by weight status, whereas feelings and dietary beliefs about weight gain differed according to level of acculturation.

### **Epidemiology and Genetics (Epidemiology and Genetics Core)**

**van 't Riet E, Dekker JM, Sun Q, Nijpels G, Hu FB, van Dam RM. Role of adiposity and lifestyle in the relationship between family history of diabetes and 20-year incidence of type 2 diabetes in U.S. women. *Diabetes Care.* 2010;Apr;33(4):763–7. Epub 2010 Jan 12. PMID: PMC2845024 [Available on 2011/4/1]**

Studies by a team lead by F. Hu and R. van Dam addressed the relative importance of the roles

of adiposity and lifestyle in the relationship between family history of diabetes and 20-year incidence of type 2 diabetes in U.S. women. Their results showed that adiposity and, to a lesser extent, specific dietary habits can explain a substantial part of the association between having a family history of diabetes and risk of type 2 diabetes.

**Hivert MF, Sun Q, Shrader P, Mantzoros CS, Meigs JB, Hu FB. Circulating IL-18 and the risk of type 2 diabetes in women. *Diabetologia*. 2009;Oct;52(10):2101–8. Epub 2009 Aug 8. PMID in process**

Studies by the groups of F. Hu and C. Mantzoros suggest a strong inverse association between levels of the soluble leptin receptor and risk of type 2 diabetes, independent of BMI, leptin, and adiponectin levels.

**Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation*. 2009;Mar 3;119(8):1093–100. Epub 2009 Feb 16. Erratum in: *Circulation*. 2009;Mar 31;119(12):e379. PMID: PMC2724471**

This report showed that those women who followed a Mediterranean diet had a lower risk of incident coronary heart disease (CHD) and stroke.

**Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr*. 2009;Apr;89(4):1037–42. Epub 2009 Feb 11. PMID: PMC2667454.**

This paper in the American Journal of Clinical Nutrition by F. Hu and colleagues, which examined data from the Nurses' Health Study, suggests that regular consumption of sugar-sweetened beverages is associated with a higher risk of CHD in women, even after other unhealthy lifestyle or dietary factors are accounted for.

**Sun Q, Townsend MK, Okereke OI, Franco OH, Hu FB, Grodstein F. Adiposity and weight change in mid-life in relation to healthy survival after age 70 in women: prospective cohort study. *BMJ*. 2009;Sep 29;339:b3796. doi: 10.1136/bmj.b3796. PMID in process**

This study provides evidence that adiposity in mid-life is strongly related to a reduced probability of healthy aging among older women and emphasizes the importance of maintaining a healthy weight from early adulthood (*BMJ*. 2009;Sep 29;339:b3796. doi: 10.1136/bmj.b3796).

**Heid IM, Huth C, Loos RJ, Kronenberg F, Adamkova V, Anand SS, Ardlie K, Biebermann H, Bjerregaard P, Boeing H, Bouchard C, Ciullo M, Cooper JA, Corella D, Dina C, Engert JC, Fisher E, Francès F, Froguel P, Hebebrand J, Hegele RA, Hinney A, Hoehe MR, Hu FB, Hubacek JA, Humphries SE, Hunt SC, Illig T, Järvelin MR, Kaakinen M, Kollerits B, Krude H, Kumar J, Lange LA, Langer B, Li S, Luchner A, Lyon HN, Meyre D, Mohlke KL, Mooser V, Nebel A, Nguyen TT, Paulweber B, Perusse L, Qi L, Rankinen T, Roszkopf D, Schreiber S, Sengupta S, Sorice R, Suk A, Thorleifsson G, Thorsteinsdottir U, Völzke H, Vimalaswaran KS, Wareham NJ, Waterworth D, Yusuf S, Lindgren C, McCarthy MI, Lange C, Hirschhorn JN, Laird N, Wichmann HE. Meta-analysis of the INSIG2 association with obesity including 74,345 individuals: does heterogeneity of estimates relate to study design? *PLoS Genet*. 2009;Oct;5(10):e1000694. Epub 2009 Oct 23. PMID: PMC2757909**

Recently published results from genome-wide association scan meta-analysis identify three loci influencing adiposity and fat distribution.

