

**Pennington Biomedical Research Center**  
**Nutrition Obesity Research Center**  
**Start Date: 2005**  
**Status: Ongoing**  
**Source of NIH Support: NIDDK**  
**Website: <http://norc.pbrc.edu>**

## **Organization and Goals**

The **Pennington Biomedical Research Center (PBRC) Nutrition Obesity Research Center (NORC)** has been designed to facilitate and promote collaborative and multidisciplinary interactions that will foster new research ideas and enhance the translation of basic nutritional research findings into the clinical arena and ultimately into practical applications. Within the chosen theme of “**Nutritional Programming: Environmental and Molecular Interactions,**” we are targeting translational research designed to understand the metabolic and environmental factors underlying nutrition- and obesity-related health problems. The tradition of obesity and diabetes research at PBRC provides an ideal academic environment to undertake interdisciplinary efforts to investigate the environmental and molecular interactions (epigenetic phenomena) that can influence the development of obesity and metabolic syndrome in adulthood.

### **Specific Aims of the Pennington NORC**

- To stimulate new and innovative research and support collaborative nutrition research among investigators at Pennington and in Louisiana. To this end, the NORC will foster communications and interactions between basic and clinical investigators, provide state-of-the-art and cost-effective Core services to support nutrition research, and enhance the translation of discoveries in basic science to human clinical investigation.
- To attract new investigators to the field of nutrition (especially nutritional programming) and to enhance their development as independent and creative investigators by allowing access to specialized training, Core resources, mentoring, and educational programs.
- To improve the training and education of students, research staff, postdoctoral fellows, and health personnel in clinical nutrition and obesity management and in nutrition and obesity research.
- To coordinate and promote community outreach activities in the greater East Baton Rouge area by providing nutrition education, nutrition and health assessments, and nutritional interventions that promote wellness, improve health, and reduce obesity.
- To reach out to Louisiana State University (LSU) scientists in Baton Rouge and at the Medical Health Science Center in New Orleans.

## **Core Laboratories**

In addition to an Administrative Core led by Eric Ravussin, Ph.D., and Donna Ryan, M.D., with the assistance of Darlene Marquis (Executive Administrator), the NORC at PBRC has three Scientific Cores. The **Human Phenotyping Core** provides services to measure energy

metabolism, body composition, insulin sensitivity, in situ biochemistry (MRS), skeletal muscle, and adipose metabolism, and to assess physical activity and food intake as well as administering behavioral interventions. The **Molecular Mechanisms Core** provides classical genomics and epigenetics support with adequate bioinformatics capacity as well as cell culture and cell imaging technologies. The **Animal Models and Phenotyping Core** provides the required animal models, including conditional transgenic or knockout animals and state-of-the-art phenotyping. Since 2009, the PBRC has embarked on an expansion of facilities and equipment including a new Clinical Research Building (opened in August 2010) and Imaging Center (scheduled to open in Summer 2011). This will catalyze an expansion in clinical and translational research, particularly in obesity. It will also propel the renovation of the existing clinic building into a Pediatric Research Clinic, which will enable the expansion of our research program in this important area. With a \$50 million State appropriation to fund the completion of the clinic, establishment of an Imaging Center, and renovation of the existing clinic, we have been able to achieve a major equipment purchase initiative. Another Statewide initiative will enhance our NORC activities; PBRC is the lead institution on the Clinical and Translational Science Award (CTSA) submission for Louisiana and has established the Louisiana Clinical and Translational Science (LA CaTS) Center with a \$1 million annual State appropriation. With exceptional institutional support and an ideal academic environment, Pennington has established a strong base of obesity/nutrition research and is poised to grow in an emerging field of “Nutritional Programming” thanks to the contribution of the NORC.

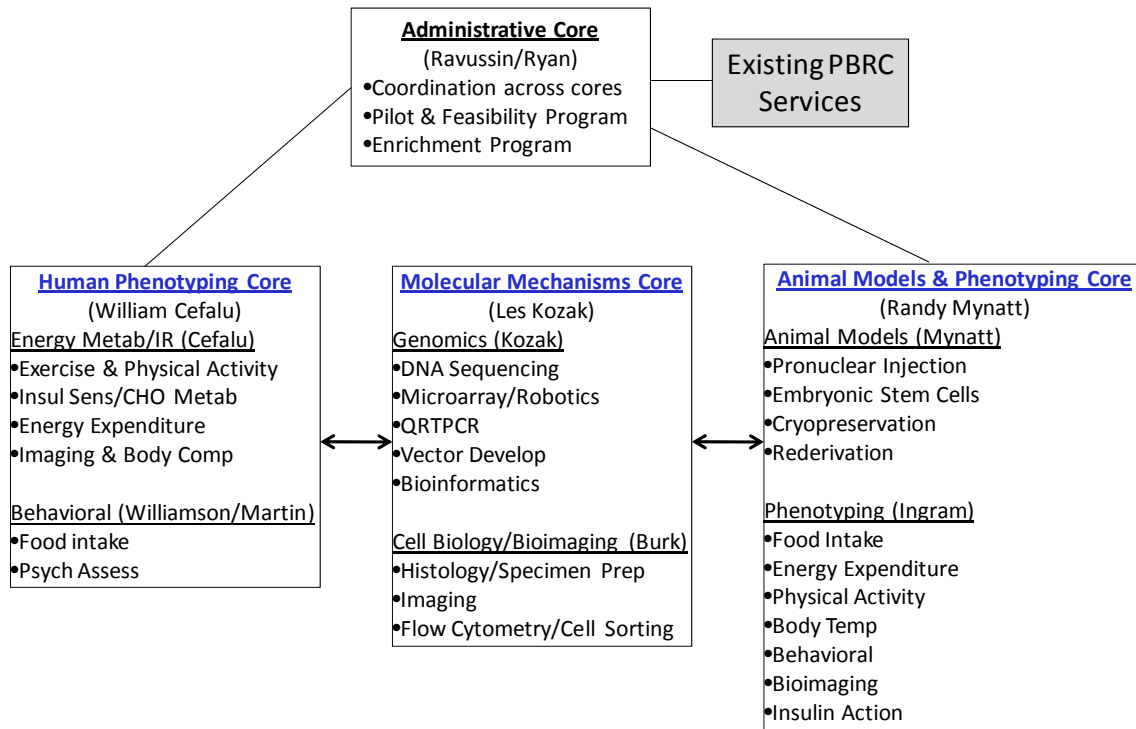
Our chosen theme is **Nutritional Programming: Environmental and Molecular Interactions**. This focus is still based on emerging interests in epigenetics phenomena such as how environmental events in prenatal and early postnatal life can influence the risk for the development of chronic diseases such as obesity, diabetes, and the metabolic syndrome in later adulthood by gene methylations and demethylations. However, like all the other NORCs, we continue to perform research studies on the impact of nutrition on health and disease. The structure of the NORC has an **Administrative Core** led by Drs. Eric Ravussin and Donna Ryan, a **Human Phenotyping Core** led by Drs. William Cefalu and Donald Williamson, a **Molecular Mechanisms Core** led by Drs. Les Kozak and David Burk, and an **Animal Models and Phenotyping Core** led by Drs. Randy Mynatt and Don Ingram. See Figure 1 on the next page.