### **Neuroscience of Obesity (Transgenic Core)**

**Hill JW, Xu Y, Preitner F, Fukuda M, Cho YR, Luo J, Balthasar N, Coppari R, Cantley LC, Kahn BB, Zhao JJ, Elmquist JK. Phosphatidyl inositol 3-kinase signaling in hypothalamic proopiomelanocortin neurons contributes to the regulation of glucose homeostasis. *Endocrinology*. 2009;Nov;150(11):4874–82. Epub 2009 Oct 9. PMID: PMC2775989 [Available on 2010/11/1]**

In studies facilitated by the Transgenic Core, the laboratories of Bradford B. Lowell and Joel Elmquist published a paper that demonstrated that phosphatidyl inositol 3-kinase signaling in hypothalamic proopiomelanocortin neurons contributes to the regulation of glucose homeostasis.

**van den Pol AN, Yao Y, Fu LY, Foo K, Huang H, Coppari R, Lowell BB, Broberger C. Neuromedin B and gastrin-releasing peptide excite arcuate nucleus neuropeptide Y neurons in a novel transgenic mouse expressing strong Renilla green fluorescent protein in NPY neurons. *J Neurosci*. 2009;Apr 8;29(14):4622–39. PMID: PMC2745949**

Dr. Lowell and the Transgenic Core also participated in studies showing the NYP-hrGFP BAC transgenic mice, generated by the Core, faithfully express GFP in all neuropeptide Y (NPY) neurons. Thus, these mice are useful to scientists who want to visualize NPY neurons. Since the GFP signal can be visualized in live tissue, these mice are extremely useful for scientists who wish to perform electrophysiologic (electrical) analyses on NPY neurons. The mice are now distributed by Jackson Labs and are being extensively utilized by numerous scientists.

### **Specific Accomplishments**

The Boston NORC and Core laboratory activities that furthered our mission and the understanding of obesity and its associated causes and consequences are summarized below by Core.

### **Administrative Core**

The Administrative Core continues to support the Center's Pilot and Feasibility Program as well as enrichment activities. Dr. Lee M. Kaplan, Associate Director for the Pilot and Feasibility Program, in conjunction with the Administrative Core, held a Pilot and Feasibility competitive application cycle beginning in October 2009. A total of 27 letters of intent were received and 15 applicants were invited to submit full applications. Subsequently, 13 full applications were submitted for funding consideration. Reviewer assignments were made by Dr. Kaplan and a Study Section was held on February 28, 2010. This application process resulted in the funding of five new projects that were funded from ARRA funds awarded to the Center. The Center continues to direct as many resources as possible, both financial and other, into the Pilot and Feasibility Program. The Center also continues to offer four \$500 travel scholarships per year to partially support the participation of junior investigators at professional meetings that relate to the Center's themes.

The Center's enrichment program continues to include a well-established Adipose and Metabolic Tissue Study Group as well as a half-day Annual Program (as described below). Both of these events are held at Boston University Medical Campus. The Administrative Core has also implemented a weekly list of educational activities related to nutrition and obesity for electronic distribution to our membership. This list includes seminars and programs at Boston University, Tufts University, Harvard University, and the Joslin Diabetes Center.

An online request for Core services has been set up. This tool will also streamline the reporting process for Core utilization as well as the process to request services. The form is currently being piloted by the Adipocyte Core.

### **Adipocyte Core**

The Adipocyte Core continues to offer its standard services:

- Preparation of animal cultured preadipocytes, isolated adipocytes, and products of these cells (including DNA, RNA, protein, and conditioned medium), and maintaining a human and rodent tissue and preadipocyte bank and database
- Providing consultative advice about experimental design in nutrition and obesity studies, institutional review board documentation, and methods involving these adipose tissue and isolated cell fractions, and their products, as well as preliminary analyses for users for analysis of gene expression (qPCR) and the analysis of gene function (using adeno-, retro-, and lentiviral vectors, and siRNA)
- Assistance with coordinating acquisition of surgical and aspirated samples of human adipose tissues. Dr. Apovian also provides training to Boston NORC members in techniques for aspiration of human adipose tissue.
- Supporting the Adipose Tissue Study Group (a seminar series run by the Core), fostering collaborative links among investigators in adipocyte biology, and continuing to provide assistance to investigators

The Adipocyte Core is also planning a mechanism that will allow Boston NORC members (including those outside of Boston University) to utilize the services of the Department of Medicine's Small Animal Phenotyping Core. With the hiring of Dr. You-Ree Cho (ARRA funds), we have been working toward adding euglycemic clamp protocols for mice and rats to the services offered. Dr. Cho also provides advice to users on the conduct of glucose tolerance tests and insulin tolerance tests.

Using ARRA funds, we purchased a dual-energy X-ray absorptiometry to measure body composition in severely obese subjects. We anticipate that the availability of this basic phenotyping method will facilitate the conduct of translational research in obesity and related disorders in our Center.

The Boston NORC Adipocyte Core proactively shares best practices and methods with other NORCs in Minnesota, Maryland, and St. Louis.

### **Clinical and Community Research Core**

The Clinical and Community Research Core was established in late 2006 to support obesity researchers working in community and clinical settings. The Core serves members of the Boston NORC whose research requires body composition/fat distribution measurements, qualitative methods, and survey research methods. It serves area investigators who are carrying out human studies on metabolic units, in clinical research facilities, and in community settings. It comprises two units: the Body Composition Unit and the Qualitative, Clinical, and Survey Research Methods Unit. The Clinical and Community Research Core serves three main functions:

- To provide qualitative methods services (training and/or facilitation for focus groups, key informant interviews, content analysis) and instrument design services for paper and web-based surveys and questionnaires
- To provide consultative services regarding the appropriate uses and limitations of qualitative, clinical, and survey research methods; data management; and measurement of body composition and behavioral risk factors for obesity in normal human subjects across the lifespan, or in human subjects with obesity, under-nutrition, or conditions that predispose to malnutrition
- To provide support and an environment stimulating interest and training in community-based and clinic-based obesity related research for junior faculty, medical residents, and doctoral and medical students

### **Epidemiology and Genetics Core**

The Epidemiology and Genetics Core serves three primary functions:

- To provide computing and data analysis services and guidance, as well as maintaining a library containing four large longitudinal data sets and public access data from national surveys that bear on obesity that are available for data analysis of nutritional and lifestyle determinants of obesity as well as morbidity and mortality consequences of obesity
- To support Boston NORC clinical and epidemiologic studies that require high-throughput genotyping and genetic data analyses
- To provide support and an environment stimulating interest and training in obesity epidemiology and genetics research for junior faculty and doctoral students

### **Transgenic Core**

The Transgenic Core provides the following services:

- Transgenics – pronuclear injection of transgenic DNA constructs
- Gene Targeting – targeting of embryonic stem cells in culture
- Gene Targeting – injection of two targeted embryonic stem cells into blastocysts
- Cryopreservation of genetically engineered mice

## **Educational Activities/Accomplishments**

The enrichment program provides a mechanism to support and amplify the central themes of the Boston NORC and draw together the various groups and institutions that comprise the Center. Since its inception, the enrichment program has consisted of seminar series, an annual Continuing Medical Education course, mini-symposia, and support for junior investigators to attend conferences and meetings that will enhance their training. This program has proved to be an enormously effective approach to stimulate discussion, develop new research directions, and foster the development of junior investigators in the field of nutrition and obesity.

The enrichment program was established with four goals:

- To support state-of-the-art seminar series that provide an educational forum for new and established investigators on wide-ranging topics in obesity and nutrition
- To provide support for specialized courses, workshops, mini-symposia, and lectures by visiting scientists in order to foster new initiatives in obesity and nutrition-related research
- To contribute to enhanced scientific understanding about the causes, consequences, and emerging treatments for obesity among clinicians and clinical investigators by contributing to and co-sponsoring the annual Harvard Obesity Course
- To encourage junior investigators and trainees interested in nutrition and obesity research by awarding scholarships to attend an obesity-related or nutrition-related scientific meeting

Information from the enrichment program is provided below. In summary, the Boston NORC's Enrichment Program continues to support its original goals.