**Administrative Core:** Eric Ravussin, Ph.D., Director; Donna Ryan, M.D., Associate Director; Darlene Marquis, Executive Administrator.

### ***External Advisory Board***

The External Advisory Board continues to provide oversight and guidance. The Board members were canvassed and agreed to the change in leadership for the Human Phenotyping Core from Dr. Steven Smith (who has left the Center) to Dr. William Cefalu. During the preparation of the Center Grant renewal in 2009, we had two webinar conferences with our External Advisory Board to discuss the progress of the Center since its inception and the future developments for the Center. The next meeting of the External Advisory Board is planned for late 2010 or early 2011 and will be conducted by webinar, with presentations by the NORC Core leaders and Pilot and Feasibility award winners.

Figure 1. Organizational Chart of Cores



*External Advisory Board Members:*

- Rudy Leibel, M.D., Chair, Co-Director Research, College of Physicians & Surgeons, Columbia University, New York, NY
- Dan Kelly, M.D., Scientific Director, Professor, Burnham Institute for Medical Research, Orlando, FL
- Brad Lowell, M.D., Ph.D., Associate Professor, Endocrinology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
- John Miles, M.D., Professor of Medicine, Department of Endocrinology, Mayo Clinic, Rochester, MN

***Internal Advisory Board (IAB)***

We have now established an Internal Advisory Board consisting of: Dr. George Bray (Chair), Dr. Timothy Church, Dr. Deep Dixit, Dr. Claudia Kappen, Dr. William Johnson, Dr. Jay Kolls (LSUHSC – New Orleans), Dr. Jackie Stephens (LSU Main Campus), and Dr. Michael Salbaum. We formed this new Board to represent a broad base of distinguished faculty who have diverse interests in nutrition and obesity.

The purpose of the IAB is to 1) oversee the activities of the NORC, so as to assure that the mission is being achieved and to advise the Executive Committee in achieving NORC goals, 2) serve as the principal group of internal reviewers for the Pilot and Feasibility Program and stimulate interest in the program within the School of Medicine, 3) participate in NORC educational activities, and 4) help in long-range planning for future NORC directions and

initiatives. The members of the IAB were chosen because of their collective expertise in areas that are important to the NORC, their experience in accomplishing goals at the PBRC or elsewhere, their influence within the administrative structure of our Institution and in other Institutions (LSU main campus and LSU Health Science Center), and other Center grants. The IAB will meet every 6 months; the chairperson of the IAB is appointed as a member of the Executive Committee and will meet with that committee every 3 months. Therefore, the IAB will be directly involved in the organization and supervision of the Pennington NORC.

### **Pilot and Feasibility Studies**

Each Pilot and Feasibility (P&F) Award winner is required to submit a progress report and provide an oral presentation of her/his research activities at the NORC External Advisory Board meetings.

#### **Pilot & Feasibility #2009–01**

**Investigator: Rea Anunciado-Koza, Ph.D., Instructor**

Title: Determine the effects of targeted inactivation of Slc25a25 on energy metabolism *in vitro* by comprehensive bioenergetic profiling of mouse embryonic fibroblasts (MEF) and mitochondria isolated from liver and skeletal muscle of Slc25a25 mice

09/01/2009–08/31/2010

Cores used: Molecular Mechanisms Core and Animal Models & Phenotyping Core

Summary: Slc25a25 is an integral protein of the inner mitochondrial membrane, which in response to Ca<sup>2+</sup> stimulation functions to shuttle ATP-Mg for Pi. In order to understand the contribution of Slc25a25 to Ca<sup>2+</sup> cycling mechanism and its importance to thermogenesis and energy balance, we conducted *in vivo* studies in Slc25a25<sup>-/-</sup> mice, and Ca<sup>2+</sup> flux and bioenergetic studies in Slc25a25-deficient MEF. Our studies show that Slc25a25<sup>-/-</sup> mice are resistant to diet-induced obesity and have reduced exercise capacity consistent with reduced metabolic efficiency. MEF lacking Slc25a25 have reduced Ca<sup>2+</sup> flux across the endoplasmic reticulum and basal mitochondrial respiration. These results demonstrate that Slc25a25 points to a crucial role for this protein in systemic energy balance and skeletal muscle function.

#### **Pilot & Feasibility #2009–02**

**Investigator: Bolormaa Vandanmagsar, Ph.D., Postdoctoral Researcher**

Title: Endothelial-mesenchymal transition, adipocyte lineage and obesity

09/01/2009 – 08/31/2010

Core used: Molecular Mechanisms Core

Summary: Scientific Progress—our NORC P&F grant is based on the hypothesis that subsets of mesenchymal cells in adipose tissue are derived from endothelial lineage and serve as adipogenic and fibrogenic precursors. We have successfully generated TekCre;R26RstopLacZ and TekCre;R26RstopEYFP (two double transgenic reporter mice) and bred them to get sufficient numbers of mice to finish the NORC P&F grant. Then we placed half of them on chow or ad libitum diet consisting of 4.5% fat (5002; LabDiet) as a control group and the other half were placed on high-fat diet consisting of 60% calories from fat (D12492i; Research Diets Inc.) to induce dietary obesity. Now we have a total of 35 to 40 lineage-tracer mice in control and high-fat groups to start our experiments.

As proposed in aim 1, we have found strong expression of EYFP in adipose tissue of TekCreEYFP reporter mice, which was detectable by fluorescence activated cell sorting (FACS). We also detected the loss of CD31 expression in TekCre marked cells indicative of endothelial-mesenchymal transition (EndMT).

Plans for the next quarter:

1. We will perform FACS analysis and sorting to quantify EndMT.
2. We have made an interesting observation that indicates inflammatory signals may impact endothelial compartment. Given strong EYFP expression in TEKCre;R26RstopEYFP mice, we plan to transfer TekCre marked cells in obese animal models of inflammation to track the mechanism and fate of endothelial cells.
3. We plan to communicate our research findings for publication in November 2010. Based on the data generated from our NORC P&F project, we plan to submit a grant application to the NIH. This proposal will help to establish that endothelial cells may serve as fibro-adipogenic precursors in obesity.

Publication: Vandannagsar B, Youm YH, Ravussin A, Galgani J, Mynatt RL, Ravussin E, Stephens JM, Dixit VD. 2010. The cvryopyrin/Nalp3/Nlrp3 inflammasome regulates obesity-induced auto-inflammation and insulin resistance. Under review – Nature Medicine.