### **Annual Program**

The Center sponsors a half-day Annual Program each year that includes a morning plenary session followed by a poster session. All meeting attendees are invited to submit an abstract for presentation in the poster session, and currently funded pilot and feasibility investigators are required to participate as a condition of their award. The recipients of the Boston NORC Travel Scholarships are expected to participate as well. The plenary session includes three invited speakers. The 2009 Plenary Session was expanded to include three currently funded Pilot and Feasibility investigators as well. As in prior years, the 2009 Plenary Session included a member of the Boston NORC Executive Committee, a member of the External Scientific Advisory Committee, and a third speaker invited from the broader community of investigators active in obesity and nutrition research. The Plenary Session in the 2010 program was designed around a theme and included a talk in each of the following areas: basic science, epidemiological studies (including genetic epidemiology), and clinical or translational investigation. Attendance at the annual program has varied between approximately 90 and 120 people, comprised of clinical investigators, basic scientists, and trainees. The Annual Program is held in conjunction with the annual meeting of the Center's External Scientific Advisory Committee so that members of this committee can attend the program. Immediately following the conclusion of the program, the Scientific Advisory Committee meets in joint session with the Center Executive Committee to discuss the progress of the Center, the scientific cores, the outcomes of the most recent Pilot and

Feasibility Program review, and other issues that may arise. A summary of the Annual Program speakers and poster presentations in 2009 and 2010 is listed below.

<b>Program Date</b>	<b>Plenary Session</b>	<b>Abstracts in Poster Session</b>
<b>June 15, 2009</b>	<b><i>Genetic Dissection of Neural Circuits Controlling Energy Homeostasis</i></b> Bradford B. Lowell M.D., Ph.D. Professor of Medicine, Harvard Medical School Beth Israel Deaconess Medical Center	Basic Science = 8 Clinical = 3 Population = 8  TOTAL = 19
	<b><i>Alternative Mechanisms of Insulin Resistance</i></b> Richard N. Bergman, Ph.D. Keck Professor of Medicine and Chair Department of Physiology and Biophysics Keck School of Medicine University of Southern California	
	<b><i>Rapid Infancy Weight Gain and Subsequent Obesity: Epidemiological Evidences</i></b> Nicolas Stettler, M.D., MSCEAssistant Professor of Pediatrics and Epidemiology The Children's Hospital of Philadelphia	
	<b>Pilot and Feasibility Presentations</b>	
	<b><i>The Use of Non-Invasive Imaging to Characterize Murine and Human Brown Adipose Tissue</i></b> Aaron Cypess, M.D., Ph.D., MMSc Instructor, Harvard Medical School Research Associate and Staff Physician, Joslin Diabetes Center	
<b><i>Neuroendocrine Modulation of Metabolic Effects in Overweight Adolescent Girls</i></b> Madhusmita Misra, M.D., MPH Assistant Professor of Pediatrics Harvard Medical School Massachusetts General Hospital		
<b><i>Determination of the Physiological Role and Metabolic Effects of Fibroblast Growth Factor 21</i></b> Michael Badman, M.D., Ph.D. Postdoctoral Fellow Beth Israel Deaconess Medical Center		

<b>Program Date</b>	<b>Plenary Session</b>	<b>Abstracts in Poster Session</b>
<b>June 14, 2010</b>	<p><b><i>Adipokines and Cardiovascular Disease</i></b>  Kenneth Walsh, Ph.D.  Aram V. Chobanian Distinguished Professor in  Cardiovascular Medicine  Director, Whitaker Cardiovascular Institute  Boston University School of Medicine</p> <p><b><i>Obesity and Other Preventable Causes of Cardiovascular Disease</i></b>  Eric Rimm, ScD  Associate Professor of Medicine, Harvard Medical School  Channing Laboratory, Brigham and Women's Hospital  Associate Professor of Epidemiology and Nutrition  Director, Program in Cardiovascular Epidemiology, Harvard  School of Public Health</p> <p><b><i>A Role for Adipose Tissue Angiogenesis in Metabolic Diseases?</i></b>  Steven R. Smith, M.D.  Scientific Director &amp; Professor  Translational Research Institute for Metabolism and  Diabetes  Florida Hospital/Sanford-Burnham Institute</p> <p><b>Pilot and Feasibility Presentations</b></p> <p><b><i>The Role of Circulating Monocytes in the Development of Obesity-Induced Inflammation and Insulin Resistance</i></b>  Jongsoon Lee, Ph.D.  Assistant Investigator, Joslin Diabetes Center  Instructor, Harvard Medical School</p> <p><b><i>Use of a Lipogenic Mutant to Investigate a Novel Link Between Carbohydrate and Lipid Metabolism</i></b>  Raphael A. Zoeller, Ph.D.  Associate Professor  Boston University School of Medicine  Department of Physiology &amp; Biophysics</p> <p><b><i>Genome-Wide Association Based Scan for Abdominal Obesity Genes in Humans</i></b>  Lu Qi, M.D., Ph.D.  Assistant Professor in Medicine, Harvard Medical School  Assistant Professor in Nutrition, Harvard School of Public  Health</p>	<p>Basic Science = 14  Clinical and  Population Studies  = 8  Education and  Resources = 2</p> <p>TOTAL = 24</p>