#### **Pilot & Feasibility #2009–03**

**Investigator: Michael Salbaum, Ph.D., Associate Professor**

Title: Embryonic epigenetics in diabetic and obese pregnancies  
09/01/2009–08/31/2010

Cores used: Molecular Mechanisms – Genomics Core

Summary: Exposure of the developing embryo to diabetes or obesity of the mother during the pregnancy can lead to teratogenic effects that result in birth defects or to long-term health consequences in the offspring, such as increased disease susceptibility much later in life. How such long-term health consequences are related to developmental events remains unclear, although a role has been invoked for epigenetic mechanisms. The central hypothesis of this project is that adverse uterine exposure alters the epigenome of the embryo. We therefore seek to determine the location of histone acetylation sites in the genome of neurulation-stage embryos, and compare histone acetylation patterns in embryos from normal, diabetic, and obese pregnancies.

#### **Pilot & Feasibility #2009–04**

**Investigator: Mingquan Zheng, Ph.D., Assistant Professor, LSUHSC**

Title: The role of Vitamin D in Th2- and Th17-related asthma  
09/01/2009–08/31/2010

Cores used: Animal Models & Phenotyping – Transgenics Core

Summary: Our central hypothesis for this award is that Vitamin D plays a role in Th17 cytokine production, and that vitamin D receptor signaling is critical for Treg/Th17 differentiation. We have accomplished that cells cultured with vitamin D had significantly lower cytokine levels. Th1 cytokines did not have a significant change with or without vitamin D. Similarly, effects were also observed in OTII mice on the C57 background (data not shown) and thus the effect of

vitamin D is not strain specific. Vitamin D treatment was associated with an increase in cell surface TGF $\beta$  in the CD4+, CD25+ T-cell population.

To understand the role of vitamin D receptor signaling for Treg/Th17 differentiation *in vivo*, we have generated conditional vitamin D receptor knockout mice by floxing the *Vdr* allele with collaborator Dr. Mynatt in the Pennington Transgenic Core. This project has contributed to our knowledge of the role of vitamin D in asthma and allergic bronchopulmonary aspergillosis (ABPA). Vitamin D and molecules in its signaling can be used successfully in preclinical models and immunotherapy for the improvement of asthma and ABPA.

This project helped me to begin my career as independent science investigator. It not only impacted my science knowledge of how vitamin D is regulated in asthma and ABPA, but also gave me opportunities to practice how to write research project, how budget research supplies and control cost. They all help me to be a successfully research investigator.

### **Current Cycle (2010–2011)**

For the P&F submission this year we developed a website to submit letters of intent and full applications electronically (<http://NORCfunding.pbrc.edu>). The process went very well. We were also able to send comments back to the applicants electronically via this website. All information is stored on the website as well as scores and reviewers' comments.

<b>Grant #</b>	<b>PI</b>	<b>Title</b>
2010–01	Ji Suk Chang	Function of mitochondrial NT-PGC-1 $\alpha$ mitochondrial DNA transcription
2010–02	Darcy Johannsen	Metabolic traits of adult sib-pairs discordant for intrauterine diabetes exposure

This year we received nine letters of intent and all of the PIs were encouraged to submit a full application. We finally received six full applications by the deadline. All were reviewed by three reviewers. All six applications came from Pennington.

Below is a listing of the grants. **The first two applications were funded.**

- 1. Function of mitochondrial NT-PGC-1 $\alpha$  in mitochondrial DNA transcription (Ji Suk Chang, Ph.D.)**
- 2. Metabolic traits of adult sib-pairs discordant for intrauterine diabetes exposure (Darcy Johannsen, Ph.D.)**
3. The role of brainstem astrocytes in the autonomic response to hypoglycemia (David McDougal, Ph.D.)
4. Regulation of fat mass expansion by Sfrp5 (Rob Koza, Ph.D.)
5. Maternal diet and neural tube defects in diabetic pregnancies (Nancy Arbour-Delahaye, Ph.D.)
6. Validation of fiber type composition in human primary myotubes compared to skeletal muscle (Sudip Bajpeyi, Ph.D.)

## **From Previous Cycles**

### **Publications**

1. The Epigenetics of Adult (Somatic) Stem Cells. Eilertsen KJ, Floyd E, Gimble JM. *Critical Reviews in Eukaryotic Gene Expression*. 2008;18(3):189–206. PMID: PMC2741686.
2. Altered expression of methyl cycle genes in preimplantation embryos exposed to culture. Kirk H, Mtando NR, Latham K, Eilertsen KJ. *Biology of Reproduction*, In Review June 2010.
3. A novel method to remotely measure food intake of free-living people in real-time: The Remote Food Photography Method (RFPM). Corby K, Martin, Hongmei Han, Sandra M. Coulon, H. Raymond Allen, Catherine Champagne, and Stephen D. Anton. *Br J Nutr*. 2009 March; 101(3): 446–456. PMID: PMC2626133.
4. Association between energy intake and viewing television, distractibility, and memory for advertisements. Martin CK, Coulon SM, Markward N, Greenway FL, Anton SD. *Am J Clin Nutr*. 2009 89: 37–44. PMID: PMC2615456.
5. The melancortin-3 receptor is required for entrainment to meal intake. Sutton GM, Perez-Tilve D, Nogueiras R, Fang J, Kim JK, Cone RD, Gimble JM, Tschop MH, Butler AA. *J Neurosci*. 2008 Nov 26; 28(48):12946–55. PMID: PMC2613653.
6. Maternal obesity is necessary for the programming effect of a high-fat diet on offspring. White CL, Purpera MN, Morrison CD. *Am J Physiol Regul Integr Comp Physio*. 2009 May;296(5):R1464–72. PMID: PMC2689819.
7. Effects of high fat diet on cognition and brain oxidative stress and inflammation: contributions of maternal diet. CL White, PJ Pistell, S Gupta, SO Fernandez-Kim, TL Hise, JN Keller, DK Ingram, CD Morrison, AJ Bruce-Keller. *Neurobiology of Disease*. 2009 Jul;35(1):3–13. PMID: PMC2699188.
8. Deficient ghrelin receptor mediated signaling compromises thymic stromal cell microenvironment by accelerating thymic adiposity. Youm, YH, Yang H, Sun Y, Smith RG, Manley NR, Vandanmagsar B, Dixit VD. *J Biol Chem*. 2009 Mar 13;284(11):7068–77. PMID: PMC2652314.
9. Axin expression in thymic stromal cells contributes to age-related increase in thymic adiposity and associated with reduced thymopoiesis independently of ghrelin signaling. Yang H, Youm, YH, Sun Y, Rim JS, Galban C, Vandanmagsar B, Dixit VD (2009). *J Leukoc Biol*. 2009 Jun;85(6):928–38. PMID: PMC271880.
10. Regional variation in adipogenesis and IGF regulatory proteins in the fetal baboon. Tchoukalova Y, Nathanielsz P, Conover C, Smith S, Ravussin E. *Biochem Biophys Res Comm*. 380:679–683, 2009. PMID: PMC2733229.

11. Elevated stearyl-CoA desaturase-1 expression in skeletal muscle contributes to abnormal fatty acid partitioning in obese humans. Hulver MW, Berggren JR, Carper MJ, Miyazaki M, Ntambi JM, Hoffman EP, Dohm GL, Houmard JA, and Muoio DM. *Cell Metabolism*. 2005. 2(4), 251–261. PMID: N/A.
12. Impaired regulation of circadian oscillators by Rev-erb $\alpha$  as a novel link between fetal malnutrition and adult disease. Sutton GM, Centanni AV, and Butler AA. *Diabetes*. IN PRESS May 2010.
13. Effects of high fat diet on splenocyte response: interactions of prenatal and postnatal exposure. Bruce-Keller AJ, White CL, Gupta S, Parrino TE, Purpera MN, Keller JN, and Morrison CD. [Will resubmit later 2010.]
14. Obesity accelerates thymic aging. Yang Y-HY, Vandanmagsar B, Rood J, Ganesh Kumar K, Butler AA, and Dixit VD. *Blood* 2009 Oct 29;114(18):3803–12. PMID: PMC2773495.
15. Activation of PPAR $\gamma$  induces premature thymic involution. Youm Y-H, Yang H, Amin R, Smith SR, Leff T, and Dixit VD. *Diabetes*. Under review.
16. Inhibition of thymic adipogenesis by caloric restriction is coupled with reduction in age-related thymic involution. Yang H, Youm YH, and Dixit VD. *J Immunol*. 2009 Sep 1;183(5):3040–52. PMID: PMC2731487.
17. Adipose-immune interactions during obesity and caloric restriction: reciprocal mechanisms regulating immunity and health span. Dixit VD. *J Leukoc Biol*. 2008 84(4):882–92. PMID: PMC2638733.
18. Chronic caloric restriction induces forestomach hypertrophy with enhanced ghrelin levels during aging. Yang H, Youm YH, Nakata C, and Dixit VD. *Peptides*. 2007 28: 1931–1936. PMID: N/A.
19. Ghrelin promotes thymopoiesis during aging. Dixit VD, Yang H, Sun Y, Youm YH, Weeraratna AT, Smith RG, and Taub DD. *J Clin Invest*. 2007 117: 2778–2790. PMID: N/A.
20. Mesoderm-specific transcript is associated with fat mass expansion in response to a positive energy balance. Nikonova L, Koza RA, Mendoza T, Chao PM, Curley JP, and Kozal LP. *FASEB*. 2008 22(11): 3925–37. PMID: PMC2574032.
21. Inter-individual variation of dietary fat-induced mesoderm specific transcript in adipose tissue within inbred mice is not caused by altered promoter methylation. Koza RA, Rogers P, and Kozak LP. *Epigenetics*. 2009 Oct; 4(7): 512–518. PMC Journal – in process.

## Grants Submitted

1. Ken Eilertsen submitted R01 (1R01 HD048088-01) grant entitled “Role of methyl cycles in mammalian preimplantation development.”

2. Corby Martin submitted an R01 (R01 DK 081142) grant entitled “Effect of exercise dose on energy balance: The ENERGY Trial.”
3. Tiffany Stewart resubmitted an R01 (1R01 DK081552-01) entitled “Genetics and binge eating behavior in humans” twice. This project includes 1,000 total participants and will be conducted in collaboration with Carlos Grilo, Ph.D., at Yale, as well as two additional replication sites (Germany, Finland).
4. Deep Dixit submitted an NIH R01 (1R01 AG034991-01) proposal in February 2009 entitled “Ghrelin, calorie restriction, and age-related thymic involution.”
5. Rea Anunicado-Koza submitted a grant application for renewal of RO1 on “Alternative thermogenic mechanisms in UCP-1 deficient mice” on March 5, 2009 (as co-principal investigator).
6. Rea Anunciado-Koza submitted an American Diabetes Association junior faculty grant on July 15, 2009, entitled "Role of Slc25a25, mitochondrial ATP-Mg/Pi carrier in skeletal muscle oxidative metabolism, insulin resistance, and type 2 diabetes.”
7. Deep Dixit submitted an NIH R01 (1R01 AG036685-01) proposal June 2009 entitled “Mechanism of obesity-induced thymic aging.”
8. Deep Dixit submitted an NIH R01 (1R01 AG034991-01) proposal June 2009 entitled “Ghrelin, calorie restriction, and age-related thymic involution.”
9. “Regulation of PPAR $\gamma$  activity in adipocytes by the ubiquitin-proteasome pathway.” Will resubmit as “Regulation of PPAR $\gamma$  in adipocytes by Siah2.”

### **Grants Awarded**

1. Rob Koza has been awarded an R21 (R21 DK074951) entitled “Epigenetic mechanisms and genes associated with the development of adiposity.”
2. Corby Martin has been awarded an R21 (5 R21 AG032231) by the NIH entitled “Validation of innovative technology to measure the energy intake of free-living humans.”
3. Greg Sutton was awarded an ADA Junior Faculty Award entitled “Aberrant clock gene expression provide an underlying mechanism involved in the metabolic syndrome of mice exposed to protein deficiency *in utero*” (1-09-JF-51).
4. Corby Martin was awarded an R03 (1R03DK083533-01) by the NIH entitled “Design and evaluation of the Remote Intervention for Diet and Exercise (RIDE),” April 2009.
5. Yourka Tchoukalova has been awarded an R03 (R03 HD060158-01) by the NIH entitled “Poor nutrition and fetal development: preadipocyte adaptation in a primate model.”

6. Matt Hulver has been awarded an R01 (1R01-DK078765-01A1) by the NIH entitled “Inflammatory regulation of lipid accumulation in skeletal muscle with obesity,” 04/01/2008–01/31/2013.
7. Matt Hulver has been awarded an R56 (1R56-DK078765-01) by the NIH entitled “Inflammatory regulation of lipid accumulation in skeletal muscle with obesity,” 01/01/2007–05/21/2008.

## Scientific Advances and Accomplishments

Listed below are some of the scientific advances and achievements by members of our NORC using the Core facilities funded by the NORC.