**Adipose and Metabolic Tissue Study Group Seminar Series.** The Adipose and Metabolic Tissue Study Group meets every 2 months for research seminars, presentations of research in progress, and grant proposals for critical review. On average, 25 investigators from Tufts University, Boston University, and Harvard University regularly attend these seminars, which are held at the Boston University Medical Campus. A list of speakers and topics appears below.

<b>Date</b>	<b>Speaker</b>	<b>Title</b>
09/22/09	Susan K. Fried, Ph.D. Section of Endocrinology, Diabetes, Nutrition Boston University School of Medicine	Cellular mechanisms regulating fat distribution in men and women
10/06/09	Marianne Wessling-Resnick, Ph.D. Department of Genetics and Complex Diseases Harvard School of Public Health	Chemical genetics of iron transport
10/20/09	Philipp E Scherer, Ph.D. The University of Texas Southwestern Medical Center at Dallas	Stepwise progression towards adipose tissue dysfunction
11/03/09	Professor Jan Nedergaard Professor Barbara Cannon The Wenner-Gren Institute Stockholm University, Sweden	Brown adipose tissue in adult humans and its metabolic consequences: origins of adipose tissues
11/10/09	Rachel Altura, M.D. Division of Pediatrics Hematology/Oncology Rhode Island Hospital	The IAP survivin regulates pancreatic beta cell proliferation
11/17/09	Rohit N. Kulkarni, M.D., Ph.D. Section of Cellular and Molecular Physiology Joslin Diabetes Center	A role for the “tribbles” protein in insulin exocytosis in human islets
12/15/09	Laurie J. Goodyear, Ph.D. Section of Metabolism Joslin Diabetes Center	Novel mechanisms regulating glucose transport in skeletal muscle AMP and beyond
01/12/10	Jose M Cacicedo, Ph.D. Postdoctoral Fellow Diabetes Research Unit Boston University School of Medicine	AMP-activated protein kinase prevents Palmitate-induced lipotoxicity in retinal pericytes: implications for diabetic retinopathy

<b>Date</b>	<b>Speaker</b>	<b>Title</b>
01/26/10	Marie E. McDonnell, M.D. Assistant Professor of Medicine Boston University Section of Endocrinology, Diabetes, and Nutrition Director, Inpatient Diabetes Program, Boston Medical Center	“Real world” diabetes therapy for the obese patient: where we are and where we need to be
02/09/10	Nicholas Stylopoulos, M.D. Gastrointestinal Unit/Weight Center Massachusetts General Hospital Instructor in Medicine Harvard Medical School Boston NORC Pilot & Feasibility Investigator	Roux-en-Y gastric bypass stimulates brown adipose tissue activity and energy expenditure in rodents
02/23/10	Anthony J.A. Molina, Ph.D. Instructor of Medicine Boston University School of Medicine	The role of mitochondrial fusion in beta cell function and the development of diabetes and obesity
03/09/10	Kostya Kandror, Ph.D. Department of Biochemistry Boston University School of Medicine	Insulin regulation of lipolysis
03/23/10	Kyongbum Lee, Ph.D. Associate Professor Chemical and Biological Engineering Tufts University	Coculture models of adipose tissue
04/20/10	Andrew Greenberg, M.D. Friedman School of Nutrition Science and Policy	MAPK inflammatory pathways in obese mice
05/04/10	Mi-Jeong Lee, Ph.D. Section of Endocrinology, Diabetes, and Nutrition Boston University School of Medicine	Glucocorticoid and TNF interactions in the modulation of adipose tissue function

<b>Date</b>	<b>Speaker</b>	<b>Title</b>
05/11/10	Heidi A. Tissenbaum, Ph.D. William Randolph Hearst Young Investigator Program in Gene Function and Expression Program in Molecular Medicine University of Massachusetts Medical School	Dissecting insulin/IGF-1 signaling in <i>C. elegans</i>
06/01/10	Thien T. Tran, Ph.D. Joslin Diabetes Center Postdoctoral Fellow BNORC Pilot & Feasibility Investigator	Metabolic effects of subcutaneous versus visceral adipose tissue

The Boston NORC co-hosted a Seahorse Bioscience Educational forum with the Mitochondria: One Organelle, Multiple Organs ARC, BUSM (Affinity Research Collaborative) on Wednesday, March 14, 2010. Dr. David Ferrick, Seahorse Bioscience, presented “Turbocharging your bioenergetic analysis: a tutorial that goes beyond the obvious.”