- **Changes in gene expression foreshadow diet-induced obesity in genetically identical mice.** Work from the NORC led to the development of a mouse model in which genetically identical animals exhibit variation in weight gain and susceptibility to obesity when exposed to a high-fat diet. These variations in obesity susceptibility already existed in the mice shortly after weaning, even before they received an obesogenic diet, and they retained this phenotype. The model is used to further investigate the origins of the current epidemic of overweight and obesity. Koza RA, Nikonova L, Hogan J, Rim JS, Mendoza T, Faulk C, Skaf J, Kozak LP. *PLoS Genet.* 2006 May; 2:e81. PMID: PMC1464831.
- **Measurement of children’s food intake with digital photography and the effects of second servings of food intake.** One of the many challenges of studying overweight, obesity, and other nutritional disorders is the difficulty of current methods to determine the quantity and quality of food intake. The NORC developed a novel method that is quick, does not intrude on the activities of the research participants, and provides an accurate estimation of food quantity and quality. Digital photographs from cell phones of plates/trays before and after eating are analyzed by trained dietitians. Martin CK, Newton RL, Anton, SD, Allen HR, Alfonso A, Han H, Stewart T, Sothorn M, Williamson DA. *Eat Behav.* 2007; 8:148–56. PMID: N/A.
- **Role of adiponectin pathway in human skeletal muscle bioenergetics.** The muscle tissue of individuals with type 2 diabetes has a reduced number and function of mitochondria. Dr. Anthony Civitarese, supported by the NORC, showed that the fat cell hormone adiponectin increases the number of mitochondria in muscle and reduces the production of harmful free radicals. The discovery of reduced adiponectin in people with type 2 diabetes points toward adiponectin, and dietary strategies to increase adiponectin, as a way to prevent diabetes. Civitarese AE, Ukropcova B, Carling S, Hulver M, DeFronzo RA, Mandarino L, Ravussin E, Smith SR. *Cell Metabolism* 2006 4(1):75–87. PMID: PMC2671025.
- **Calorie restriction increases muscle mitochondrial biogenesis in healthy humans.** More recent data on mitochondrial biogenesis was published in PLoS Medicine. Our studies showed that 6 months of 25% caloric restriction is associated with an increase in mitochondrial capacity of more than 30%. This increase is probably mediated by increased adiponectin concentration in parallel to SIRT1 activation leading to PGC1- $\alpha$  activation and

mitochondrial biogenesis. Civitarese AE, Carling S, Heilbronn LK, Hulver MH, Ukropcova B, Deutsch WA, Smith SR, Ravussin E; CALERIE Pennington Team. *PLoS Med.* 2007; 4:e76. PMID: PMC1808482.

- **Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism.** Butler et al. discovered a novel gene encoding a secreted peptide (adropin) that may be a new factor in obesity and insulin resistance. Early studies suggest that loss of this gene causes glucose intolerance and fatty liver. Using gene therapy, Butler et al. demonstrated that increasing adropin improves metabolic profile in obese animals. A synthetically produced form of the peptide can also reverse the metabolic syndrome associated with obesity in mice. Adropin may be valuable as a therapeutic target for treating obesity and/or insulin resistance. Kumar KG, Trevaskis JL, Lam DD, Sutton GM, Koza RA, Chouljenko VN, Kousoulas KG, Rogers PM, Kesterson RA, Thearle M, Ferrante AW Jr, Mynatt RL, Burris TP, Dong JZ, Halem HA, Culler MD, Heisler LK, Stephens JM, Butler AA. *Cell Metab.* 2008; 8:468–81. PMID: PMC2746325.
- **The melanocortin-3 receptor is required for entrainment to meal intake.** Dr. Gregory Sutton, one of our P&F recipients, discovered that feeding dams a diet deficient in protein results in offspring that have hypoactivity and display altered circadian physiology (mice are active during the daytime rather than normal nocturnal periods of activity). Mice exposed to a protein deficient diet *in utero* have altered clock gene oscillation in the liver as well as altered genes regulating glucose and lipid metabolism at an early age. These discoveries can lead to future pharmacological interventions in order to reverse metabolic instability. Sutton GM, Perez-Tilve D, Nogueiras R, Fang J, Kim JK, Cone RD, Gimble JM, Tschöp MH, Butler AA. *J Neurosci.* 2008; 28:12946–55. PMID: PMC2613653.
- **Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates.** There is great controversy on the role of macronutrients (fat, carbohydrate, protein) on the degree of weight loss achieved during caloric restriction. A total of 811 overweight adults were randomly assigned to one of four diets for 2 years; percentages of energy derived from fat, protein, and carbohydrates was 20%, 15%, and 65% respectively; 20%, 25%, and 55%; 40%, 15%, and 45%; and 40%, 25%, and 35%. The average weight loss was 4 kg regardless of the macronutrient content of the diet. Reduced-calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasize. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA. *N Engl J Med.* 2009; 360:859–73. PMID: PMC2763382.
- **Role of hypoxia in obesity-induced disorders of glucose and lipid metabolism in adipose tissue.** Adipose tissue dysfunction is increasingly recognized as a key component of many diseases including obesity, diabetes, and cardiovascular diseases. The reasons for adipose tissue becoming dysfunctional are unclear. Work from the laboratory of Jianping Ye discovered that the adipose tissue is hypoxic in obese rodents and associated with inflammation and macrophage infiltration. This work used the Animal Models and Phenotyping Core and the Molecular Mechanisms Core. Yin J, Gao Z, He Q, Zhou D, Guo Z, Ye J. *Am J Physiol Endocrinol Metab.* 2009; 296: E333–42. PMID: PMC2645021.

- **Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response.** The studies by Dr. Ye were extended to humans by Drs. Pasarica and Smith (NORC Human Phenotyping Core and Molecular Mechanism Core). They confirm a low pO<sub>2</sub> in obese adipose tissue; the low oxygen tension was associated with a low capillary density and inflammation similar to what was observed in the animal studies. Pasarica M, Sereda OR, Redman LM, Albarado DC, Hymel DT, Roan LE, Rood JC, Burk DH, Smith SR. *Diabetes* 2009; 58:718–25. PMID: PMC2646071.
- **Adipose-immune interactions during obesity and caloric restriction: reciprocal mechanisms regulating immunity and health span.** Dr. Vishwa Deep Dixit (NORC P&F) discovered that resident T-cell populations in the adipose tissue of rodents are key contributors to the increased pro-inflammatory cytokines found in the obese. Compared to conventional T cells in secondary lymphoid organs, the adipose tissue lymphocytes (ATLs) produce distinct pro-inflammatory cytokines that contribute to activation of adipose tissue macrophages. This work provides the first evidence that, in addition to adipose macrophages, ATLs are key constituents of adipose tissue and regulate adipose tissue inflammation. Dixit VD. *J Leukoc Biol.* 2008; 84: 882–92. PMID: PMC2638733.
- **Development of an Internet/population-based weight management program for the U.S. Army.** Overweight and poor fitness are significant readiness problems for the U.S. Military. The PBRC Health Psychology Laboratory developed an Internet-based intervention called Healthy Eating and Lifestyle Training Headquarters (HEALTH) to provide a convenient program that specifically addresses weight gain prevention, weight loss, healthy nutrition, and improved fitness, using military standards for healthy weight and fitness. The development of this program utilized the expertise offered by the NORC Human Phenotyping Core to develop information technology that promotes healthy behavior. The efficacy of this intervention is being tested in two pilot studies and in a randomized controlled trial. Stewart T, May S, Allen R, Bathalon G, Lavergne G, Sigrist L, Ryan D, and Williamson D. *Journal of Diabetes Science and Technology* 2008;2:116–126. PMID: PMC2769719.
- **Increased obesity in children living in rural communities of Louisiana.** Dr. Williamson and his team recently conducted a randomized controlled trial testing primary and secondary weight gain prevention programs in schools located in rural Louisiana (the prevention program is called LA Health). In a paper that describes the overweight and obesity status of these children at baseline, obesity substantially exceeded national prevalence rates in all ethnic groups and in both boys and girls. Methods developed by the NORC Human Phenotyping Core were utilized in the data collection and analysis for this study. Williamson DA, Champagne CM, Han H, Harsha D, Martin CK, Newton RL, Ryan DH, Sothorn MS, Stewart TM, and Webber LS. *Int J Pediatr Obes.* 2009;4:160–5. PMID: PMC2725211.
- **Characterization of the metabolic and physiologic response from chromium supplementation in subjects with type 2 diabetes.** There is great controversy in the role of chromium (Cr) supplementation in human nutrition. This study used state-of-the-art metabolic techniques in a well-characterized cohort of individuals with type 2 diabetes representing a wide range of both phenotype and parameters assessing whole body insulin

action. This study was the first to show that Cr levels after supplementation do not differ between responders and non-responders, and provides the first comprehensive assessment of physiological and biochemical characteristics of individuals who responded to Cr with improvement of insulin sensitivity. Another novel finding was that tissue lipids are decreased in subjects randomized to Cr. Cefalu W.T, Rood J, Qin J, Sereda O, Levitan L, Anderson R.A., Zhang XH, Martin C, Wang ZQ, Newcomer B. *Metabolism* 2010 May;59:755–62. PMC Journal – in process.

- **Changes in gene expression foreshadow diet-induced obesity in genetically identical mice and early nutritional environment determines the capacity for adipose tissue expansion by modulating genes of caveolae structure.** Work from the NORC led to the development of a mouse model in which mice that are genetically identical exhibit variation in weight gain and susceptibility to obesity when exposed to a diet similar to the U.S. diet. This variation in susceptibility to diet-induced obesity is strongly linked to the genes associated with cell signaling in fat tissue. Additional studies indicate that the critical time period for nutritional programming for susceptibility to obesity is the period when fat tissue is being generated. This model will be used for further studies to investigate the origins of the current epidemic of overweight and obesity. (1) Koza RA, Nikonova L, Hogan J, Rim JS, Mendoza T, Faulk C, Skaf J, Kozak LP. *PLoS Genet.* 2006 May;2:e81. PMCID: N/A. (2) Kozak LP, Newman S, Chao P-M, Mendoza T, and Koza RA. The early nutritional environment determines the capacity for adipose tissue expansion by modulating genes of caveolae structure (*PLoS One*, in press).
- **Maternal diet and epigenetic programming *in utero*.** Two NORC P&F grants, both entitled “Maternal Diet and Epigenetic Programming,” were aimed at measuring imprinted gene expression and cytosine methylation levels in organs of fetuses and newborns whose mothers were fed a low-fat, high-fat, or control diet. A number of imprinted genes were identified as differentially expressed and associated with diet in several organs including liver, kidney, and pancreas. To our surprise, we were not able to demonstrate that the differences in gene expression were associated with changes in promoter (or regulatory regions) methylation. We went on to examine expression levels of genes associated with methyl metabolism in mouse and monkey embryos exposed to culture. Together, our data suggests that suboptimal culture (e.g., environment and nutrition) altered methyl metabolism and epi-gene/protein expression that could introduce long-lasting perturbations. Publications: (1) Eilertsen KJ, Floyd E, and Gimble JM. The epigenetics of adult (somatic) stem cells. *Critical Reviews in Eukaryotic Gene Expression* 2008;18(3):189–206. PMCID: PMC2741686. (2) Kirk H, Mtando NR, Latham K, and Eilertsen KJ. Altered expression of methyl cycle genes in preimplantation embryos exposed to culture. *Biology of Reproduction*. In review June 2010.

### Specific Accomplishments

- *Researchers from across the continent gathered to learn the latest in imaging technology and its use in diagnosing and treating dementia and Alzheimer’s disease.* Led by PBRC Associate Executive Director, **Jeffrey Keller, Ph.D.**, the 2-day symposium became a precursor to the possibilities that will be generated by the completion of PBRC’s new

imaging center next year. According to Keller, “This meeting outlined the use of imaging technology to understand and find treatments for diabetes, obesity, and Alzheimer’s disease.” Construction will begin on the new imaging center on PBRC’s campus shortly after the completion of the current clinical research building.

- *The 2010 10<sup>th</sup> Annual Irene W. Pennington Wellness Day for Women* was a great success, drawing more than 700 women to health and wellness programs and free health screenings for disease prevention. The event was partially sponsored by our NORC.
- *Louisiana’s Report Card on Physical Activity and Health for Children and Youth*. The primary goal of the Louisiana Report Card on Physical Activity and Health for Children and Youth is to assess the level of physical activity and sedentary behaviors in Louisiana children and youth, the level of facilitators and barriers of physical activity behavior, and their related health outcomes. The development of this report card was guided by a Research Advisory Committee, composed of scientists and professionals who collaborated on the selection of indicators and the assignment of grades. Louisiana’s overall grade for 2009 = D. More information about the Report Card is available via the following link: [http://www.pbrc.edu/report\\_card/](http://www.pbrc.edu/report_card/). The event was partially sponsored by our NORC.

### **Educational Activities/Accomplishments**

Pennington continues to organize two or three scientific symposia each year on topics of interest to NORC members. These 2-day meetings allow top international scientists to visit the PBRC and interact with members of the NORC. Meeting proceedings and conclusions are published on the PBRC website <http://www.pbrc.edu/division-of-education/scientific-symposia> and in scientific journals. The last two symposia were “Imaging in Translational Research” held March 28–29, 2010, and co-chaired by Brian Gold, Ph.D., of the University of Kentucky and Jeffery Keller, Ph.D., from Pennington; and “Emerging Issues in Energy Balance, Adipocyte Biology & Developmental Origins of Chronic Disease” held November 9–10, 2009, and co-chaired by Claude Bouchard, Ph.D., of Pennington; Rudolph Libel, M.D., of Columbia University; and Masanobu Kawakami, M.D., of Jichi Medical School in Japan.

Members of the NORC (Ravussin, Bray, Ryan) participated in undergraduate teaching of medical students at LSU Health Sciences Center in New Orleans by teaching seminars on nutrition and obesity as a regular part of the curriculum. Members also continued their participation in the summer research training program for medical students that allows students to spend time in research laboratories and attend Pennington seminars and speaker presentations.