The Boston NORC has continued to endorse and support the annual Harvard Obesity Course. This highly regarded and well-attended course provides science-based continuing medical education for physicians, nurses, nutritionists, and other health care professionals working in the area of obesity. Each year, several Boston NORC investigators contribute to the course as co-directors or faculty. Sponsorship of this continuing medical education course offers several advantages to Boston NORC. The 24th International Conference on Practical Approaches to the Treatment of Obesity was held at the Royal Sonesta Hotel, Cambridge, MA, on June 17–19, 2010.

For a second year, the Qualitative and Survey Research Methods Unit lead by Dr. Raymond Hyatt (Clinical and Community Research Core) convened a qualitative research working group that meets at Tufts University School of Medicine. This group includes researchers from several schools and departments at Tufts University and is open to all Boston NORC members. At this year’s meeting in October 2009, Dr. Hyatt and Stacy Penna, Business Development Manager, QSR International, led a webinar on NVIVO 8. The session explored ways in which the NVIVO software can support qualitative data analysis and reporting and was very interactive with many questions raised by the audience. We continued to make this software available to graduate students and researchers via a site license at Tufts University. Meetings and events are currently being planned for the coming year.

The Epidemiology and Genetics Core held a mini-symposium entitled “Gene-Environment Interactions in Obesity” at the Harvard School of Public Health on April 28, 2009. Speakers included Drs. Paul W. Franks, Lu Qi, and Peter Kraft. Drs. Frank Hu, Core Director, and Rob van Dam, then co-Director, moderated the session. A total of 77 individuals registered to attend the symposium, and it is estimated that at least that many were in attendance during the 3-hour symposium.

## **Benefits and Interactions Resulting From the Existence of the NORC**

Boston NORC's enrichment programs, pilot and feasibility programs, and Core services continue to provide an important mechanism to foster collaborative, multidisciplinary research in nutrition and obesity in the Boston area. A list of "Obesity and Nutrition-related Seminars" is sent out weekly to efficiently inform our members of events at nearby institutions and Centers. The Executive Committee and the individual Core laboratories continue to organize additional programs to enhance collaborative research efforts. For example, Drs. Greenberg (Tufts) and Fried (BU) were funded for an R24 seeding grant to plan interdisciplinary studies on sex differences in adipose tissue and its metabolic consequences in obesity, entitled "Sex Differences in Adipose Tissue Biology and Its Role in Obesity-Associated Diseases." Boston NORC Cores all focus on mentoring junior investigators with advice on research strategies and techniques, and facilitating preliminary experiments that will place grant proposals in competitive positions. We anticipate that the NORC's continued sponsorship of workshops, seminars, and forums will help identify gaps in research that might be addressed by new research proposals. Regardless, such discussions should help promote discussions between basic and clinical scientists, an area that the NORC continues to assess and develop. It is our intention that these efforts will lead to a better understanding of obesity and the role of nutrition in the prevention of chronic disease.

The existence of the Boston NORC has benefited nutrition education efforts for medical and graduate students at Boston University School of Medicine. Dr. Fried is Director of a revamped and revitalized Graduate Program in Medical Nutritional Sciences, and Dr. Lenders, a NORC member, is spearheading efforts to incorporate a vertically integrated nutrition curriculum for medical students at the Boston University School of Medicine. Dr. Apovian also won internal support for a Nutrition Fellowship in the Section of Endocrinology, Diabetes, and Nutrition. Notably, Boston NORC Cores provide leverage and support for the formation and implementation of a number of "Affinity Research Collaboratives," interdisciplinary groups of investigators focusing on obesity-related chronic disease, that are funded by the Evans Biomedical Research Foundation (Department of Medicine, Boston University School of Medicine and Boston Medical Center).