Pennington NORC faculty participated in Pennington’s four Mentoring Groups designed to assist in the training and career development of less experienced researchers. The Pennington Mentoring Groups include: the Genetics and Stem Cell Mentoring Group led by Dr. Claude Bouchard; the NeuroScience Group led by Dr. Jeff Keller; the Clinical, Behavioral, & Population Science Mentoring Group led by Dr. Peter Katzmarzyk; and the Cell Physiology and Metabolism Group led by Dr. Nikhil Dhurandhar. Each mentoring group is composed of 20 to 30 junior and senior level faculty. Groups meet at least once per quarter (some groups have met monthly) to focus

group members on relevant research issues and funding sources. Care has been taken to address training needs of junior level investigators, particularly in the area of grant proposal writing.

A fundamental goal of postdoctoral training at Pennington is to provide postdoctoral fellows with the knowledge and skills to enable them to perform high quality research and develop competitive research proposals for submission to external funding sources such as the National Institutes of Health.

We have two institutional training grants in place. One entitled "Obesity: from Genes to Man" funded by the NIDDK, and another entitled "Training in Botanical Approaches to Combat Metabolic Syndrome," funded by the National Center on Complementary and Alternative Medicine, NIH. Dr. Phillip Brantley, Enrichment Director for the NORC, is the director of both the T-32 grants and nearly all their faculty are members of the NORC.

We have been able to recruit highly qualified fellows for these programs. There are approximately 45 total postdoctoral fellows at PBRC, many of whom are mentored by NORC faculty. Along with working side by side in research activities with our faculty mentors, postdocs attend a two-semester graduate course entitled "Molecular and Clinical Nutrition," take seminars on grant writing, participate in weekly postdoc data presentation seminars, and complete "Responsible Conduct of Research" seminars.

We continue to produce two to three NORC newsletters per year. These are sent to members and posted on the NORC website. Another issue is scheduled for release in July 2010.

Finally, the NORC sponsors seminars and visiting professors as listed below.

#### **List of Visiting Speakers in 2009–2010 (Cosponsored by PBRC and NORC)**

September 10, 2009

Dr. Robert Considine

Indiana University School of Medicine, Division of Endocrinology

"Hepatocyte Growth Factor in Adipose Tissue Angiogenesis"

Hosted by: Jackie Stephens

September 17, 2009

Dr. Michael Clare-Salzler

Interim Chair, Professor, and Stetson Chair in Experimental Pathology/Director, Center for Immunology and Transplantation Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine

"Immunopathogenic Mechanisms that Cause Type 1 Diabetes"

Hosted by: Wil Cefalu

October 1, 2009

Dr. Henri Brunengraber

Chair, Dept. of Nutrition Center, Case Western Reserve University

"Potential of Anaplerotic Medium-chain Triglycerides for the Dietary Treatment of Inborn Errors of Long-chain Fatty Acid Oxidation"

Hosted by: Tom Gettys

October 8, 2009

Dr. Jack Yanovski

Head, Unit on Growth & Obesity, PDEGEN, Eunice Kennedy Shriver National Institute of Child Health & Human Development, National Institutes of Health “Pediatric Obesity Syndromes: Beyond Leptin and the Melanocortin 4 Receptor”

Hosted by: Nikhil Dhurandhar

October 15, 2009

Dr. James Ntambi

Katherine Berns Von Donk Steenbock Professor of Biochemistry and Professor of Nutrition, University of Wisconsin at Madison, Department of Biochemistry “Role of Stearoyl-CoA Desaturase in Metabolism: Implications in Human Diseases”

Hosted by: Nikhil Dhurandhar

November 5, 2009

Dr. Steven Kliewer

Departments of Molecular Biology and Pharmacology, University of Texas Southwestern Medical Center “Metabolic FGFs: From Feast to Famine”

Hosted by: Deep Dixit

November 12, 2009

Dr. Gary Shaw

Department of Pediatrics, Division of Neonatal & Developmental Medicine, Stanford University Medical School

“Nutrients, Genes, and Human Birth Defects”

Hosted by: Claudia Kappen

November 19, 2009

Dr. George Thomas, Interim Director & Strauss Professor of Cancer Research, Genome Research Institute, University of Cincinnati Medical Center

“Nutrient Signaling Places mTORC1 and S6K1 at the Crossroads of Obesity and Cancer”

Hosted by: Jianping Ye

December 3, 2009

Dr. Klaus Kaestner

Department of Genetics, Institute for Diabetes, Obesity and Metabolism, University of Pennsylvania School of Medicine

“Cdx2—Master Regulator of the Intestinal Epithelium”

Hosted by: Michael Salbaum

December 10, 2009

Dr. Avinash Bhandoola

Department of Pathology & Laboratory Medicine, University of Pennsylvania School of Medicine

“Hematopoietic Stem and Progenitor Cells in Aging: Implications for T cell Development and Function”

Hosted by: Deep Dixit

January 14, 2010

Dr. Michael Clare-Salzler

Interim Chair Professor and Stetson Chair in Experimental Pathology/Director, Center for Immunology and Transplantation Department of Pathology, Immunology, and Laboratory Medicine, University of Florida College of Medicine

“Immunopathogenic Mechanisms that Cause Type 1 Diabetes”

Hosted by: Wil Cefalu

January 21, 2010

Dr. Thomas Lutz

Institute of Veterinary Physiology, Vetsuisse Faculty University of Zurich and Centre for Integrative Human Physiology, Switzerland

“Control of Eating and Body Weight by Amylin”

Hosted by: Hans Berthoud

January 28, 2010

Dr. Joanne Slavin

Department of Food Science and Nutrition, University of Minnesota

“Dietary Fiber and Body Weight: Gut Hormones, Gut Microflora, or Something Else?”

Hosted by: Roy Martin

February 11, 2010

Dr. Mark Mattson

Chief, Laboratory of Neurosciences—NIA

“Dietary Energy Intake and Brain Health: A Challenging Situation”

Hosted by: Eric Ravussin

February 18, 2010

Dr. Bina Joe

Physiological Genomics Laboratory, Department of Physiology and Pharmacology, University of Toledo College of Medicine

“Under Pressure to Find Genetic Elements Controlling Blood Pressure”

Hosted by: Claude Bouchard

February 25, 2010

Dr. Arlan Richardson

Senior Research Career Scientist (STVHCS), Director, Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center at San Antonio, Texas Research Park Campus

“Is the Oxidative Stress Theory of Aging Dead?”

Hosted by: Don Ingram

March 4, 2010

Dr. Ken Fujioka

Director, Nutrition and Metabolic Research, Scripps Clinic, Department of Diabetes and Endocrine

“Current Treatment Options for the Morbidly Obese Patient: From Initial Visit to Follow Up of Nutritional and Metabolic Problems”

Hosted by: Frank Greenway

March 11, 2010

Dr. Laurie Goodyear

Harvard Medical School, Joslin Diabetes Center, Research Division

“Novel Signals Regulating Glucose Transport: AMPK and Beyond”

Hosted by: Eric Ravussin

March 25, 2010

Dr. Robert Henry

Dept. of Medicine, University of California San Diego

“Update on Adiponectin Regulation”

Hosted by: Eric Ravussin

April 1, 2010

Dr. David Sinclair

The Paul F. Glenn Laboratories for the Biological Mechanisms of Aging, Harvard Medical School

“The Sirtuins: Ancient Survival Genes that Promote Defenses Against Diseases of Aging”

Hosted by: Don Ingram

April 15, 2010

Dr. Cathy Kotz

GRECC and MN Obesity Center, Graduate Programs in Neuroscience and Nutrition, VA Medical Center and University of Minnesota

“Role of Orexin in Non-exercise Activity Thermogenesis (NEAT) and Obesity”

Hosted by: Hans Berthoud

April 22, 2010

Dr. David Pettitt

Sansum Diabetes Research Institute

“Long Term Effects of the Hyperglycemic Intrauterine Environment”

Hosted by: Eric Ravussin

May 6, 2010

Dr. David Jenkins, Director

Risk Factor Modification Centre, St. Michael's Hospital, Canada Research Chair in Nutrition and Metabolism, Department of Nutritional Sciences, University of Toronto, Canada

“The Glycemic Index, Dietary Portfolio and Fiber in the Treatment of Disease”

Hosted by: Cathy Champagne

May 13, 2010

Dr. John Buse

Department of Medicine, University of North Carolina School of Medicine

“Cardiovascular Outcome Studies and Type 2 Diabetes”

Hosted by: William Cefalu

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

### **Administrative Core (Eric Ravussin/Donna Ryan)**

- The Research Base Funding went **from \$18,403,447 to \$32,414,095 in direct costs, i.e. a 76% increase.**
- **More than 200 publications** resulted from the NORC support to its members.
- The NORC support (with some Institutional supplementary support) has funded 21 P&F grants resulting in 14 publications (and six more in revision), 15 grant submissions (13 NIH and 2 ADA), and seven awarded (six NIH and one ADA).
- We have now **103 members of the NORC**, 88 at Pennington, eight at the LSU main campus, two at the LSU Health Sciences Center in New Orleans, and five other.
- The **three Scientific NORC Cores** provided services to 82 scientists at more than seven institutions across Louisiana and Mississippi.
- The Core has yielded **important discoveries** in the field of obesity and metabolic syndrome research.
- The NORC Cores established and developed **novel techniques and procedures** now available to NORC members.

### **Human Phenotyping (William Cefalu/Donald Williamson)**

- The Core supported work resulting in 87 publications.
- The Core instituted rigorous quality control measures for all the measurements provided.
- The Leadership of the Core progressively reduced and consolidated services from eight to now four sub-Cores.
- The Core validated two new measures of insulin sensitivity (glycolysis rate and urinary C-peptide), one of them being entirely developed at our Center (C-peptide urinary excretion rate).
- The Core is presently implementing a full series of metabolic turnover rates using stable isotopes and plans to provide these services to the University of Colorado NORC in Denver. Dr. Jean-Marc Schwarz is providing us with almost monthly consulting trips for expertise in stable isotopes methods.
- The Core generated preliminary data for more than 75 grant submissions, with 58 of them being funded and using the Core during the past grant cycle.
- The Core developed and implemented a two-tiered billing system for services.
- The Core helped the NORC to increase the Research Base Funding from \$18,403,447 to \$32,414,095 in direct costs, i.e., a 76% increase.
- The Core developed and implemented a monthly education/tutorial and mentors its young clinical investigators through an organized system.

- The Exercise and Physical Activity Core added Dr. Timothy Church, M.D., as a consultant in the design and implementation of population-specific exercise interventions and Dr. Catrine Tudor-Locke as a consultant in the assessment of free-living energy expenditure with accelerometry and step counters.
- The Insulin Sensitivity and Carbohydrate Metabolism Sub-Core developed the 6,6 deuterated glucose-oral glucose tolerance test, initiated studies with measures of glucose and glycerol turnover with stable isotope tracers, and standardized the data processing and database upload for clamps.
- The Imaging Sub-Core acquired and validated whole body nuclear magnetic resonance as a precise measure of body composition, developed the <sup>31</sup>P ATP synthesis rate measurement and maximal ATP synthesis rate measurement, and developed the magnetic resonance imaging measurement of epicardial adipose tissue and organ size.
- The Psychology Sub-Core developed a digital photography system of foods as a means to measure food intake. The team developed a web-based system for Diet and Behavioral Adherence and Internet Data Collection and developed a new Body Morphology Assessment technology.

### **Molecular Mechanisms (Les Kozak/David Burk)**

- More than 100 publications have resulted from this Core's support of research by NORC members.
- More than 15 new projects were funded based on preliminary data from this Core.
- More than 64 independent research groups from PBRC investigators accessed the services of this Core. The Core has established itself as an important service provider and has supported 82 scientists at more than seven institutions across Louisiana and Mississippi, thus increasing collaboration among investigators in this region.
- The Core has yielded important discoveries in the field of obesity, including the discovery of adropin, a novel secreted protein that regulates glucose homeostasis, and SLC25A25, an ATP-Mg<sup>++</sup>/inorganic phosphate transporter of the inner mitochondrial membrane that determines metabolic efficiency through its regulation of electron transport and oxidative phosphorylation.
- The PBRC has contributed more than \$754,533 to develop state-of-the art genomic and bioimaging technology, including Next Generation DNA Sequencing.
- The Molecular Mechanisms Core is participating in an effort to address a need for bioinformatics expertise by expanding its effort to establish a Bioinformatics/Computational Biology Resource and regionally in the Southeastern United States by developing collaborations with biostatistical geneticists at the University of Alabama.

### **Animal Models & Phenotyping (Randy Mynatt/Don Ingram)**

- The unique feature that we offer compared to most other Cores is a "turn-key" service for generating knockout mice at a price well below commercial cost (\$10,000 vs. \$50,000) for NORC investigators. These services are offered not only to our NORC members but also to researchers from other institutions.
- By having a full-time person (funded solely from the NORC) devoted to the design and construction of the targeting vector, we have created an efficient, money-saving service for NORC investigators.

- We have successfully produced mice carrying floxed alleles for PBRC faculty, LSU (Health Science Centers at New Orleans and Shreveport and the School of Veterinary Medicine), the University of Tennessee, Virginia Polytechnical Institute, the University of Arizona, and Scripps Research Institute.
- In addition to the generation of mice, we offer state-of-the-art metabolic and behavioral phenotyping services.
- At least 70 publications have resulted from this Core's support of research by NORC members.
- Eleven new projects were funded based on preliminary data from this Core.
- More than 30 investigators accessed the services of the Core. The Core has established itself as an important service provider and supported scientists at more than eight institutions across the United States, thus increasing collaboration among investigators.
- The Core has yielded important discoveries in the field of obesity, including the discovery by Dr. Butler of adropin, a novel secreted peptide that regulates glucose homeostasis.